The Efficacy of Local Anaesthetic Infiltrated at the Incision Site for Post-Operative Pain Management Following Abdominal Surgery: An Application to Fast-Track Surgery

Sumithra Krishnan

Discipline of Surgery, The University of Adelaide &

The Department of Clinical Pharmacology, The Queen Elizabeth Hospital

For Submission as a Doctorate of Philosophy in Medicine

August 2011

THE UNIVERSITY
of ADELAIDE

TABLE OF CONTENTS

DECLARATION

I, Sumithra Krishnan certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the university to restrict access for a period of time.

....

Sumithra Krishnan Date

ACKNOWLEDGEMENTS

The completion of this thesis owes much to many people. Firstly, I would sincerely like to thank my supervisor's- Professor Ray Morris for his kindness, support, good-nature and continual positive encouragement even during the more challenging times; and Professor Peter Hewett for his guidance, kindness and expertise. I have certainly been lucky to have worked with two such knowledgeable and approachable Supervisors! Special thanks are also due to Dr. John Field for his expertise and guidance in the statistical analysis of this project.

To all my colleagues, in the Clinical Pharmacology Department and Colorectal Surgical Department, I gratefully acknowledge your overall guidance, support and advice. I am also thankful and appreciate the contributions of the Pharmacy Department, Anaesthetic Department, Acute Pain Services Team and nursing staff from the Pre-Admission Clinic, operating theatres, Recovery Unit, High Dependency Unit, and S2 Ward, who without their help and kindness, this study would not have been possible.

I would also like to acknowledge Surgical Synergies for providing the Painbusters and the Faculty of Health Sciences, The University of Adelaide, and the Queen Elizabeth Hospital Research Foundation for financially supporting this study.

I would like to thank all my family for their constant encouragement, in particular my Mother and Father for their warmth and support and my Grandfather who was the motivating influence in all my academic endeavours. Lastly, I would like to dedicate this thesis to the memory of my late Grandmother, Chinna Krishnan.

ABSTRACT

Post-operative pain is the most commonly encountered and therapeutically difficult problem on a surgical ward. Pain can be a preventable outcome of surgery but its treatment is inadequate for many patients, as 30-70 % of patients continue to suffer from pain post-operatively. Current pharmacological approaches used for pain management consist mainly of opioids, which cause serious adverse effects and may increase patient morbidity and prolong recovery. Therefore, this may be reduced with appropriately delivered local anaesthesia, as a favourable adjuvant.

The aim of this study was to test whether a continuous 96 hour infusion of the local anaesthetic, levobupivacaine, using a commercial infiltration device (Painbuster®, IFlow Corp, USA), delivered into the deeper muscle layers where pain fibres penetrate, can minimise or eliminate the need for opioid analgesia following laparoscopic or open abdominal surgery. The novel aspects of the study include the higher dosage of the local anaesthetic, the longer duration of infusion, and the location of the catheter in the deeper tissue layers aimed at maximising response, all as part of a fast-track surgery approach.

Patients scheduled for laparoscopic or open abdominal surgery who consented into this randomised double-blinded placebo-controlled trial, were allocated (2:1) to receive either the active drug (0.5% levobupivacaine infusion) or placebo (0.9% saline infusion) in the Painbuster®. Blood samples were collected over the 96 hr infusion period in order to measure the total plasma levobupivacaine concentration and patients were placed under a fast-track surgery protocol intended to enhance recovery. Patients had available opioids via a patient-controlled-analgesia system for break-through pain. Pain scores and total opioid consumption were used as an index of efficacy.

Eighty-one patients were recruited in the study: laparoscopic active (n=31); laparoscopic placebo (n=20); open active (n=24) and open placebo (n=6). The four treatment groups were well controlled for age, body mass index and gender. There was a trend towards lower opioid consumption and pain scores in the open active group compared to the open placebo group, however, paradoxically the

laparoscopic active group had higher opioid consumption and pain levels than the laparoscopic placebo group at particular time-points, which may be influenced by the presence of stomas, drains and gender differences. Although a significant difference in length of hospitalisation was evident between laparoscopic and open cases (laparoscopic- 6.5 days; open- 9.8 days, p= 0.003), the active treatment was not associated with an earlier time of bowel movement and mobilisation nor reduction in hospitalisation. The mean patient total plasma levobupivacaine concentrations were below the toxicity threshold, but need to be interpreted in the light of increased protein binding (to AAG) post-operatively, as total concentrations may over-estimate the risk of toxicity.

These findings suggest that a 96 hr continuous local anaesthetic infusion post abdominal surgery may be a favourable method of pain control in patients undergoing open surgery. This could be due to the well located catheter, the increased local anaesthetic concentration and a longer post-operative infusion period.

PUBLICATIONS AND PRESENTATIONS DURING CANDIDATURE

Publications

Krishnan S, Tou S, Hewett P, Karatassas A, Field J, Morris R. Continuous local anaesthetic infusion in open and laparoscopic colorectal surgery: a double blind randomised study. For submission to the Aust NZ J Surg, Manuscript in Preparation.

Published Abstracts

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: An interim analysis. *Proc 29th Aust Pain Soc Mtg*. p100. 2009.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: An interim analysis. *Basic Clin Pharmacol Toxicol* 105(S1):61. 2009.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J. Does the infusion of local anaesthetic at the incision site provide adequate pain relief following abdominal surgery? An interim Analysis. *Ther Drug Monit* 31(5):663. 2009.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery. *Basic Clin Pharmacol Toxicol.* 107(S1):390-1. 2010.

Conference Presentations

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: An interim analysis. Australian Pain Society Meeting, April 2009, Sydney, Australia.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: An interim analysis. TQEH Research Day, Oct 2009, Adelaide, Australia.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: An interim analysis. Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT), December 2009, Sydney, Australia.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: An interim analysis. European Association for Clinical Pharmacology and Therapeutics (EACPT), July 2009, Edinburgh, UK.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery. WorldPharma, July 2010, Copenhagen, Denmark.

Krishnan S, Morris RG, Hewett P, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery. TQEH Research Day, Oct 2010, Adelaide, Australia.

Morris RG, Krishnan S, Hewett PJ, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the surgical incision site for post-operative pain management following abdominal surgery. Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT), 2010, Melbourne, Australia.

Krishnan S, Morris RG, Hewett PJ, Karatassas A, Tonkin J, Field J. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery. Royal Australasian College of Surgeons (RACS) Annual Scientific Meeting. May 2011, Adelaide, Australia.

Krishnan S, Field J, Hewett PJ, Tou S, Karatassas A, Morris RG. Local anaesthetic infused at the incision site for post-operative pain management following abdominal surgery: A double blind randomised study. Tripartite Colorectal Meeting, July 2011, Cairns, Australia.

Krishnan S, Morris RG, Hewett PJ, Karatassas A, Tonkin J, Field J. 96 hr levobupivacaine infiltration for post-operative pain management. A protein binding issue. Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT), 2011, Perth, Australia.

Awards

Best Poster Presentation Winner, TQEH Research Day, Oct 2010, Adelaide, Australia.

LIST OF ABBREVIATIONS

AAG	Alpha1-acid glycoprotein
ACTH	Adrenocorticotropic hormone
APS	Acute Pain Services
BMI	Body Mass Index
Cb	Bound drug concentration
CCK	Cholecystokinin
CGRP	Calcitonin gene-related peptide
Cl_{int}	Intrinsic clearance
CONSORT	Consolidated Standards of Reporting Trials
Ct	Total drug concentration
Cu	Unbound drug concentration
DOSA	Day of Surgery Admission
FDA	Food and Drug Administration
Fu	Unbound Fraction
Fu%	Fraction unbound (as a percentage)
HAL	Hand Assisted Laparoscopy
HPLC	High Performance Liquid Chromatography
ICU	Intensive Care Unit
IV	Intravenous
LA	Laparoscopic Active
LLOQ	Lower Limit of Quantification
LP	Laparoscopic Placebo
NMDA	N-Methyl-D-aspartic acid
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Open Active

OP	Open Placebo
PAC	Pre-Admission Clinic
PCA	Patient Controlled Analgesia
PCEA	Patient Controlled Epidural Analgesia
PCOA	Patient Controlled Oral Analgesia
PHR	Peak Height Ratio
PROSPECT	PROcedure SPECific postoperative pain managemenT
QC	Quality Control
TQEH	The Queen Elizabeth Hospital
Tmax	Time to peak concentration
VAS	Visual Analogue Scale
VNRS	Verbal Numerical Rating Scale

CHAPTER 1: INTRODUCTION

CHAPTER 1- INTRODUCTION

This Chapter sets the background of local anaesthetic infusion into the incision site for post-operative pain following abdominal surgery and subsequently into the bigger picture of its application in fast-track recovery techniques following surgery. The first section of the introductory chapter will elucidate the basic principles of pain and why post-operative pain is a problem and the current available treatment modalities used to treat it. The second section will lead on to the use of local anaesthetics, factors that influence effectiveness of local anaesthetics and the measurement of its concentration in the circulation. The third section will provide details of colorectal disease states, the types of abdominal incisions and the novel concept of fast-track recovery from surgery. This chapter concludes with the research objectives of this thesis.

1.1 Pain

1.1.1 The Classification and Nature of Pain

Pain is a major public health issue that exists in the world (Brennan and Cousins, 2004). Pain is experienced by everyone regardless of age, gender and economic status and will affect all of us at some stage in our lives. As proclaimed by British Psychologist Havelock Ellis, (1939) “pain is a part of life, to reject it is to reject life itself.” Although, pain is a normal experience, it is the extent and severity of pain that is problematic. As emphasised by Pain Specialist Professor Michael Cousins at the recent Australian National Pain Summit “Pain is one of the biggest health issues in Australia today- every bit as big as cancer, AIDS and coronary heart disease” (MBF, 2009). This is supported by the fact that pain is the most common reason for seeking medical help and accounts for over 50% of patient admissions into an emergency department (Cordell et al., 2002).

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant and emotional experience arising from actual or potential tissue damage or described in terms of such

damage" (International Association for the Study of Pain, 1986). This emphasises that pain is a subjective, rather than sensation-prone experience (Australian and New Zealand College of Anaesthetists et al., 2010, Benhamou, 1998). Pain is a multi-factorial event that is involved in processes in the brain that utilise structures that are implicated in cognition, emotion and sensation (Macintyre et al., 2010, Chapman, 2005). As reinforced by Clancy and McVicar, (1992) "The experience of pain is dependent upon the integrated function of the nervous system. Therefore to say pain is either body or mind is meaningless".

Pain can be further classified into categories in order to distinguish its origin and subsequent treatment, as shown below in Figure 1. Pain can be classed as either nociceptive or non-nociceptive.

Figure 1: The classification of pain. (Adapted from www.PainClinic.org 2009)

Nociceptive pain originates from pain receptors. Nociceptive pain occurs when normal nerves transmit information relating to tissue damage to the central nervous system (Fink, 2000). In contrast to this, non-nociceptive pain arises from the central or peripheral nervous systems. It does not involve the activation of specific receptors as the pain experienced is a result of signals sent by nerve dysfunction.

As nociception can occur without pain, it is also important to understand that pain can occur without nociception.

Nociceptive pain can either be classed as somatic or visceral. Somatic pain, often referred to as musculoskeletal pain involves the skin, muscles, ligaments and joints. It is characterised by a sharp and localised pain sensation. Symptoms such as cramping, swelling and bleeding may be present. It involves the activation of nociceptors for temperature, pressure, stretch, inflammation and a decrease in tissue oxygen concentrations. Visceral pain is a result of injury to an internal organ, primarily in the thorax, abdomen and pelvis. Pain receptors within these cavities respond to inflammation, stretch and reductions in oxygen concentrations. This type of pain is not well-localised and is characterised by a constant deep ache with cramping. It can arise from gastro-oesophageal reflux, peptic ulcers or inflammatory bowel disease and often produces referred pain, which is pain experienced at a site different to its origin.

Non-nociceptive pain can be classed as either neuropathic or sympathetic. Neuropathic pain occurs when structural or functional adaptations to the peripheral or central nervous systems appear secondary to injury (Mather and Cousins, 1992). Nerve injury can be a result of nerve degeneration, pressure, inflammation or infection. It is characterised as burning, tingling, numbness, weakness, throbbing or shooting pain. Sympathetic pain is due to increased activity in the sympathetic, peripheral and central nervous systems. There are no specific pain receptors involved and it can occur after soft tissue injury and fractures, leading to Complex Regional Pain Syndrome. It is characterised by hypersensitivity at the site of injury and the limb affected (www.PainClinic.org, 2009; accessed January 2011)

Based on the classification in Figure 1, pain can be further categorised in order to understand its nature. The five categories consist of: acute pain, sub-acute pain, which is the progression of acute into chronic pain, recurrent pain such as migraines, chronic non-cancer pain and cancer related pain (Ranney, 1996). Each of the above mentioned types of pain can involve the different components of pain, as stated in Figure 1. For example, cancer pain can be acute, chronic, visceral or somatic, depending on the type and stage of the disease.

The distinction between acute and chronic pain requires further explanation. Acute pain is a sudden onset of injury that results in damage to body tissues, which may lead to both visceral and somatic pain. For example, during abdominal surgery both visceral and somatic nerves are stimulated. The body responds to the most intense pain first, which is why the visceral pain would be experienced first over the somatic pain. Acute pain is usually of limited duration and lasts for hours, days or weeks and is due to tissue damage, inflammation, a short-lived disease or a surgical procedure (Australian and New Zealand College of Anaesthetists et al., 2010, Fink, 2000). In contrast, chronic pain continues past the time required for healing and usually persists for a duration of more than three months. It deteriorates over time and decreases the quality-of-life and is said to affect approximately 20% of the population in the developed world (Macintyre et al., 2010). The cause(s) of chronic pain is not necessarily clearly defined and can be somatic, visceral, neuropathic or sympathetic in origin. It is progressively becoming more accepted that chronic pain is a continuum of acute pain (Macintyre et al., 2010, Bond and Breivik, 2004)

Whilst it is important to appreciate the existence of various types of pain and how they interact and co-exist, nevertheless, the focus of this thesis will be on post-operative pain in the acute pain setting.

1.1.2 The Development of the Theories of Pain

The theories of pain help us to elucidate and understand the origin of pain, the concepts of pain, what pain is and why we feel it. Over the last 330 years, our perception of the theory of pain has expanded from the hypotheses theorised by French philosopher and scientist René Descartes through to the phenomena of spinal sensitisation and central nervous system plasticity proposed by psychologist, Ronald Melzack and neuroscientist Patrick Wall. This section will provide a review on firstly the specificity theory, pattern theory, gate control theory and conclude with the neuromatrix theory of pain.

Specificity Theory

The theory of pain historically dates back to the propositions of French Philosopher René Descartes in the 17th century. Descartes primarily theorised that a noxious stimulus activates specific pain receptors and fibres, which consequently send pain impulses through a pathway in the spinal cord to a pain centre in the brain (Fink, 2000). This was the foundation of the specificity theory and also implied that simply cutting this pain pathway would alleviate all pain (Melzack, 1993, Melzack, 1999), as historically depicted in Figure 2.

Figure 2: This diagram as depicted by René Descartes (1596-1650) in Tractatus De Homine (Treatise of Man) in 1664, illustrates the theory of pain transmission. As the foot comes into contact with a noxious stimulus, the withdrawal reflex occurs and a message is sent to the pain centre in the brain via a pain pathway (adapted from (DeLeo, 2006)).

This theory furthermore illustrated that there was a strong link between pain and injury and that the severity of the tissue damage was correlated to the magnitude of pain experienced by the individual (DeLeo, 2006). The intensity of the stimulus was linked to the intensity of pain. Hence a higher stimulus intensity and consequent pain pathway activation would result in a more intensified pain experience (Brannon and Feist, 2000). It was argued that pain was a specific sensation, independent from other sensations (Marks et al., 2005).

Despite the revolutionary nature of the specificity theory, it is associated with many weaknesses. It failed to take into account the psychological aspects of pain and that pain fibres also respond to mechanical and thermal stimuli. Furthermore, it could not account for pain in the absence of tissue damage or apparent variations in pain perception in individuals with seemingly equivalent tissue damage (Main and

Watson, 1999). Another shortcoming is that the relationship between the intensity of the stimulation and pain intensity are not proportional, as originally proposed (Main and Watson, 1999). In addition to this, the belief that cutting the pain pathway would alleviate pain proved to be another drawback. This principle was contradicted by numerous clinical cases, which found that cutting the pain pathway paradoxically resulted in an increase of pain symptoms, due to nerve damage, which can consequently lead to central unremitting pain. Regrettably, this model was historically perceived as factual rather than theoretical, so mis-directed further study, research and treatment of pain for more than three centuries (Marks et al., 2005).

Pattern Theory

The pattern theory of pain integrated with and supplemented the hypotheses of the specificity theory. The pattern theory proposed that the nerve fibres which carried the pain signal could also transmit thermal and mechanical stimuli. As with the specificity theory, it also alleged that pain perception was proportional to the amount of tissue damage (DeLeo, 2006). This theory arose due to weaknesses in the specificity theory, discussed above. In 1874, Wilhelm Erb, a German neurologist elucidated that a pain signal is produced by any sensory receptor, rather than a pain receptor, if the stimulation is intense enough. Hence the pattern of stimulation, described as the pain intensity over time and area, not the type of receptor, dictated whether nociception resulted or not. This was supported by another German neurologist Alfred Goldscheider, who theorised that sensory fibres accrue in the dorsal horn of the spinal cord and only signal pain once a threshold was reached. A century later, supporting evidence for this theory was proposed by Dutch neurosurgeon, Willem Noordenbos, who proposed that damage along fibres with a large diameter may hinder the signal present in smaller diameter fibres, which reinforced that pain intensity was modulated by the pattern of stimulation (Marks et al., 2005).

To summarise, these theorists essentially anticipated that the stimulation of nociceptors resulted in a pattern of impulses that were summated in the dorsal horn of the spinal cord and that pain perception

occurred once the level of the summated output was greater than a threshold for the pain to be transmitted to the cortex.

Like the specificity theory, there were evident shortcomings in the pattern theory. Two primary weaknesses of this theory were evident. Firstly, the number of different types of specific receptors required for this theory to be confirmed had not been demonstrated to exist. Secondly, the pattern theory like the specificity theory, is a linear model of pain, which does not take into account any psychological aspects of pain, including examples such as phantom limb pain, and injury without pain perception (Todd and Kucharski, 2004).

Gate Control Theory

As shown in the specificity and pattern theories, the psychological aspects of pain were not taken into consideration or associated with physical injury. This association was clinically affirmed as in the 1950's when patients suffering from chronic pain with no underlying disease pathology were sent to psychiatrists (Marks et al., 2005, Melzack, 1993). Doubtful of Descartes' specificity theory of pain, Canadian psychologist Ronald Melzack and British neuroscientist Patrick Wall proposed their gate control theory of pain in 1965, which further revitalised research in the field of pain. Melzack and Walls proposed that the dorsal horn of the spinal cord functions as a gate, which either inhibits or permits the transmission of nerve impulses from the noxious stimulus from the receptors to the brain. The gating is determined by the diameters of the active peripheral fibres (A-delta fibres that carry sharp pain; C fibres that carry dull pain and A-beta fibres that carry messages of light touch) conjointly with the dynamic action of brain processes. The processing of pain occurs in an integrated matrix throughout the neuroaxis of the central nervous system at three levels of modulation: the peripheral (intervention at the periphery via the blockade of pain); spinal (activation of the inhibitory processes that gate pain at the spinal cord and brain) and supraspinal levels (interference of central processes with the perception of pain). Supplementary to this, the gate is additionally modulated by specialised nerve impulses that arise

in the brain and travel back down the spinal cord to regulate this process This is known as the central control trigger and stimulate either A-beta or C fibres by conveying sensitive messages to the gate, therefore, confirming the role of cognitive processes in the transmission of pain (Melzack, 1999). Conditions that either open or close the gate are tabulated in Table 1.

Table 1: Conditions that open or close the gate (adapted from http://homepage.ntlworld.com/gary.sturt/health/pain.htm, accessed January 2011).

Despite the conceptual knowledge gained from the development of this theory, a residual weakness evident in the gate control theory is its inability to explain prominent pain conditions such as chronic pain and phantom limb pain (DeLeo, 2006, Melzack, 1993, Wall, 1978). However, attempts to overcome this were further researched and expanded by Melzack in the notion of the neuromatrix theory.

Neuromatrix Theory

This theory highlights the multi-dimensional properties in the perception of pain such as an individual's genetic make-up, prior pain experience, psychological history, cognitive knowledge and general life stress. It is characterised by "neurosignature patterns of nerve impulses generated by a

widely distributed neuronal network- “the body-self neuromatrix”” (Melzack, 1993) To date, it is the most comprehensive theory in relation to pain (Melzack, 1999).

The neuromatrix theory of pain arose from the re-conceptualisation of the gate control theory by Melzack. As mentioned above, pain as a result of acute noxious stimuli has been extensively researched although no model has fully explained the basis of chronic pain syndromes, which display no perceptible injury and pathology. The neuromatrix theory suggests that firstly either perceptual, homeostatic and behavioural sequences following injury are activated by the output patterns of the neuromatrix or secondly it is the result of multiple other inputs acting on the neuromatrix (Melzack, 1999). This model is illustrated in Figure 3.

Figure 3: Factors which contribute to the patterns of activity generated by the body-self neuromatrix. It is comprised from sensory (S), affective (A) and cognitive (C) neuromodules. The output patterns from the neuromatrix generate the multiple dimensions of the pain experience and homeostatic and behavioural responses (Source: Melzack, 2001).

The development of the different theories of pain has contributed to the understanding of the concept of pain. Further research, in particular in the area of the brain will only enhance our understanding. The

different theories of pain provide the basis of the neurobiological mechanisms of pain, which will be reviewed in the following section.

1.1.3 Neurobiological Mechanisms of Pain

It is important to understand the basic mechanisms of pain in order to obtain an insight into the specific pathways that can be modulated to prevent it and hence ensure optimal post-operative pain management. Pain commences with nociception. Tissue damage, stress and injury leads to the activation of nociceptors, which lowers the activation thresholds leading to action potential transmission to the dorsal horn of the spinal cord. The process of nociception simultaneously effects motor, emotional and sensory areas of the brain (Kelly et al., 2001). The mechanism of pain consists of two states. Firstly, peripheral sensitisation which comprises activation of peripheral nociceptive afferent neurons by noxious stimuli and secondly, central sensitisation, in which the afferent neurons generate the pain sensation (Lierz and Punsmann, 2001, Chapman, 2005).

Overview

As illustrated in Figure 4, mechanical, chemical and thermal stimuli activate nociceptors in the periphery. Once activated, action potentials are conducted through fast, small diameter myelinated A-delta fibres or slow, unmyelinated C-fibres (Yue, 2007, Levine et al., 1993, Clancy and McVicar, 1992). The impulses firstly pass through the dorsal root (which contain bodies of these neurons) and propagate to the dorsal horn of the spinal cord where peripheral nerve axons synapse with interneurons (primarily in laminae I, II and V of the dorsal horn).The nociceptive pathway transmits signals from the dorsal horn of the spinal cord to the thalamus and other brain regions via the ascending pathways of the spinothalamic and thalamocortical tracts; from the periphery to central processing areas in the brain (Yue, 2007, Ochroch et al., 2003). Descending inhibitory pathways are activated by psychological and environmental factors (Besson, 1997). Noxious stimuli, whose signals have been transmitted to the cerebral cortex, are only perceived as pain if specific areas of the brain, such as the anterior cingulate

gyrus of the limbic system, are activated (Ochroch et al., 2003). Therefore each point along the nociception pathway can be targeted to reduce pain.

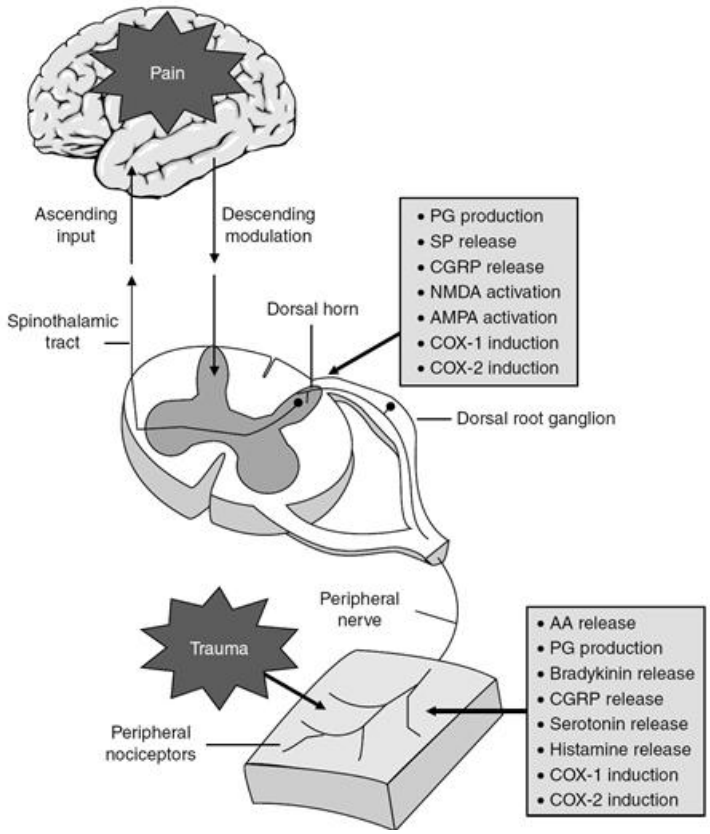

Figure 4: The nociceptive pathway, highlighting the involvement of mediators and receptors involved in peripheral and central sensitisation. AA= arachidonic acid; AMPA= 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CGRP= calcitonin gene-related peptide; COX= cyclo-oxygenase; NMDA= N-methyl-D-aspartate; PG= prostaglandin; SP= substance P (Adapted from (Ochroch et al., 2003))

Peripheral sensitisation

Peripheral sensitisation is induced at the site of injury. Peripheral sensitisation leads to primary hyperalgesia, which responds to both mechanical and thermal stimuli at the site of the injury (Macintyre

et al., 2010). Tissue damage results in the release of a multitude of chemical mediators, as shown in Figure 4, which is involved in nociception and inflammation. The mediators involved in peripheral sensitisation include Substance P, bradykinin, histamine, calcitonin gene-related peptide (CGRP) and serotonin (Kawamata et al., 2002). They excite the nociceptors or increase their sensitivity at the site of injury (primary hyperalgesia). Substance P is released from damaged A-delta and C-fibres and leads to vasodilatation and oedema formation. The release of Substance P also results in the activation of phospholipase A_2, which in turn catalyses the production of arachidonic acid, which is broken down by cyclo-oxygenase leading to the production of prostaglandins and leukotrienes (Ochroch et al., 2003). Prostaglandins lower the activation threshold for sensory neurons. Bradykinin, which is released as a result of tissue damage, causes the release of prostaglandins and histamine via the degranulation of mast cells (Lierz and Punsmann, 2001). Serotonin is directly released from mast cells and platelets. It activates sensory neurons which in turn increases nociceptive activity. Serotonin also amplifies the inflammatory responses of bradykinin, histamine and leukotrienes. Furthermore, serotonin provides a further connection between the peripheral nervous system and central nervous system hence advancing the process of central sensitisation. CGRP is released as a consequence of prostaglandin stimulation. CGRP also increases blood flow and oedema formation (Ochroch et al., 2003). Therefore, the combination of all the mediators described above enhances peripheral sensitivity to noxious stimuli. The activation thresholds of sensory neurons are reduced, while the magnitude of stimuli with potential for nociceptive production is increased. Hence, the central nervous system is now associated with increased nociceptive activity, enabling the occurrence of central sensitisation.

Central Sensitisation

Central sensitisation occurs at the dorsal horn of the spinal cord, the brainstem and the brain (Main and Watson, 1999). Central sensitisation occurs when nociceptive input increases the response of neurons that transmit pain in the central nervous system (Yue, 2007). Central sensitisation leads to secondary hyperalgesia. Studies suggest that secondary mechanical hyperalgesia occurs after injury and not after

the sensitisation of primary afferent nerve fibres (Brennan et al., 2005). Normally low threshold A-beta mechanoreceptors produce pain as an outcome of changes that have occurred in the sensory processing of the spinal cord. Secondary hyperalgesia takes place in undamaged skin near the site of injury and unlike primary hyperalgesia, it only responds to mechanical not heat stimuli (Brennan et al., 2005).

As shown in Figure 4, central sensitisation is the enhancement of spinal cord neurons in response to nociceptive input. This can lead to hyperalgesia and allodynia. Peripheral and central sensitisation can co-occur. Substance P and CGRP, which are released in the dorsal horn as a consequence of nociceptive input from the periphery, can stimulate the release excitatory amino acid neurotransmitters such as aspartate and glutamate (Kawamata et al., 2002, Ochroch et al., 2003). It is at this level, where Melzack and Wall's (1999) gate control theory of pain is set to occur as signals in the A beta fibres of a peripheral nerve can potentially alter the sensitivity of the post-synaptic cells to painful stimuli appearing in A and C delta fibres (Melzack, 1999). These excitatory neurotransmitters act on 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. Once these receptors are activated, they increase the duration of function of dorsal horn nuclei and lower the threshold for afferent nerve conduction, hence allowing enhanced nociceptive input in the brain.

Contraindications in this mechanism

The cause of the above mentioned peripheral injury and inflammatory mediated pain may be different to the aetiology of post-operative pain hence resulting in different analgesic pharmacology (Brennan et al., 2005, Dirks et al., 2002).

This aetiological difference is evident by contraindications in the hypersensitivity of NMDA and cyclo-oxygenase inhibitors between constant, prolonged pain to that of post-operative pain. Brennan (2005) evaluated studies on incisional pain mechanisms using different experimental pain models, concluding

that spinal NMDA receptor agonists that weaken hypersensitivity in prolonged pain are not effective in post-operative pain. This finding was supported by Yue (2007), as discussed below. Furthermore, hypersensitivity after post-operative pain is hindered by intrathecal cyclo-oxygenase-1 but not cyclo-oxygenase-2 inhibitors, supporting the differences in the mechanisms of hypersensitivity of post-operative pain compared to inflammatory or peripheral injury induced pain (Macintyre et al., 2010). Nociceptive impulses may trigger an extensive increase in spinal cord excitability. This spinal cord hyper-excitability, resulting from a large amount of nociceptive impulses elicited by C fibre afferent changes in the spinal cord may be sustained constituting an underlying mechanism of post-operative pain (Wang et al., 2007).

Another study conducted by Yue (2007) showed that excitatory amino acids such as glutamate and aspartate were higher following surgery and returned to baseline levels on post-operative day one. This suggested that they were involved earlier in spinal sensitisation than previously thought. In contrast, the inhibitory amino acid, glycine, peaked at post-operative day one and returned to baseline on day two. This showed that the release patterns of amino acids after surgery are different from inflammatory pain, suggesting that different types of pain utilise different neurotransmitters and receptor systems (Wang et al., 2007).

It is not well understood how the different nociceptive mechanisms account for the intensity and duration of post-operative pain. Hence it could possibly at least partially explain why post-operative pain continues to be under-managed Yue (2007). It would be highly desirable to identify and understand these mechanisms more explicitly and target a treatment(s) that manage this.

1.1.4 Variations in the Perception of Pain

There are many contributing factors which can have an impact on an individual's perception of pain. Some of these factors can include: co-existing medical conditions, cultural factors, genetics, a history of substance abuse, a history of neuropathic or chronic pain or variations due to the extremes of age from infants to the elderly (Turk, 1993). Although these factors are significant, in the following discussion, a particular emphasis will be placed on the psychological aspects of pain, including the placebo effect and gender specific differences that are evident in the perception of pain.

1.1.4 (a) Psychological Aspects of Pain

Psychological factors impact the perception of pain. This has been shown experimentally, as positron emission tomography (PET) scans of the brain have revealed that individuals react differently to incoming pain, hence leading to differences in pain perception (Chapman, 2005). As stated by Walters (1963), the impulses in the pain fibres and pathways "are no more the pain than the visual impulses from the retina are the perceptual fields of colour and pattern that present to us when our eyes are open." Walters also reinforces that it should be referred to as noxious stimulation rather than a painful stimulation.

There are three psychological theories of pain. Firstly, it is theorised that pain is an outcome of hostility. The second theory speculates that pain arises in patients that have a particular personality type who complain about their pain as a form of communication. Thirdly, it is theorised that pain arises as a consequence of a threat to the integrity of the body (Main and Watson, 1999).

A variety of emotional factors can impact the severity of pain. For example, pain can be exacerbated in patients that are tired, depressed or at night when the brain is less actively engaged. Depression measured prior to surgery was furthermore linked to higher levels of post-operative pain (Walters, 1963). Further, pessimistic and negative attitudes are correlated with poor pain relief and have a

detrimental effect on physiological functioning. Of significance is the psychological state of anxiety, which is common in a pre- and post-operative setting. Similar to pain, anxiety is a natural response to a harmful event. Symptoms of anxiety include nausea, dizziness, headache, muscle tension and an increase in heart rate (Merskey, 1968). High levels of anxiety are correlated with an increase in pain perception and a higher intensity of post-operative pain (Symreng and Fishman, 2004). Consequently, methods used to decrease anxiety may also reduce pain (Clancy and McVicar, 1992, Macintyre et al., 2010). Interestingly, medications used for psychopharmacological treatment, including alpha$_2$-agonists, lithium, antidepressant, anticonvulsants, stimulants, neuroleptics and benzodiazepines, can be prescribed for pain management, hence supporting the association between anxiety and pain (Symreng and Fishman, 2004).

A study conducted by Taenzer (1986) investigated the levels of post-operative pain, mood and analgesic requirement, using a psychological battery of tests on 40 patients undergoing cholecystectomy. His group demonstrated that patient variables such as anxiety, depression and a history of chronic pain syndrome were correlated to pain and could therefore be used to predict patient post-operative outcomes. Conversely, the assessments of anxiety and pain the day before surgery were not significantly linked to high levels of post-operative pain. Hence it is more effective if medical staff assess the patient's normal emotional status rather than their pre-operative emotional status when identifying patients that are at risk of suffering from elevated levels of post-operative pain (Taenzer et al., 1986). This study supports the significance of psychological factors in the perception and the intensity of post-operative pain.

The Placebo Effect

A placebo is an inert treatment. It "is an intervention designed to simulate medical therapy, but not believed (by the investigator or clinician) to be a specific therapy for the target condition" (Brody, 1985). Placebo treatment is commonly used in clinical trials to eliminate observer bias in experimental settings

as well as psychological effects on the subject (Benedetti, 2007, Taenzer et al., 1986). The application of placebo controlled studies to distinguish any perceived reduction in pain stimulus between active or sham treatments is particularly important so as to discern any significant effect(s) associated with the active treatment over sham treatment, provided that the patient is unaware of the treatment received (Watson et al., 2009).

A placebo effect is a change in the condition of the patient that can be attributed to the importance of being treated rather than any specific pharmacological properties of the experimental agent, whereas the placebo response is change observed in a patient following the administration of a placebo (Watson et al., 2009). There are numerous factors that influence the placebo response. The expectations of the patient can have an impact on their response, as highly compliant patients have better results than non-compliant patients. Further, a friendly and positive attitude shown by clinical staff towards the patient has an added effect on placebo treatments. Placebo treatments are the most effective in patients with high anxiety levels, although it is not clear whether this reduction is a full or only partial effect of the placebo treatment (Turner et al., 1994).

In 1978, it was proposed that the placebo response was mediated by endogenous opioids, as studies had demonstrated that a naloxone administration reduced the incidence of a placebo response and also increased pain scores in patients who had previously shown a strong placebo response (Turner et al., 1994, Brody, 1985). Placebo therapy has even been shown to imitate the action of active medications as shown by response curves and even apparent cumulative carryover effects after treatment has stopped (Turner et al., 1994). Placebo therapy is often associated with side-effects, especially non-specific effects, such as drowsiness, nausea, constipation and headaches (Lasagna et al., 1958).

As opposed to exerting a positive response, placebo therapy can also exert a negative effect, which can potentially worsen pre-existing symptoms, this is known as the nocebo effect (Turner et al., 1994).

Unlike placebo effects which are mediated by endogenous opioids, nocebo effects are thought to be mediated by cholecystokinin (CCK), as depicted in Figure 5. A nocebo is anxiogenic, hence CCK stimulates nocebo hyperalgesia by converting anxiety into pain (Benedetti, 2007, Turner et al., 1994). Nocebo hyperalgesia is antagonised by the anxiolytic drug, diazepam, reinforcing its anxiogenic properties.

Figure 5: The activation of functionally opposing endogenous opioid system (placebo analgesia) and CCK system (nocebo hyperalgesia). (Adapted from (Benedetti, 2007))

1.1.4 (b) Gender Differences and Pain Perception

Gender differences in pain and analgesia are apparent. Many studies have shown that females are more sensitive to pain, report higher levels of pain following surgery and are at greater risk of developing chronic pain conditions in comparison to males (Benedetti, 2007).

Differences in pain perception between females and males can be attributed to neurobiological, biological and psychosocial reasoning (Miyazaki and Yamamoto, 2009, Fillingim et al., 2009, Aslaksen et al., 2007, Kallai et al., 2004, Craft et al., 2004). Neurobiological differences can be due to hormonal influences. Females encounter fluctuations in their hormone levels due to pregnancy, menopause and changes in their menstrual cycle, whereas males experience fewer fluctuations in their hormone levels across their lifespan (Fillingim et al., 2009, Fillingim and Gear, 2004, Craft et al., 2004). In pre-menopausal females, higher levels of estradiol correlated with increased pain sensitivity to thermal stimuli, whereas post-menopausal females not requiring hormone replacement therapy experience pain responses similar to males. The hormonal changes also lead to an increase of the inflammatory response in females. The inflammatory response triggers the release of inflammatory cytokines, growth factors and peptides released from C fibres. Spinal N-Methyl-D-aspartic acid (NMDA) receptor activation and nitric oxide production are also involved in nociceptive processing (Fillingim et al., 2009).

It has been argued that psychosocial reasons could possibly date back to the evolutionary roles of females and males. As males predominantly had a hunter role, they would experience a higher frequency of somatic pain such as traumatic injury associated pain, whereas females endured more visceral pain related to menstruation and pregnancy (Fillingim et al., 2009, Miyazaki and Yamamoto, 2009). Furthermore, males have the intention of impressing the opposite gender by withstanding pain, whereas females tend to show increased sensitivity to pain, with the intention of eliciting the protective behaviour of males (Craft et al., 2004).

Interestingly, the gender of the experimenter interacting with the subject/patient has an influence on the reporting of pain, consequently impacting the reliability, accuracy and validity of pain research. As the reporting of pain typically occurs to another person, the effect this person may have is vital (Kallai et al., 2004). A study conducted by Aslaksen and colleagues (2007) hypothesised that male subjects who reported less pain when tested by a female experimenter also had a lower physiological response (heart

rate and skin conductance levels) to pain. Furthermore these researchers aimed to determine if males tested by either female or male experimenters showed the same physiological response to pain but reported it differently depending on the gender of the experimenter. This was conducted by inducing heat pain at 48 °C on the forearm of 32 male and 32 female subjects. Three female and three male experimenters collected data and assessed the pain intensity levels of the subjects. Aslaksen concluded that there were no significant physiological interactions evident in the measurement of the physiological parameters. Physiological changes were not influenced by the gender of the experimenter. However, the lower levels of pain reported by male subjects to female experimenters were most likely attributed to psychosocial reasons (Aslaksen et al., 2007). In contrast, females reported the same level of pain regardless of the gender of the experimenter. This is significant when subjective emotions are assessed as part of pain therapy. This finding was supported by Kallai (2004) who investigated the effect of the gender of the experimenter on 80 male and 80 female subjects undergoing the cold-pressor pain test. The subject's pain threshold, pain tolerance and pain intensity were measured. In relation to pain tolerance, a significant difference ($p= 0.043$) was evident between the gender of the experimenter and the gender of the subject, demonstrating that subjects had a higher pain tolerance when tested by an experimenter of the opposite gender, as shown in Figure 6.

Figure 6: The average pain tolerance (seconds) for male and female subjects when tested by an experimenter of the opposite gender. Error bars indicate the SEM (Kallai et al., 2004).

Conceivably, they exert this behaviour in order to impress the opposite gender, or a range of other gender-related psychosocial interaction issues, that impact upon the response given. Therefore, in clinical settings it is important to consider the contribution of the gender of the clinician, nurse, other attending staff, family or friends may have on the pain levels reported by patients.

In the future, to enhance the effectiveness of pain relief it is evident that the gender of the patient and assessor needs to be taken into account.

1.1.5. Pain Measurement

In order to advance treatments and research into pain and improve pain management, the accurate assessment of a patient's current pain is needed (Kawamata et al., 2002, Revill et al., 1976). As pain is a subjective experience, there is no impartial method of quantifying it. Hence pain measurement remains problematic to researchers as there is no simple relationship between the pathology and intensity of pain that a patient may report (Macintyre et al., 2010, Chapman, 2005, Turk, 1993).

The measurement of pain is complex and hence difficult to measure. There are many disadvantages and limitations associated with the measurement of pain. Most methods of pain assessment rely on the subjective response, mental interpretation of the patient and the circumstances when asked, hence not accounting for the array of physical, neurophysiologic or psychosocial aspects of pain. What is being interpreted at a mental level does not correlate well with its biological basis (Fink, 2000). In the majority of the literature, assessment of pain is only performed while the patient is at rest. Criticism evident with this is that the efficacy of different treatment modalities may only be evident while the pain is assessed during functions such as coughing and mobilisation (Kehlet, 1994). Post-operative pain should be measured several times a day, furthermore it is important that emphasis is placed on the current level of pain rather than a general question that may be tempered by past pain (Benhamou, 1998).

Regardless of this subjectivity, the measurement of pain is still a valuable tool, particularly in tracking pain over days to weeks within individual patients. However, the patient's willingness to report pain and the effects of the pain stimulus must be taken into consideration (Benhamou, 1998). Despite the range of different types of pain assessment tools, to be discussed below, the quality of each tool is dependent on the ability of the questioner, such as an empathetic nature and an understanding of the patient's pain experience (Revill et al., 1976). Furthermore, it is important to note that the patient reporting the pain should be evaluated on a whole and not just their pain per se (Fink, 2000).

There are many different methods available for the estimation of pain. As pain is an individual and subjective experience, measurements of pain are largely based on self-reporting (Chapman, 2005). Techniques of pain measurement consist of more involved methods such as the WILDA approach and the MacGill Pain Questionnaire to straight-forward methods that can easily be used to measure the intensity of pain such as the verbal rating scale, visual analogue scale (VAS) and the verbal numerical rating scale (VNRS). The WILDA approach of pain assessment takes into account the five fundamental components of pain such as Words to describe the pain, Intensity (0-10), Location, Duration and Aggravating and alleviating factors. It also takes into consideration how pain affects daily actions like sleep, if the patient is experiencing other symptoms such as nausea or constipation and checks clinical features of the patient such as vital signs and medication history (Chapman, 2005). The McGill Pain Questionnaire has been developed to measure the multi-dimensional properties of pain such as the patient's present pain intensity, a torso diagram where the patient indicates the location of their pain and their pain rating index based on adjectives from 20 different categories (Macintyre et al., 2010). Although the multi-dimensional aspects of pain, such as it location, intensity and emotional effects are evaluated in the WILDA approach and the McGill Pain Questionnaire, its complexity makes it problematic for common and repetitive use in surgical patients. Therefore, it is limited in its use for research purposes. Verbal rating scales uni-dimensionally describe the magnitude of the pain experienced. The verbal rating scale is an example where words such as mild, moderate severe and

excruciating are used to describe pain (Turk, 1993). The VAS is the most commonly used scale for assessing pain intensity (Macintyre et al., 2010) of the patient. The patient is presented with a 100 mm line on a piece of white paper, with one end of the line representing "no pain at all" and the other representing "the worst pain imaginable". The individual marks the line, indicating their intensity of pain along the scale (Revill et al., 1976). Whilst the VAS is subjective, it is advantageous as it is simple to use, easy to administer, non-invasive, reasonably accurate when compared to other methods, minimises communication barriers through language, reproducible and has a wide choice of ratings (Botti et al., 2004, Benhamou, 1998). Although the VAS is used extensively and has the benefit of assessing pain longitudinally through a course of treatment in an individual, it does require sufficient levels of visual perception, motor function and cognitive ability to convert the sensation of pain into a distance measure (Coll et al., 2004, Benhamou, 1998). The verbal numerical rating scale (VNRS) is an 11 point scale. It comprises of a scale from 0 to 10, where 0 represents no pain and 10 represents the worst pain imaginable. Patients verbally report a number from 0 to 10 that most accurately indicate the intensity of their pain. It is essential to keep pain scales consistent, for example, "0" should always represent "no pain". In a clinical setting, VNRS are regularly favoured due to their simple administration, relatively consistent results and their correlation with the VAS (Macintyre et al., 2010).

Many studies have demonstrated that the validity and effectiveness of the VAS and VNRS to be approximately equivalent. Breivik (2000) compared the sensitivity of a four-category verbal rating scale to the VNRS and VAS using a simulation model. It was deduced that the verbal rating scale was less sensitive than the VAS and therefore not interchangeable with it, while the VNRS and the VAS were equally effective in comparing post-operative pain intensity due to its linear properties. The three pain rating scales were likewise compared and reviewed by Williamson and Hoggart (2005) who came to the same conclusion as Breivik (2005). Bijur et al., (2003) assessed the comparability of the VNRS to the VAS in 103 patients presenting with acute pain in an emergency department. VNRS and VAS measurements were taken at presentation and later on at 30 min and 60 min after the initial reading. A

regression analysis indicated a strong correlation (r = 0.94. 95% CI + 0.93 to 0.95), as shown below in Figure 7, between VNRS and VAS at all time points, suggesting VNRS and VAS are interchangeable for acute pain measurement.

Figure 7: The relationship between the verbal numerical rating scale (NRS) and visual analogue scale (VAS). The regression line (y-intercept= -0.34; slope = 1.01) shows a strong relationship between the two measures. (Source: Bijur et al., 2003).

Therefore, the VNRS and VAS can be used interchangeably. However, for consistency, in this present study the VRNS was adopted as the measurement tool of choice due its simplicity and ease of administration. It is important to note that all methods do suffer from the subjectivity of the pain experience of the individual patient when applying these methods. For example, whilst there would be strong concordance at the "zero" end of these scales, one would expect divergence further up the scale as the "most pain imaginable" is a very individual interpretation by each patient, and so complicate comparisons between patients in the clinical trial scenario (Figure 7) may even show such divergence at higher pain levels as illustrated by the increasing scatter.

1.1.6 Post-Operative Pain Control

Despite advancements in the understanding of the physiological basis of pain, the development of new analgesics, different strategies and techniques of analgesic administration, hospital acute pain service teams and the creation of many health bodies which are typically established with the aim of standardising and optimising pain management, post-operative pain continues to remain under-managed. This is attributed to a gap between improvements in pain knowledge and its effective application into providing adequate treatment (Liu et al., 2006, Kehlet, 1994, Loan and Morrison, 1967).

Post-operative pain is constant surgically related pain that is aching in nature and located in the vicinity of the surgical site. Activities such as ambulation and coughing can often heighten the basal level of pain. It is a self-limiting condition that often improves over a short period of time (Klopfenstein et al., 2000). Approximately 30 to 86 % of patients experience moderate to severe pain following surgery, with post-operative pain being the most common reason for post-discharge re-admission (Botti et al., 2004, Sinatra, 1991).

The cause of post-operative pain is multi-factorial and can be due to: superficial or deep incisions to the skin, subcutaneous tissue and organs; the site and nature of the surgical procedure; nerve compression; positional bed sores; coagulation and trauma; issues at the site of intravenous administration such as needle trauma, extravasation and venous irritation; problems associated with drains and nasogastric and endotracheal tubes; respiratory issues from the endotracheal tube, coughing, sneezing and deep breathing; movement and ambulation; surgical complications and other factors such as urinary retention and tight dressings (Macintyre et al., 2010, Loan and Morrison, 1967).

Although, post-operative pain is an expected outcome of surgery, if left unrecognised and/or undertreated, it may prolong hospitalisation and increase the incidence of hospital re-admission (Klopfenstein et al., 2000, Chung, 1998, Fink, 2000, Oates et al., 1994, Gottschalk et al., 2002).

Untreated post-operative pain can also have adverse effects on organ function, the psychological condition of the patient, and may lead to an increase in the prevalence of the progression of acute pain into chronic pain, hence compromising recovery. These aspects are to be further elucidated.

Detrimental effects of post-operative pain on organ function are evident through changes to the cardiovascular, respiratory, gastrointestinal, genitourinary, neuroendocrine and musculoskeletal systems (LeBlanc et al., 2004, Botti et al., 2004, Kehlet, 1994, Coll et al., 2004). These adverse effects are shown in Table 2.

The psychological condition of patients is also affected adversely by unrelieved postoperative pain and may present as anxiety, depression, fear, fatigue, insomnia, aggressiveness and a negative behaviour.

Furthermore untreated post-operative pain can progress to chronic pain, potentially resulting in delayed recovery and disability. Factors predisposing patients to chronic pain include: pre-operative factors such as repeat surgery, pre-operative anxiety, female gender and psychological vulnerability; intra-operative factors such as procedures that have a risk of nerve damage; and post-operative factors such as depression, anxiety and acute moderate to severe pain (Macintyre et al., 2010, Pasero, 2003b). Therefore, the negative effects of unrelieved post-operative pain emphasise the need for effective analgesic treatment.

Table 2: The detrimental effects of untreated post-operative pain on organ function.

Physiological System	Detrimental Effects
Cardiovascular	The sympathetic nervous system is activated leading to hypertension, tachycardia, increased myocardial demand for oxygen and decreased coronary vasoconstriction, which in turn leads to myocardial ischaemia or infarction
Respiratory	Post-operative pain leads to a splinting diaphragm. The phrenic nerve which provides the only motor supply to the diaphragm is inhibited hence resulting in a reduced lung volume and atelectasis. Furthermore, sputum retention and poor cough leads to post-operative pneumonia and hypoxaemia
Gastrointestinal	Gastrointestinal effects such as activation of the spinal reflex arc leading to gastric and intestinal motility dysfunction, resulting in post-operative ileus
Genitourinary	Effects urinary retention
Neuroendocrine	Stress hormones such as cortisol, catecholamines and interlukin are released resulting in hyperglycaemia, protein breakdown, increased coagulability, the impairment of wound healing and immune function and sodium and water retention leading to an increase in metabolic demand
Musculoskeletal	Muscle spasms can occur which reduce respiratory function and mobility which increases the risk of deep vein thrombosis and peripheral vasoconstriction

The problem of post-operative pain was demonstrated in a study conducted by McHugh and Thoms (2002), who highlighted the problem of post-operative pain in 102 patients following a range of day surgery procedures. As shown in Figure 8, 80 % of all patients in this study were still experiencing pain at day 4 following surgery. Figure 9 shows the patients' rating of their pain experience. On day 2, out of

the 80 % of patients that experienced pain, 21 % of patients regarded their pain to be severe. This can be attributed to a lack of proper pain management due to a poor evaluation of the severity of the patients' pain and an under-utilisation of recent pharmacological advancements to be discussed below (McHugh and Thoms, 2002).

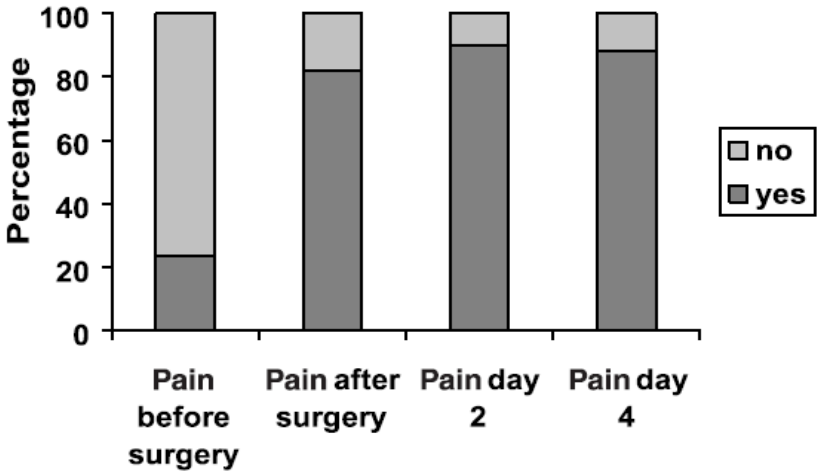

Figure 8: The percentage of patients experiencing pain (McHugh and Thoms, 2002).

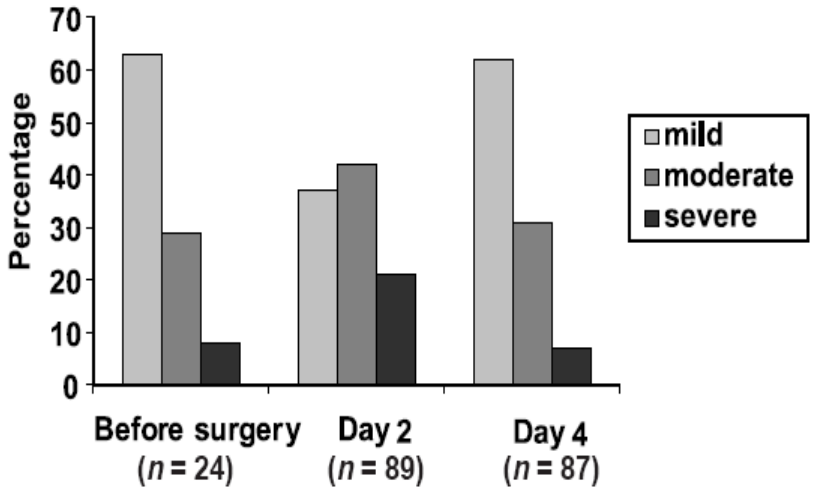

Figure 9: The patients' rating of their pain experience, measured before surgery and day 2 and day 4 post-operation (McHugh and Thoms, 2002).

This problem was confirmed by Oates (1994) who assessed 206 patients and found that 34% continued to suffer from moderate to severe pain 24 hr after surgery. In the patients that experienced severe pain, it was found that only 36% received adequate analgesic treatment. Nurses attributed this to patients being either too sleepy, refusing the dose or not requesting their need for medication (Oates et al., 1994). These two studies both highlight the problem of post-operative pain, the need for effective pain relief and difficulties that exist in the adequate management of post-operative pain.

The goal of post-operative pain relief is to: provide comfort to the patient, to inhibit the trauma produced by nociceptive impulses in order to dull the pain response and to enhance the recovery of organ function and patient mobility (Sinatra, 1991). Currently, many studies (Bond and Breivik, 2004, Botti et al., 2004, Loan and Morrison, 1967, Yun, 2007, Rowbotham, 2001) have shown the inadequacy of post-operative pain management, as high pain levels continue to be present following surgery. This is significant as adequate pain control translates into beneficial patient outcomes.

The problem of inadequate post-operative pain management can be attributed to the reasons shown in Table 3.

Table 3: Reasons contributing to patients receiving inadequate pain relief following surgery. (Adopted from Klopfenstein et al., 2000, Fink, 2000 and Kehlet, 1994).

Reasons for inadequate post-operative pain management
• Insufficient education and training among clinicians, nurses, students and patients
• Knowledge of health professionals in translating research into the science, into assessment and treatment of pain
• Clinicians are left with a vast amount of information and neglect the basics such as the correct choice of treatment, associated side effects, the level of surveillance and its cost-effectiveness compared to other treatments
• Improper assessment and lack of knowledge
• Lack of communication about pain treatment between clinicians, nurses and patients
• Inter-patient variability in the efficacy of analgesics and the subjective and multi-factorial nature of pain
• Contradictory and conflicting attitudes and practices between staff
• No proper systematic recording of patient's pain intensity and efficacy of their analgesia
• Pain assessment done only at rest, therefore incomplete assessment of effectiveness of analgesia
• Lack of public awareness of pain management
• Patients are under-dosed due to fears of adverse drug reactions, addiction or poor understanding of the actions of the drugs

This problem of post-operative pain and the need for its adequate treatment has been further accentuated by the establishment of acute pain services and regulatory organisations. Acute pain service teams have been introduced into many hospital systems to aid in the prevention of post-operative pain by delivering a more standardised specialised function, rather than a more ad hoc system provided by many clinical or nursing staff that risks many of the failings listed in Table 3. The roles of the acute pain service teams are extensive. They consist of educating patients and staff,

researching new treatments, introducing and overseeing advanced 'best practice' analgesic techniques, improving current analgesic treatments, standardising pain management protocols and guidelines, a 24 hr availability, collaborating with other medical staff and auditing pain services and techniques (Fink, 2000, Sinatra, 1991).

An array of professional health bodies and regulatory guidelines have been developed to achieve appropriate pain control. Examples include the: World Health Organisation (WHO) analgesic ladder for pain relief; the Joint Commission on Accreditation of Healthcare Organizations (JCAHO); the Australian Pain Society (APS) and the PROcedure SPECific postoperative pain managemenT (PROSPECT) website (http://www.postoppain.org/), that is utilised as a clinical tool for post-operative pain management following procedure-specific surgical interventions (Philip et al., 2002).

In summary, post-operative pain is an adverse issue resulting in detrimental consequences that affect a large proportion of patients following surgery. Although many reasons for pain mismanagement have been explained, of particular importance is the appropriate use of pharmacological agents. These are considered further below.

1.1.7 Current Pharmacological Management of Post-Operative Pain

The problem of post-operative pain discussed above highlights the need for appropriate and improved management to treat this problematic, distressing and under-treated condition. There are a variety of pharmacological agents such as: systemic α_2-agonists, glucocorticoids, anti-epileptic drugs, tricyclic anti-depressants, bradykinin, substance P and NMDA receptor antagonists that can be used to treat post-operative pain in some circumstances (Mather and Cousins, 1992). Furthermore, non-pharmacological interventions such as heat or cold therapy and transcutaneous electrical nerve stimulation (TENS) can be applied (Macintyre et al., 2010, Gottschalk et al., 2002, Besson, 1997). However, this thesis will focus on the current and conventional modalities used to treat post-operative

pain from the common and extensively used pharmacological agents of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetics through to the various routes of administration such as patient-controlled analgesia (PCA), epidural use, pre-emptive analgesia and continuous wound infusions to the multi-modal approach of analgesia, with each to be further discussed in this section.

1.1.7 (a) Pharmacological Agents

The commonly used pharmacological agents described in greater detail in this section, include opioids, NSAIDs and local anaesthetics.

1.1.7 (a) i. Opioids

Opioids have been used for centuries for the treatment of post-operative pain (Besson, 1997). Current examples of opioids include morphine, fentanyl, oxycodone, codeine and pethidine. Opioids exert their effect in the central nervous system and the peripheral nervous system including the wall of the gut and peripheral tissues (Kehlet et al., 1996). Opioids act on opioid receptors (mu (μ), delta (δ) and kappa (κ)), which are located in many different areas such as the primary afferent neurons, spinal cord, midbrain and thalamus that are involved in the transmission of pain. They inhibit the release of neurotransmitters in the pre-synaptic nerve terminal as well as the post-synaptic neuron, where they have an inhibitory effect (Chahl, 1996).

Opioids are advantageous as they provide analgesia and sedation and can be inexpensive in relation to other pain relieving medications (Lierz and Punsmann, 2001). Analgesic effect is produced on several levels of the nervous system. Firstly, they reduce the negative and emotional effects of pain in the limbic system by inhibiting the release of neurotransmitters from primary afferent terminals in the spinal cord. Secondly, they activate the descending inhibitory pathways in the medulla and periaquaeductal matter, thereby inhibiting the processing of the ascending nociceptive pathway at a spinal and supraspinal level. Lastly, on a spinal level, opioids inhibit incoming nociceptive action potentials and modulate pain

perception (Chahl, 1996). Opioids are more effective at providing analgesia, during rest rather than motion, therefore best used with a combination therapy approach (Mather and Cousins, 1992). Furthermore, opioids reduce the surgical stress response, displaying a positive effect on stress hormones, intra-operatively and early in the post-operative period (Kehlet et al., 1996).Although opioids may provide relief from pain and can be economical, the frequency and range of their side effects are a significant economic burden on health care systems (Philip et al., 2002). These systemic adverse effects are described in Table 4.

In addition, opioid use is also a problem in patients with certain co-morbidities. Neurologically, high doses can lead to fits and should therefore be avoided in patients with epilepsy. Patients with renal dysfunction excrete opioids slower, although this results in increased analgesia, sedation and respiratory depression are likewise increased (Lierz and Punsmann, 2001). Furthermore, some patients elect not to use opioids as they are anxious about becoming addicted, hence endure unnecessary pain and resultant co-morbidities (Kuhn et al., 1990).

Table 4: The adverse effects associated with opioid use. (Adapted from: (Gan et al., 2003, DiNicola, 2003, Lierz and Punsmann, 2001, Kehlet et al., 1996, Mather and Cousins, 1992))

Organ System	**Adverse Effect**
Gastrointestinal	-Incidence of post-operative nausea and vomiting is approximately 30 to 80 %. This is due to the stimulation of the vomiting centre in the brain -Constipation, ileus, a delay in gastric emptying, gastrointestinal paralysis, a reduction in secretions and an increase in bilary tone
Respiratory	-Respiratory depression due to the reduced sensitivity of the respiratory centres in the pons and medulla oblongata to carbon dioxide -Decreased suppression of the cough reflex and a reduction in the sensitivity to hypoxaemia, chest wall compliance, respiratory rate, tidal volume and expiratory force
Cardiovascular	-Brachycardia and hypotension (when co-administered with benzodiazepines)
Musculoskeletal	-Muscle rigidity involving abdominal and thoracic muscles which intervenes with ventilation, involves muscles of extremities such as the jaw, a potential difficult problem if an airway needs to be maintained in a critical patient
Endocrine	-Fluid retention due to the release of the antiduretic hormone, mediated by dopamine receptors in the hypothalamus
Urinary	**-**Negative impact on urinary bladder function which leads to urinary retention
Other	-Confusion, delirium, sedation, pruritus and headache

The two types of opioids that are used in this study are fentanyl and oxycodone. Fentanyl is a strong μ-opioid receptor agonist that can be used for anaesthesia and breakthrough pain. Fentanyl can be administered intravenously, transdermally, intramuscularly, epidurally, orally, sublingually or buccally. It has a rapid onset of action and short duration of action. Fentanyl is approximately 100 times more

potent than morphine. It is metabolised hepatically by CYP3A4 and has half-life of 186- 222 minutes in volunteers and 490- 522 minutes in surgical patients (Bower and Hull, 1982). Approximately 60% of the drug is excreted unchanged in the urine, although only a small proportion remained unchanged over the four days (Dahl, 2011). Fentanyl is approximately 80 to 85% protein bound. The side-effects of fentanyl are consistent with that of other opioids; however, less nausea and histamine-related itching is evident in comparison to morphine (Mayes and Ferrone, 2006). The risk of dependence with continual use of fentanyl is medium to high and fentanyl use has also been linked to sudden respiratory depression due to either reduced sedation, early carbon dioxide retention or saturation of the body fat compartment in patients with rapid body fat loss (Regnard and Pelham, 2003). Oxycodone is a μ-opioid receptor agonist, although its affinity to this receptor is approximately 20 times less than that of morphine (Kalso, 2007). Oxycodone can be administered orally, intravenously, intramuscularly, intranasally, subcutaneously, transdermally, rectally and epidurally. It is primarily metabolised hepatically by CYP3A4 and secondarily by CYP2D6. After an oral dose, the peak plasma concentration of oxycodone is reached after one hour and 19% of the drug is excreted unchanged in the urine. Oxycodone is 45% protein bound. The side-effects associated with oxycodone are the same as other opioids as described above. In addition, there is a risk of withdrawal if oxycodone is abruptly discontinued (Lalovic et al., 2006).

1.1.7 (a) ii. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs consist of non-selective NSAIDs and COX-2 selective inhibitors (coxibs). Examples include ibuprofen, naproxen, and ketorolac. NSAIDs are used for the relief of mild to moderate post-operative pain and the option of reducing opioid consumption (Creekmore et al., 2004).

NSAIDs generate analgesia and decrease inflammation by inhibiting prostaglandin production in the peripheral tissues and central nervous system. This reduction in the response to noxious stimuli can decrease peripheral and central sensitisation. NSAIDs inhibit cyclo-oxygenase enzymes, which exists

as two isoenzymes, COX-1 and COX-2. COX-1 is involved with gastric mucosal integrity and renal and platelet function and COX-2 is involved with tissue injury response, oedema and hyperalgesia (DiNicola, 2003).

NSAIDs are advantageous in comparison to opioids as they do not have the same systemic effects that lead to respiratory depression and inhibition of gastric emptying (Ochroch et al., 2003). Nonetheless, there are disadvantages associated with NSAID use. Side-effects include: peptic ulcers and bleeding, the inhibition of platelet aggregation, bronchospasm, renal impairment and allergies. NSAIDs also have a delayed onset of action and its absorption is variable. NSAIDs are contraindicated in patients with asthma, renal impairment, drug hypersensitivity, heart problems and hypovolaemia. Long-term use of NSAIDs has also been reported to increase the risk of arterial thrombosis and myocardial infarction (DiNicola, 2003). A prominent example of this was noted with the controversy of rofecoxib (Vioxx®). Cardiovascular risks of rofecoxib were evident in 2000, four years prior to its market withdrawal. The Food and Drug Administration (FDA) found an estimate of 27,000 cases of acute myocardial infarctions and sudden cardiac death in the USA from 1999-2003, concluding that this would be avoided if celecoxib was used instead of rofecoxib (Horton, 2004). However, much of this adverse event was associated with high doses that are no longer clinically used.

Although NSAIDs are useful analgesics they are inadequate for the treatment of the most severe post-operative pain and must be used in combination with other analgesics (DiNicola, 2003, Macintyre et al., 2010). Hence it is a popular component of multi-modal analgesia protocols to be discussed below in Section 1.1.7 (c).

1.1.7 (a) iii. Local Anaesthetics

Local anaesthetics have been used extensively in minor surgical procedures for many decades, but only in relatively recent years been applied to the management of post-operative pain following more major

surgery. Examples of local anaesthetics include lignocaine (lidocaine), bupivacaine, ropivacaine and levobupivacaine. Local anaesthetics function by inhibiting the transmission of pain from the nociceptive afferent nerves at the surface of the incision. Furthermore, local anaesthetics can block the local inflammatory response to injury, which in turn sensitises nociceptive receptors adding to pain and hyperalgesia (DiNicola, 2003). Pain relief with local anaesthetics has found applications in several surgical procedures including those involving the lower body. These drugs have an inhibitory effect on stress response and especially when adrenaline is included in the formulation, lowers blood loss, pulmonary infections and thrombo-emboltic related complications (Kehlet, 1994). The development of anaesthesia is correlated to the diameter and myelination of the affected nerve fibre. Small fibres are more sensitive and myelinated fibres are blocked before non-myelinated fibres. Clinically, the loss of nerve function begins as a loss of pain, temperature, touch, proprioception and muscle tone, which is why subjects still feel touch but not pain (Tuckley, 1994).

Although local anaesthetics provide effective analgesia with minimal side effects, local anaesthetic toxicity can result in concentration-related adverse effects. The adverse effects range from numbness, dizziness, tinnitus, blurred vision, drowsiness, through to convulsions, respiratory depression and cardiovascular system depression at higher concentrations. However, if cardiac collapse occurs due to local anaesthetic toxicity, lipid emulsification has proved to be effective in resuscitation (Tuckley, 1994, Mather and Cousins, 1992). The properties of local anaesthetics are discussed further in Section 1.2.

1.1.7 (b) Routes of Administration

Opioids, NSAIDs and local anaesthetics can be administered through a variety of routes. Examples of the different routes include: oral, transdermal, intramuscular, subcutaneous, intrathecal, intravenous and epidural administration. Each of these routes are associated with advantages such as ease of administration and disadvantages such as variable rates of absorption and the need for continuous monitoring (Kehlet et al., 1996, Blackford et al., 2008, Philip et al., 2002, Lierz and Punsmann, 2001).

The methods of patient-controlled analgesia, epidural administration, pre-emptive analgesia and continuous wound infiltrations are further discussed.

1.1.7 (b) i. Patient Controlled Analgesia (PCA)

The concept of patient controlled analgesia (PCA) originated in the 1960's and enables patients to receive their medication on demand in response to their own perception of break-through pain over and above basal analgesic therapy, such as the continuous analgesic infusion rate administered as selected by the attending medical staff. This is typically actioned by the patient pushing a button to introduce extra doses of intravenous opioids through a pump. The clinician determines the initial bolus dose of the opioid to be administered through the pump, the intermittent injection dose size by the patient, the lockout interval, and sets the upper limit to the amount of opioid that can be injected within a specified time interval (usually one to four hours) (Lierz and Punsmann, 2001).

There are advantages and disadvantages associated with PCA usage. PCA is advantageous as patients have a sense of being in control of their pain (Mather and Cousins, 1992, Sinatra, 1991, DiNicola, 2003, Paul et al., 2010). It is associated with higher levels of patient satisfaction and decreased levels of post-operative pain with less medication in contrast to nurse-controlled analgesia (Lierz and Punsmann, 2001). Patients can continue to maintain therapeutic concentrations of analgesics and allow rapid treatment for break-through pain by not having to await availability of nursing staff. Moreover, it is more cost-effective in comparison to epidural analgesia (Sinatra, 1991, Paul et al., 2010).

Nonetheless, there are disadvantages associated with PCA usage. PCA is generally quite costly due to the equipment involved and availability at the time, the drugs required and the nursing time involved in setting it up and monitoring usage (Macintyre et al., 2010). In addition, this technique is not suitable for children and patients with mental disabilities as pain relief is received on a breakthrough basis, administration is not available in the unconscious or sleeping patient (Macintyre et al., 2010).

Furthermore, PCA usage is a multi-step process, leaving the potential for error at each step. These problems are associated with the programming and setup of the PCA pumps, which can result in serious or even fatal outcomes due to human error (DiNicola, 2003). Common errors consist of the incorrect drug concentration, wrong dosage or lockout time of the opioid, leading to inadequately controlled pain or overdose. Furthermore, setup errors and pump malfunctions have led to medication mistakes (Paul et al., 2010). Paul and colleagues (2010) reviewed data of three hospitals over a seven year period to assess the risk of adverse events associated with PCA usage. They found that out of 25,198 patients treated, errors occurred in 0.25 % of cases, with a third resulting in detrimental effects to the patient (Paul et al., 2010). However, proper education can prospectively reduce these errors. Dosing errors also occur with patient confusion or mishaps that result in the PCA button being pressed. For example, when the patient accidentally presses the PCA button when intending to press the nurse-call button, raise or lower the bed mattress or even change the television station on the over-bed monitor. Such incidents are more likely in the difficult to communicate, the elderly and confused and/or anxious patients. These are all scenarios that would be common place in the post-surgical ward.

There are several factors that impact on PCA consumption. For example, the elderly require less opioids whereas the obese require more opioids post-operatively (Paul et al., 2010). Anxiety and depression have been linked to a higher number of PCA demands (Sinatra, 1991). Studies involving PCA usage have found that females consume less opioid in contrast to males (Macintyre et al., 2010). Nicotine can have an effect on pain perception and hence opioid consumption. This is of clinical relevance as many patients abruptly stop smoking on admission to hospital. Nicotine stimulates the central nervous system and blunts nociceptive activity. Its withdrawal in dependent patients can result in anxiety, depression, irritability, restlessness, decreased heart rate and weight gain (Fillingim et al., 2009). Importantly it leads to lower pain thresholds following surgery. Evidence by Creekmore et al., (2004) indicates that patients who are current or former smokers, who were suspended from cigarettes on hospital admission had significantly higher opioid consumption in contrast to non-smokers. This was

confirmed by (Woodside, 2000) who found smokers deprived of nicotine required a significantly greater amount of opioid following surgery than non-smokers. Hence medical staff should be vigilant to ensure that smokers are adequately dosed with more opioid analgesia than non-smokers. In some circumstances it may be necessary to administer nicotine in relevant patients to minimise their pain experience (Creekmore et al., 2004).

1.1.7 (b) ii. Epidural Administration

The epidural route of administration is used for enhanced pain relief, for moderate to severe pain. Drugs used for epidural analgesia include opioids, local anaesthetics or opioid-local anaesthetic combinations. Epidural analgesia can be administered by three different methods: bolus dosing (although a steady analgesic level is hard to sustain); continuous infusions, or by the use of patient controlled epidural analgesia (Macintyre et al., 2010).

Epidural administration inhibits the transmission of afferent pain pathways at the spinal cord level and has an effect on efferent motor fibres leading to muscle relaxation. Epidural administration with opioids carries the drug closer to the site of action at the opioid receptors, resulting in smaller doses in contrast to systemically administered opioids (Pasero, 2003b).

There are positives associated with epidural use. Epidural opioids decrease pain intensity and atelectasis whereas epidural local anaesthetics decrease the systemic effects of opioids, pulmonary complications and deep vein thrombosis (Pasero, 2003b, Carr, 1993). Epidurals are also safe in patients assessed with low risks such as American Society of Anaesthesiologists (ASA) 1 and 2 category patients (DiNicola, 2003). It also reduces pain scores in comparison to patients using PCA (Sinatra, 1991).

Despite this, the risk of major complications associated with epidural use has led to its decline (Blackford et al., 2008, Burstal et al., 1998). Complications resulting from epidural administration comprise of dural puncture, epidural haematoma and abscess and nerve root trauma. Adverse effects from local anaesthetic epidural administration can include hypotension, paraesthesia and motor weakness. Epidural administration of opioids can lead to urinary retention, pruritus and herpes simplex. It can also result in respiratory depression, which may only be present up to 18 hr after morphine is administered and high occurrences of nausea and vomiting due to the rostral flow of the cerebrospinal fluid to the chemoreceptor trigger zone in the brain (Blackford et al., 2008). Furthermore, the failure rate is about 10 – 20%, resulting in early cessation of the infusion (Sinatra, 1991).

1.1.7 (b) iii. Pre-emptive Analgesia

Pre-emptive analgesia is a treatment that prevents the alteration of sensory processes that enhance post-operative pain management (Blackford et al., 2008, Kissin, 2005). Pre-emptive analgesia is used to reduce pain intensity and analgesic use following surgery (Ong et al., 2005). Drugs used in pre-emptive treatment include NSAIDs, opioids, local anaesthetics and NMDA antagonists (McQuay, 1995).

The mechanism of pre-emptive analgesia involves the inhibition of release of inflammatory mediators prior to the activation of both peripheral and central sensitisation, involving both the primary afferent and spinal dorsal horn neurons. Theoretically, it should prolong the entire duration of noxious stimulation (Kehlet, 1994, Dahl et al., 1992). Clinically, the concept of pre-emptive analgesia has been explained by two different approaches. The first approach involves demonstrating a decrease in pain intensity or analgesic use. Study designs compared pre-operative treatment to non pre-operative treatment groups. The second approach involved testing whether a treatment administered prior to surgery is more effective than the treatment administered following the operation (Kissin, 2010). This approach was the most common study design for pre-emptive analgesia, as discussed below.

Although pre-emptive analgesia theoretically seems attractive, many studies have found it ineffective in the alleviation of post-operative pain. Studies have been conducted to consider whether treatments implemented prior to surgical procedures are more effective than either the same treatment applied after the surgical procedure or no treatment at all. A meta-analysis of 66 studies using either: epidural analgesia, peripheral local anaesthetic infiltrations, systemic NMDA receptor antagonists, systemic NSAIDs and systemic opioids as pre-emptive analgesic interventions was conducted by Ong (2005). The studies compared the effectiveness of the same treatment provided before surgery to following surgery. Measures included pain intensity and complementary analgesic consumption. Significant effects were noted with epidural analgesia, local anaesthetic infiltration and systemic NSAIDs; conversely, there was no added benefit with the pre-operative administration of opioid and NMDA receptor antagonist use. However, there are criticism of this work that impacts the validity of the results. Firstly, issues exist within the pre-treatment versus post-treatment design of the study. In the pre-treatment group, nociceptive input after surgery, may instigate apparent pain hypersensitivity, thereby reducing the difference between the two groups. A second concern is differences in the concentrations of the drug. Differences in the administration protocol of the drug between the two groups results in markedly higher concentrations in the post-treatment group, thereby reducing the difference between outcomes of the two groups (Ong et al., 2005). In contrast, a systematic review by Kissin and co-workers (2005) assessed 80 studies based on the previous trial design. They concluded that the clinical benefit from pre-emptive analgesia was minimal for the management of post-operative pain. In an earlier study, Moiniche and co-workers recommended more stringent criteria be adopted for such trials included in the analysis and a different method of pain score calculations accounting for a more accurate representation of pre-emptive analgesia for the various types of analgesic interventions (Moiniche et al., 2002).

Problems relating to the concept of pre-emptive analgesia arise from: the different approaches used to determine pre-emptive analgesia, validation of the direct pharmacological effect of a specific treatment,

intensity of the noxious stimuli, differences in drug concentrations between study groups and outcome measures (Kissin, 2005). An additional problem relates to the terminology and definitions of pre-emptive analgesia. Many clinical trials have viewed pre-emptive treatment as pre-operative or pre-incisional, and not as the prevention of dorsal horn sensitisation (Kissin, 2005, Carr, 1996). For example, clinical trials that have administered NSAIDs or opioids pre-operatively are used to assess the efficacy of pre-emptive analgesia, although theoretically incorrect as it was administered before the incision rather than preventively, prior to the occurrence of nociception (Carr, 1996).

Future multimodal studies involving pre-emptive analgesia should focus on the duration of the intervention and complete blockade of the nociceptive stimuli (Moiniche et al., 2002). It should also be used in combination with opioids, neural blocks, and drugs acting on the spinal cord in contrast to uni-modal pre-emptive analgesic techniques.

Local anaesthetic drugs can be administered through a variety of routes and methods. These comprise epidural blocks, as previously discussed, regional blocks, peripheral nerve blocks and intermittent or continuous blocks. However, they are not administered orally due to extensive first-pass metabolism (Macintyre et al., 2010).

Peripheral nerve blocks, which involve direct injection of the local anaesthetic near the peripheral nerves are safe and provide effective analgesia, however they have a relatively short duration of action (Kissin, 2005). Such blocks are also associated with technical difficulties such as the technique used for locating the nerve, the type of continuous catheter equipment, and the choice of local anaesthetic. Ultrasound guidance and nerve stimulator guidance are being utilised to reduce catheter failure rate (Kissin, 2005).

Intravenous infusions are beneficial as they can avoid the unpredictability of drug absorption noted with intramuscular injections, while delivering more adequate effects. Furthermore, iv administration also

averts the consequences of the release of further drug into the circulation once the infusion has ceased unlike intramuscular drug administration, where absorption persists even after all the drug is injected (Kehlet, 1994). A disadvantage of intravenous infusion is that the average plasma drug concentration can fluctuate from four to six-fold amongst similar patients. In some patients the variance can be as much as a ten-fold difference, if the same doses were injected into patients with varying body weight. This is due to a difference in blood volume (Miller, 1994). Local anaesthetic injected directly into the wound provides better pain relief than spinal anaesthesia as shown by a reduction in pain scores (both at rest and movement), opioid consumption, post-operative nausea and vomiting and a length of hospitalisation. Patient satisfaction is also increased and there is no difference in the rate of wound infections (Macintyre et al., 2010).

1.1.7 (b) iv. Transversus Abdominal Plane Block

The transversus abdominal plane (TAP) block is increasingly being used for post-operative pain relief following abdominal surgery. It consists of blocking the peripheral nerves, which anaesthetises the abdominal wall however its effectiveness is topical. In order to assess the benefits of a TAP block, Charlton and colleagues (2010), conducted a Cochrane review involving five studies (236 subjects). They concluded that the presence of a TAP block, compared to a placebo control or no TAP block resulted in reduced post-operative morphine consumption 24 hours (mean difference- 21.95 mg, 95% confidence interval CI 37.91 to 5.96) and 48 hours (mean difference- 28.50 mg, 95% CI 38.92 to 18.08) but not at two hours post-operation. This was supported by a meta-analysis of 86 patients in a TAP block group compared to 88 patients in a non-TAP block group by Siddiqui (2011). Siddiqui concluded the presence of a TAP block reduced the need for morphine consumption and provides better post-operative pain relief. However, this evidence is limited and there has been no noted reduction in post-operative nausea, vomiting and sedation (Charlton et al., 2010).

1.1.7 (b) v. Continuous Wound Infiltration Devices

Whilst various continuous wound infiltration devices are available commercially, the present study adopted one that is an elastomeric pump attached to a catheter with a terminal portion that delivers the infiltrate along its length. The terminal portion is placed into the surgical incision site at the end of the surgical procedure and continuously infuses the local anaesthetic drug at the user-selected flow-rate and duration (potentially for several days post-surgery) (Pu, 2006). This constant infiltration inhibits the transmission of nociceptive impulses from the surgical site e.g. midline wound to the spinal cord (Liu et al., 2006). Continuous infiltrations diminish the need for repeated local anaesthetic injections. It is a simple technique, technically efficient, provides analgesia, reduces opioid derived side effects and it is portable and ambulatory (Thorson and Faria, 2001, Polglase et al., 2007, Cheong et al., 2001)

Despite the potential benefits of continuous wound infiltration devices, their usage in a range of surgical procedures has been associated with inconsistent results. A systematic review by LeBlanc (2004) assessed 42 randomised controlled trials consisting of 2,141 patients using continuous wound infiltration devices in randomised controlled trials that evaluated pain scores and opioid consumption. Most studies used bupivacaine or ropivacaine ranging in concentration from 0.2 % to 0.5 %. Trials consisted of orthopaedic surgery, cardiothoracic surgery, general surgery and gynaecology-urology surgery. The results were inconsistent as some studies showed an infiltration of saline was just as effective as a local anaesthetic infiltration. However, no incidences of systemic local anaesthetic toxicity were reported and wound infections were minimal (LeBlanc et al., 2004). Consequently, it would be beneficial to ascertain approaches where the effects can be optimised and delivered more consistently.

Although there is support for use in herniotomies, the use of such infiltration devices is not well established for most major colorectal procedures (Thorson and Faria, 2001, Polglase et al., 2007, Singh et al., 2007). A study by Beaussier and colleagues (2007) investigated the role of a continuous pre-

peritoneal infusion in 21 patients that had received 0.2% ropivacaine compared to 21 patients that received a saline infusion for 48 hr post-open colorectal resection. It was concluded that the ropivacaine group displayed reduced morphine consumption and improved post-operative pain relief compared to the saline group. Karthikesalingam (2008) conducted a meta-analysis of five trials consisting of 542 laparotomies to assess the evidence for continuous wound infiltration with local anaesthetics following colorectal surgery. There was a significant decrease in post-operative pain scores using a VAS on day 3 however this was not present on days 1 and 2. Furthermore significance was noted in terms of reduced opioid consumption although there was no difference in length of hospitalisation or return of bowel function between study groups receiving the local anaesthetic infiltration or control groups. Karthikesalingam (2008) concluded that although a promising technique, there is not any conclusive evidence of the benefits. Therefore, he recommended further large scale studies to establish any benefits. This finding was supported by a systematic review conducted by Moiniche (1998), who concluded that due to inadequate evidence and variable effects, larger, well designed controlled trials were essential before local anaesthetic infiltrations could be regarded as the optimal treatment following abdominal surgery.

Further to the systematic reviews, two separate studies conducted by Cheong (2001) and Baig (2006) investigated the benefits of continuous wound infiltration devices in patients undergoing major colorectal surgery. There were similarities and differences evident between the two studies. The study by Baig (2006) had an analgesic regimen of 2 subcutaneous Painbuster® catheters with 0.5 % bupivacaine at a flow rate of 4 ml/hr for 72 hr post-operation. Thirty five patients had the local anaesthetic infiltrated through the catheter whilst the other 35 patients had a saline infiltration, an intravenous morphine PCA was used for breakthrough pain relief. Likewise, Cheong (2001) used a 0.5 % bupivacaine infiltration, whereas the flow rate was set at 2 ml/hr and lasted for a duration of 60 hr post-operation. Cheong (2001) compared 35 control subjects using the wound infiltration technique to 35 patients receiving an intravenous morphine PCA. Pain scores were equivalent between the two treatment groups in both

studies, although Baig (2006) noted a decrease in the pain scores on day 2 post-operation, whereas Cheong (2001) observed this reduction on day 1. A reduction in opioid consumption was highly significant in both studies. Opioid usage by Baig (2006) showed a reduction in opioid usage of 43% ($p < 0.04$) in the treatment group compared with the control. This difference was more pronounced in the study by Cheong (2001) who showed a decrease of 93% ($p < 0.001$) between the groups. Superficially, this difference appears surprising given that the Cheong study used a lower infiltration rate (2 versus 4 ml/hr) of the same concentration bupivacaine (both 0.5%). However, there were noteworthy differences in the opioid support offered to patients. Surprisingly, the Cheong study provided their control patients with morphine through a PCA, whereas the treatment group received subcutaneous morphine on request resulting in unequal access to morphine between the groups. Furthermore both studies established that there was no significant difference in length of hospitalisation among the treatment and control groups.

Negative findings may be related to the ineffective placement of the catheter. In the above studies, the catheter was inserted in the subcutaneous layer. This would require the local anaesthetic to diffuse to the sensory nerve fibres. Hence, one could anticipate potential for treatment failure in those patients where the distance for this diffusion represents a barrier to efficacy (perhaps the more obese patients). In contrast, catheter tunnelling within the rectus sheath and transversus abdominis plane may have provided more effective pain relief by infusing the drug closer to the site of action, being the sensory nerve fibres. One can readily conceive that correct catheter placement is a contributing factor to the success or failure. For example, for midline incisions nerve endings need to be blocked that proceed on either side of the abdomen to the spinal cord as well as the full length of the incision so as to include all sensory nerves. Whereas oblique or transverse incisions on the abdominal wall may involve fewer pain fibre pathways along one to three dermatomes. So appropriate catheter placement is required to ensure that these specific nerves are receiving sufficient analgesia (Blackford et al., 2008, Cheong et al., 2001).

Furthermore, PROSPECT has not recommended the use of continuous wound infusions for open colonic resections partly due to the fact that clinical trials have been underpowered. Hence, the clinical advantages of continuous wound infiltration devices may be compromised through lack of appropriate evidence to prove its effectiveness. Therefore, this device was adopted as the pharmacotherapeutic model of choice in the present study in order to reduce post-operative pain following abdominal surgery.

1.1.7 (c) Multi-modal Analgesia

Multi-modal analgesia is based upon the use of multiple analgesic drug classes or treatment techniques with the aim of providing complementary therapy targeting different points in the neurological pathways relevant to pain perception. It results in fewer side effects and lower total doses of analgesics (Dahl and Kehlet, 1991, Jin and Chung, 2001). Recently, the trend has been to shift away from finding the ideal analgesic to using a combination of techniques (Kehlet, 1994).

Multi-modal analgesia consists of a combination of NSAIDs and opioids for minor to moderate pain and a combination of opioids and local anaesthetics, utilised as continuous infusions or nerve blocks, for moderate to severe pain (Blackford et al., 2008). NSAIDs inhibit the initiation of pain in the periphery, whereas local anaesthetics have a fast onset of action and can have a duration of action for up to 12 hr and weaken pain signals in the central nervous system, and opioids have a slower onset of action but can last as long as 24 hr (Thorson and Faria, 2001, Jin and Chung, 2001). Techniques can also consist of the addition of alpha$_2$-adrenergic antagonists and NMDA receptor antagonists such as ketamine. The development of substance P blockers and bradykinin antagonists, which modify the inflammatory wound response of pain have the potential to be implemented in multi-modal approaches (Blackford et al., 2008, Pasero, 2003b)

Multimodal analgesia is advantageous due to lower complication rates, a reduced length of hospitalisation and shorter anaesthetic and recovery times. It is also associated with lower rates of

progression to chronic pain syndromes (Kelly et al., 2001). Despite the advantages, a deep understanding of the pathophysiology of pain and pharmacologic interventions is essential to prevent potential unexpected drug interactions. In addition, the majority of studies in multi-modal analgesia have focused on the efficacy of the treatment rather than the occurrence of side effects (Kehlet, 1994).

A study by Blackford (2008) used a multi-modal approach for post-operative pain management following abdominal surgery. The approach consisted intra-operatively of morphine, ketamine, clonidine, tramadol, parecoxib and paracetamol. A morphine PCA, oral paracetamol and tramadol were used post-operatively. In patients with pre-existing chronic pain conditions, gabapentin and low dose ketamine were administered. This technique was analysed retrospectively in patients that had lower abdominal incisions for colorectal surgery. This multi-modal approach was compared to epidural analgesic use. The benefits of multi-modal analgesia were noted by Blackford and colleagues to be 'statistically significant', although surprisingly no p-value was stated. Significant differences apparent included: hospital stay (10 versus 13 days), shorter anaesthetic time (20 versus 32 min) and a decline in analgesia related adverse effects and complications, with pain scores remaining comparable to the epidural treatment (Blackford et al., 2008).

To conclude, the use of opioids, NSAIDs, local anaesthetics, and other drugs, together with various administration routes and strategies such as epidurals, pre-emptive analgesia, and multi-modal analgesic techniques, all have positive and negative aspects associated with their use. The choice of pharmacological treatment should be dependent upon the efficacy of the agent, its safety, and ease of administration, economic viability and the advantages of its application in comparison to other alternatives. The use of continuous wound infiltration techniques has proved to be a promising in the alleviation of post-operative pain, but appears to require refinement strategies that deliver more reproducible outcomes. Therefore, it will be the primary focus as the method of choice in the present study.

1.2 Local Anaesthetics

1.2.1 The Development of Local Anaesthetics

Over the last two centuries, the development of local anaesthetics has been of high significance as it has offered new opportunities in pain management following 'minor' surgical techniques and post-operative care. However, there is increasing interest in their usage for more major surgery as well.

The properties of local anaesthesia were first discovered by Austrian ophthalmologist Carl Koller. In 1884, Koller performed the first surgical procedure under local anaesthesia by administering cocaine to the eye (Martin-Duce, 2002, Cousins and Mather, 1980). This technique rapidly became widespread throughout Europe and America. However, the use of cocaine was associated with many deaths, and patients were becoming addicted. This subsequently led to the synthesis of pure cocaine in 1891. From this, new amino ester local anaesthetics, such as amethocaine, benzocaine and tetracaine, were synthesised between 1891 and 1930. Esters are not very stable in solutions and their metabolism resulted in the production of para-aminobenzoate (PABA), which is associated with severe allergic reactions (Tuckley, 1994). Concurrent to this, from 1898 to 1972 amino amide local anaesthetics were synthesised. They were relatively stable in solution and hypersensitivity reactions were rare in contrast to ester local anaesthetics. Examples of amide local anaesthetics included lignocaine (also known as lidocaine), etidocaine, mepivacaine and bupivacaine. Bupivacaine, which was synthesised in 1957 and introduced for clinical use in 1965, was of particular interest due to its long duration of action and clinical applications. However, its use was associated with numerous reports of central nervous system and cardiovascular related toxicity. The recognition of the presence of optically active isomers of the local anaesthetic, mepivacaine, led to the development of ropivacaine and later levobupivacaine, which were pure S-(-) enantiomers of racemic bupivacaine. The chemical structures of levobupivacaine, ropivacaine and bupivacaine are shown in Figure 10. Levobupivacaine and ropivacaine are very similar in structure but a slight difference is evident in the length of its side chain. The toxic effects of these enantiomeric

forms, which will be further discussed in this chapter, were extensively studied before introduction into the market in the late 1990's (Ruetsch et al., 2001).

Figure 10: The comparison of the structures of ropivacaine, bupivacaine and levobupivacaine. (Source: Leone et al., 2008).

1.2.2 Comparison and Selection of Local Anaesthetic Agent

The selection of an appropriate local anaesthetic agent will impact on the adequacy of post-operative pain relief achieved. Commonly used local anaesthetics, such as lignocaine, bupivacaine, ropivacaine and levobupivacaine will be further discussed to justify the local anaesthetic selected for this study.

Although lignocaine has a reduced toxicity profile in comparison to bupivacaine, it also has a shorter duration of action. This was illustrated in a study by Rygnestad et al. (1999) who investigated the epidural infusion of lignocaine in comparison to bupivacaine in 52 randomised patients undergoing lower abdominal surgery. The highest plasma bupivacaine concentration was 5.42 mg/L, which was slightly higher than the maximum lignocaine concentration of 5.04 mg/L. The literature states that concentrations associated with the onset of central nervous system toxicity in man for lignocaine and bupivacaine are 2.81- 9.84 mg/L and 1.73- 3.46 mg/L, respectively. Although the concentration of bupivacaine exceeded this threshold, toxicity was not evident. A possible explanation for this may be its high affinity of binding to alpha-1-acid glycoprotein (AAG). This protein has been shown to increase in concentration, in plasma following surgical trauma (Berrisford et al., 1993), resulting in a reduced unbound fraction (Fu). Hence, whilst the total drug concentration is elevated the unbound bupivacaine concentration (the pharmacologically active moiety) in the surgically-stressed patient with elevated AAG

is relatively similar to a non-stressed patient with lower total bupivacaine concentrations where these toxicity thresholds were established (in relatively healthy patients/volunteers). This concept is further illustrated in Figure 11. Hence Rygnestad et al. (1999) concluded that both local anaesthetics proved to be safe in their study.

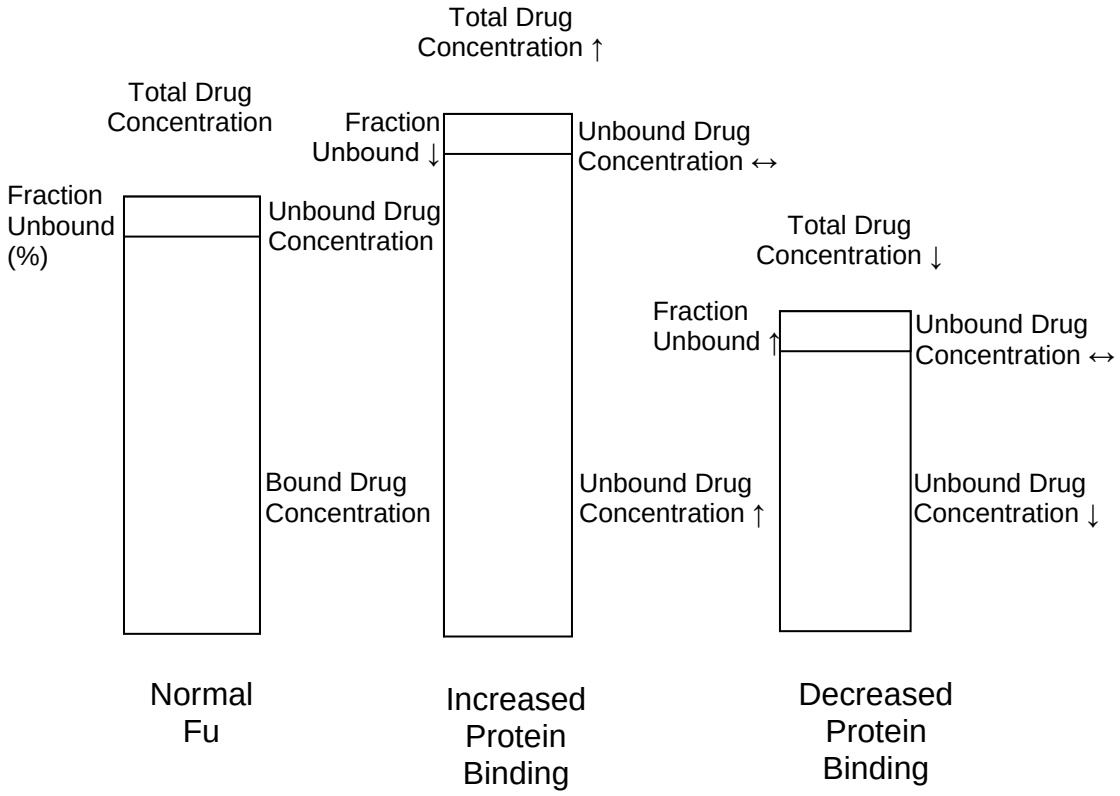

Figure 11: The concept of protein binding for low clearance drugs in the normal state, state of increased protein binding and state of reduced protein binding.

Furthermore, the duration of anaesthesia was investigated following the subdermal injection of 0.2% lignocaine and 0.5% bupivacaine in healthy subjects. The mean (±SD) duration of action of bupivacaine (231 ± 135 min) was four times longer than lignocaine (62 ± 39 min) (Fariss et al., 1987). This was supported by Swerdlow and Jones (1970) who established that the duration of anaesthesia of 0.25% bupivacaine (199 ± 33.4 min) was significantly longer than 1% lignocaine (127.6 ± 17.4 min) in patients that were intradermally injected with the two local anaesthetics. Therefore, the longer duration of action

of bupivacaine can be used to advantage in clinical situations that demand such, in preference to lignocaine.

For several decades, bupivacaine has been the most extensively used long-acting local anaesthetic of choice. However, its toxicity has been of concern. It has been reported that there have been six cases of concurrent seizures or cardiac arrest requiring prolonged resuscitation. Furthermore, there have been cases of deaths resulting from the unintentional intravascular injection of bupivacaine (Casati and Putzu, 2005). This is because bupivacaine has a narrower margin between the dose, or more accurately the plasma bupivacaine concentration, necessary to produce seizures and cardiac collapse in contrast to other local anaesthetics.

Therefore, fatalities due to toxic cardiovascular effects of bupivacaine in the late 1970s, led to research into its structure activity relationship with regard to its toxicity (Albright, 1979). Amide local anaesthetics, such as bupivacaine are chiral molecules, which mean that it is possible to obtain two different three-dimensional structures, termed stereoisomers, around its chiral centre. Enantiomers are a pair of stereoisomers, which have identical chemical and structural formulas but a different spatial orientation of their components. Even though these molecules have identical physiochemical properties, the three dimensional structural differences between the enantiomers have stereo-selective properties, hence differences in their biological activity are evident (Thomas and Schug, 1999). Bupivacaine is known as a racemic solution as it consists of equal amounts of its two enantiomers, levo- or S (-) bupivacaine and dextro- or R (+) bupivacaine. The enantiomers have different affinities for sodium, potassium and calcium ion channels (Leone et al., 2008, Arias, 2002).

The S- enantiomer has a safer pharmacological profile in contrast to its R- partner. Therefore, the pure S- (-) bupivacaine enantiomer (levobupivacaine) was synthesised and approved for use by the United States Food and Drug Administration (FDA) in 1999 (Burlacu and Buggy, 2008). In comparison to the R-

(+) enantiomer, levobupivacaine has a higher degree of protein binding, a lower volume of distribution, a higher plasma clearance and hence a shorter half life (Thomas and Schug, 1999). Its reduced incidence of toxicity can be due to its decreased distribution into brain and myocardial tissue (Thomas and Schug, 1999). Levobupivacaine and ropivacaine are long-acting local anaesthetics which have been developed due to its greater safety margin compared to bupivacaine. Evidence of severe toxicity, such as seizures and cardiac arrest with prolonged resuscitation was noted after unintentional intravascular bupivacaine injections (Albright, 1979, Macintyre et al., 2010, Cheng et al., 2002).

Several studies have confirmed the advantages of levobupivacaine over bupivacaine. Gristwood and Greaves (1999) found that levobupivacaine had a reduced effect on myocardial contractility and QTc prolongation, which are the initial signs of cardiotoxicity when compared to bupivacaine. Gristwood (2000) demonstrated that levobupivacaine is as equally efficacious as bupivacaine at similar doses and concentrations. The lethal intravascular doses that initiate lethality in awake sheep was 78% higher with levobupivacaine than bupivacaine (Gristwood, 2002).

Levobupivacaine and bupivacaine are comparable in terms of anaesthetic potency. Kopacz (2000) performed a randomised, double-blinded study assessing the onset, extent and duration of sensory and motor blocks produced by 0.75% levobupivacaine in comparison to 0.75% bupivacaine in patients undergoing lower abdominal surgery. All three parameters were similar between the two local anaesthetics supporting the equivalent potency between them (Kopacz et al., 2000). Higher plasma levobupivacaine concentrations were evident prior to the first signs of systemic toxicity; and no or minimal signs of cardiovascular toxicity were apparent after the effects of central nervous system toxicity. Ropivacaine is 40-50% less potent than levobupivacaine and bupivacaine due to its lower lipid solubility. However, with an equipotency dosage ration of 1.5:1, it can have a similar clinical profile (Leone et al., 2008).

The lethal dose of levobupivacaine is 1.3 to 1.6-fold higher than bupivacaine, thereby providing it with a safety advantage (Foster and Markham, 2000). Stewart and Kellett (2003) conducted a double-blinded cross-over study to compare the central nervous system and cardiovascular toxicity of levobupivacaine and ropivacaine administered intravenously in healthy male subjects. When the two drugs were administered at equivalent doses and infusion rates, there were no differences evident at the first sign of central nervous system symptoms (Stewart and Kellett, 2003). This has been supported by numerous studies (Bardsley et al., 1998, Knudsen et al., 1997, Scott et al., 1989), which have all concluded that levobupivacaine and ropivacaine show less neurotoxicity than bupivacaine as 10 -25% higher doses of these two drugs are required to show the first onset of central nervous toxicity in comparison to bupivacaine. The estimated mean total dose of levobupivacaine that induced severe arrhythmias in sheep after intravenous administration was 277 mg, which was significantly greater than bupivacaine at 156 mg (Chang et al., 2000).

The lower toxicity of levobupivacaine compared to bupivacaine and its greater potency over ropivacaine were the primary reasons for selection as the local anaesthetic of choice in this study.

1.2.3 Pharmacological Aspects of Levobupivacaine

The structure of levobupivacaine (shown in Figure 12), has a systematic name of (S)-1-butyl-N-(2,6-dimethyl phenyl piperidine-2-carboxamide and consists of a lipid-soluble hydrophobic aromatic ring and a charged hydrophilic amide group (Tuckley, 1994). The molecular formula of levobupivacaine is $C_{18}H_{28}N_20$ and it has a molecular weight of 288.43. The solubility of levobupivacaine in water is 100 mg/mL at 20°C. Furthermore, levobupivacaine has a partition coefficient of 1,624 and a pKa of 8.09, which is the same as bupivacaine (Abbott, 2006).

Figure 12: The structural formula of levobupivacaine, * indicates the chiral centre (MIMS, 2008).

These physiochemical properties of levobupivacaine provide the basis of the pharmacodynamic and pharmacokinetic properties of the drug, i.e. what the drug does to the body and what the body does to the drug, respectively.

1.2.3 (a) Pharmacodynamics of Levobupivacaine

Mechanism of Action

The mechanism of action of levobupivacaine is like that of other local anaesthetics and occurs via two processes, as shown in Figure 13. Firstly, local anaesthetics reversibly inhibit the transmission of action potentials in sensory, motor and sympathetic nervous fibres by the specific binding of the local anaesthetic molecule to the voltage-dependent sodium channel (Leone et al., 2008, Burlacu and Buggy, 2008, Edgcombe and Hocking, 2005, Arias, 2002, Foster and Markham, 2000) . It keeps these channels in an inactive state so that no further depolarisation can occur, hence preventing the conduction of normal action potentials (Thomas and Schug, 1999). This effect is mediated within the cell; therefore the local anaesthetic must cross the cell membrane prior to exerting this effect. The second mechanism involves the disruption of ion channel function by the incorporation of the local anaesthetic molecule in the cell membrane. This is mediated by the un-ionised local anaesthetic form acting outside the cell membrane (Edgcombe and Hocking, 2005). The sensitivity of nerve fibres to local anaesthetics vary according to their size and level of myelination. Small fibres are more sensitive than large fibres and

myelinated fibres are blocked before non-myelinated fibres. The loss of nerve function begins as the loss of pain, temperature, touch, proprioception and skeletal muscle tone, which explains why touch is experienced and not pain while using local anaesthetics (Edgcombe and Hocking, 2005).

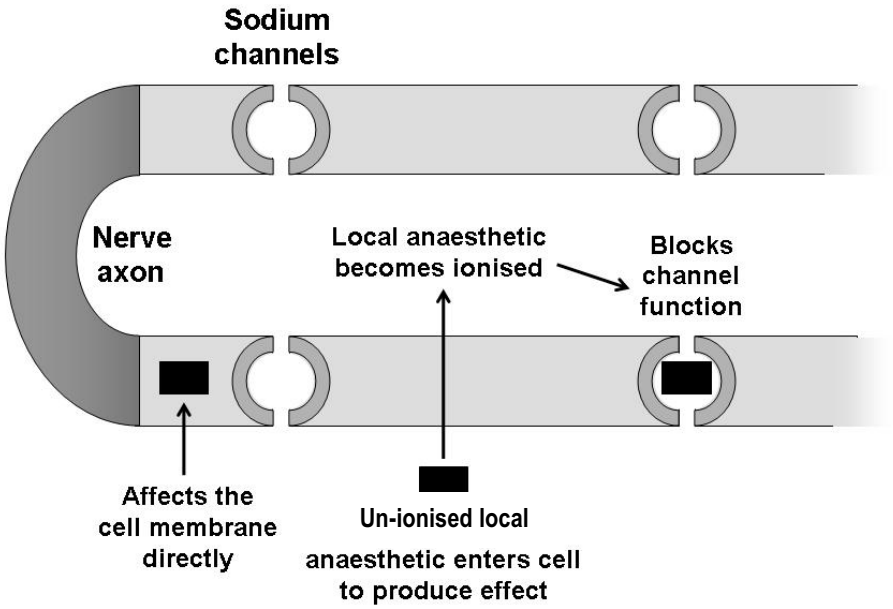

Figure 13: The mechanism of action of the local anaesthetic levobupivacaine. (Source: Edgcombe and Hocking, 2005)

Onset of Action, Potency and Duration of Action of Levobupivacaine

The onset of action, potency and duration of action of levobupivacaine are significant variables that define its effect on the body.

The pKa is the main factor that determines the onset of action. The pKa is the pH at which 50 % of the molecules are free base and 50 % of the molecules are ionised. The pKa of levobupivacaine is 8.09 (Arias, 2002). For example, if bicarbonate is added to levobupivacaine, the pH increases, which leads to a higher percentage of free base molecules, crossing the cell membrane, hence pharmacological activity is more rapid. Conversely, if the pH is low in circumstances such as infections, there are less

free base molecules available to cross the membrane, hence resulting in reduced activity. The typical onset of action of levobupivacaine is approximately 15 min (Arias, 2002, Whiteside and Wildsmith, 2000).

Potency is related to the lipid solubility of the local anaesthetic (Leone et al., 2008, Casati and Putzu, 2005). The more lipophilic local anaesthetics penetrate the nerve membrane with greater ease, so more readily block conduction and hence have greater potency (Leone et al., 2008). For example, levobupivacaine is more potent than ropivacaine because it is more lipid soluble (Sinnott and Stricharts, 2003).

The duration of action is dose-dependent and varies according to the anaesthetic technique adopted. It is correlated to the degree of protein binding and is influenced by the vasoactivity of the local anaesthetic (Whiteside and Wildsmith, 2000).

1.2.3 (b) Levobupivacaine Pharmacokinetics

Pharmacokinetic studies of levobupivacaine have been carried out using intravenous administration in healthy volunteers (as summarised in Table 5) to avoid the variability associated with absorption following intramuscular or subcutaneous administration (Gristwood and Greaves, 1999) Levobupivacaine is never administered intravenously in clinical practice (Arias, 2002, Foster and Markham, 2000). Therefore clinical studies have been undertaken using epidural and regional blocks.

Table 5: The pharmacokinetic parameters following 40 mg levobupivacaine, administered intravenously in 11 healthy volunteers (Adapted from (Gristwood and Greaves, 1999)).

1.2.3 (b) i. Systemic Absorption

Levobupivacaine, like other amide local anaesthetics displays biphasic systemic absorption, which is related to the relative rates of absorption from the aqueous and lipiodal structures in the area of the injection. The initial rapid phase is followed later by a slow phase, in which its uptake is dependent on the extent of local tissue binding. Drugs that are highly bound to proteins are removed from the nerve tissues at slower rate. This leads to a slower systemic absorption and an extended duration of action (Thomas and Schug, 1999). In the first phase, the peak plasma levobupivacaine concentrations (Cmax) and the time this occurs (tmax) is an expression of the rate of absorption (Thomas and Schug, 1999). Absorption and disposition pharmacokinetics cannot be obtained from a plasma concentration-time profile due to the 'flip-flop kinetics' after epidural administration. This unusual phenomenon occurs when the secondary absorption rate is slower than the elimination rate, so the terminal slope of a dose-interval profile represents this absorption rather than the elimination rate. In order to overcome this, a stable-isotope method which concurrently measures the absorption and disposition kinetics are used (Simon et al., 2004).

Local anaesthetics are lipid-soluble, hence their diffusion across membranes are not rate-limiting (Tucker, 1986, Cousins and Mather, 1980). The systemic absorption of local anaesthetics is dependent on the vascularity of the tissue, the site of administration, the dosage of the local anaesthetic and the presence of vasoactive compounds (such as co-administered adrenaline).

Regional Blood Flow and the Site of Administration

Previous studies from our group in both animal models as well as humans have considered the effect of regional blood flow. In a sheep model, Morris (1993) used lignocaine as the test drug (with or without co-administered adrenaline together with radio-isotope- technetium), to show the influence of regional blood flow at the injection site as a factor of local anaesthetic absorption and correlated the disappearance of isotope from the injection site with the appearance of lignocaine in the circulation at sites of high and low blood flow. They also showed a delayed disappearance of isotope and appearance of lignocaine in the circulation when the site was vaso-constricted with the co-administered adrenaline. These effects were also reported in two clinically relevant studies (Karatassas, 1992, Karatassas et al., 1993) with sites of different regional blood flow. The first site selected was the neck as a site of relatively high blood flow, where carotid endarterectomy is performed under local anaesthesia. The absorption of lignocaine was demonstrated to be rapid and the Cmax approached the toxicity threshold following standard dosages. In contrast, inguinal hernia repair performed under lignocaine local anaesthesia was selected as the lower abdomen is a region of relatively low blood flow. At this site the absorption of lignocaine was protracted with a much lower Cmax, well below the toxicity threshold, despite using the same dosages of local anaesthetic. These clinical results are shown in Figure 14. These authors concluded that there was a greater toxicity risk in regions of higher vascularity, whereas larger doses could be injected with safety into sites that are poorly vascularised without risking toxicity for increased clinical pain management. Clinical implications and dosage recommendations for infiltration anaesthesia should therefore take into account the regional blood flow at the site of administration.

Figure 14: The effect of regional blood flow of the injected site as a determinant of lignocaine absorption (Karatassas et al., 1993).

Concentration and Dosage of Levobupivacaine

As with lignocaine discussed above (Karatassas et al., 1993), the concentration of levobupivacaine in plasma following therapeutic administration depends on the dose and also the route of administration, as absorption from the site of administration is affected by the vascularity of the tissue (Whiteside and Wildsmith, 2000, Smith, 2007). The maximum concentration of levobupivacaine in plasma concentration (Cmax), and the area under the plasma levobupivacaine concentration versus time curve (AUC) are proportional to the dose (Foster and Markham, 2000), so the drug exhibits linear kinetics in this clinical range.

Table 6 shows the pharmacokinetic data for levobupivacaine following two different routes of administration with varying doses. Levobupivacaine administered at concentrations of 5.0 mg/mL and 7.5 mg/mL (dose received 75 mg and 112.5 mg respectively) are approximately dose-proportional when administered epidurally. This was also the case after 2.5 mg/mL and 5.0 mg/mL (dose received 1 mg/kg and 2 mg/kg respectively) were used for brachial plexus block (Abbott, 2006). This suggests that the therapeutic administration is dependent on the dose and route of administration as absorption from the site of administration is influenced by the vascularity of the tissue.

Table 6: Studies conducted in healthy volunteers displaying the pharmacokinetic data of levobupivacaine (adapted from (Foster and Markham, 2000)).

	Route			
Pharmacokinetic Parameter	**Epidural**		**Brachial Plexus Block**	
Concentration (mg/mL)	5.0	7.5	2.5	5.0
Dose Received	75 mg	112.5 mg	1 mg/kg	2 mg/kg
Number of patients	9	9	10	10
Cmax (µg/mL)	0.582	0.811	0.474	0.961
Tmax (hour)	0.52	0.44	0.50	0.71
AUC (0-infinity) (µg.hr/mL)	3.561	4.930	2.999	5.311

The literature reports the potential plasma levobupivacaine threshold for cardiovascular and neurotoxicity to be 2.6 mg/L. Allegri et al. (2010) evaluated the variability of plasma levobupivacaine concentrations following continuous epidural infusion in 23 patients undergoing major abdominal and urological surgery. Patients received an epidural infusion of 0.125% levobupivacaine and sufentanil 0.8 µg/mL, 5 ml/hr for 48 hr post-operatively. Arterial blood samples were taken at various time-points up to

60 hr post-epidural bolus (in contrast to infusion) dose. All patients displayed a distinct increase in plasma levobupivacaine concentrations during the 48 hr infusion period. The highest concentration noted was at the 48 hr time-point at the end of infusion, as shown in Figure 15. The median plasma levobupivacaine concentration was 0.95 mg/L (range 0.1 - 2.1 mg/L). Ninety-one per cent of patients had safe total (bound plus unbound) levobupivacaine concentrations within the range of 0.5 – 2.0 mg/L. The remaining 9% did not reach the concentrations linked to the threshold of cardiovascular and neurotoxicity of 2.6 mg/L. Although Allegri et al. (2010) did not measure the AAG concentrations; they predicted the gradually increasing plasma levobupivacaine concentrations were due to changes in plasma protein binding correlated to post-operative increases in AAG concentrations, and to the flip-flop pharmacokinetics of levobupivacaine (discussed earlier), in which the absorption rate of levobupivacaine after epidural administration is slower than its elimination rate. Regardless of the wide inter-patient variability in plasma levobupivacaine concentrations, concentrations reported by the literature to be toxic were not attained.

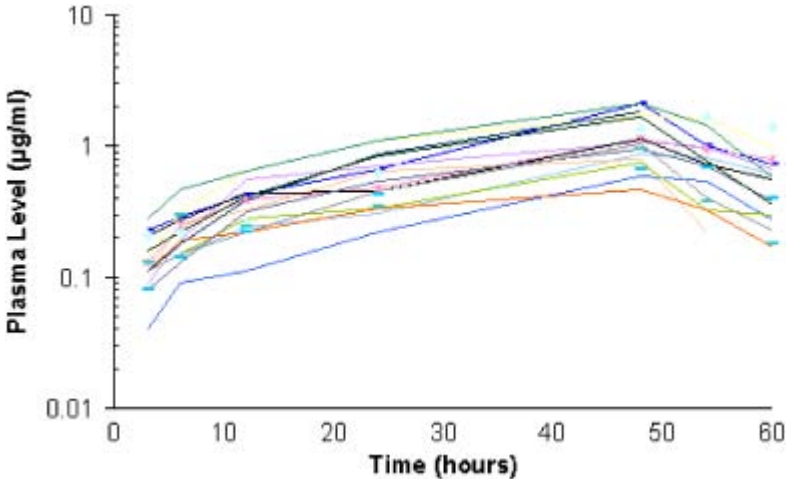

Figure 15: Plasma levobupivacaine concentrations during and after a continuous 48 hr epidural infusion in 23 patients undergoing major abdominal and urological surgery (Allegri et al., 2010).

The assumptions of Allegri et al. (2010) were supported by Rygnestad et al. (1999) who showed a marked increase in both plasma lignocaine and bupivacaine concentrations during continuous epidural infusion, which was significantly (lignocaine: $r= 0.77$, $p< 0.001$, bupivacaine: $r= 0.60$, $p< 0.001$) correlated with increases in AAG concentrations, suggesting there was no increase in the free concentrations of these drugs.

An increase in the dose affects the onset, potency and duration of anaesthesia. An increased dose reduces the time of onset but increases the degree of motor blockade, sensory blockade, the area of blockade and the peak plasma drug concentration (Cousins and Mather, 1980). The total dosage of local anaesthetics administered is a product of the concentration of local anaesthetic in the infusion solution and the volume infused. For example, the dose may be maintained by administering a larger volume even of a lower concentrated solution or conversely a reduced volume of a more concentrated solution. Not surprisingly therefore, increasing both the volume and concentration has been linked with a high rate of hypotension and a delayed block regression (Kopacz et al., 2000, Cox et al., 1998). The quality of analgesia has been determined by the concentration of levobupivacaine rather than its volume. A study by Dernedde et al., (2003) showed that the same dose of levobupivacaine gave the same quality of analgesia in relatively high concentration and small volume (3 mL/hr of 0.5% levobupivacaine or 2 mL/hr 0.75 % levobupivacaine) or small concentration and large volume (10 mL/hr of 0.15% levobupivacaine) via continuous epidural thoracic infusions with less motor block and increased haemodynamic stability. However, in clinical practice, a more concentrated solution is more likely to be used.

Recommendations in Europe, for post-operative pain management in adults, suggest the levobupivacaine dose should not exceed 18.75 mg/hr, whereas in the United States doses of up to 25 mg/hr for post-operative pain management are recommended. The dosage recommendation of levobupivacaine for post-operative pain management via epidural infusion is a concentration of 0.25%,

at 10 to 15 mL/hr or 12.5 to 18.75 mg/hr for minimal to moderate motor blockade. In circumstances where levobupivacaine is combined with other agents such as opioids, the dose of levobupivacaine should be reduced (Abbott, 2006).

Vasoconstrictors

Depending upon the application, vasoconstrictors may be added to local anaesthetics to enhance their potency and increase their duration of action. This is because most local anaesthetics have a vasodilatory effect and may be readily absorbed after administration. So concomitant vasoconstrictors increase absorption time and reduce Cmax and may therefore, decrease systemic toxicity associated with such peak concentration (Tuckley, 1994, Thomas and Schug, 1999). Vasoconstrictors, in particular adrenaline, increase the degree of motor and sensory blockade, the duration and area of blockade and decrease the time of onset and peak plasma drug concentrations (Cousins and Mather, 1980).

1.2.3 (b) ii. Systemic Disposition

Systemic disposition of levobupivacaine comprises distribution throughout the body, its metabolism and elimination from the body.

Distribution

Levobupivacaine is distributed widely throughout the body, with an apparent volume of distribution of approximately 67 L after an intravenous dose of 40 mg in healthy subjects as shown in Table 5.

Distribution can be described by a compartmental model that consists of three phases. The α-phase consists of the rapid uptake from plasma by highly perfused tissues. This is followed by the β-phase which comprises a slower uptake into the muscle and fat. This occurs concurrently with metabolism and excretion, the γ-phase (Thomas and Schug, 1999). The distribution of levobupivacaine is dependent on the extent of tissue and plasma protein binding. Distribution takes place in organs in proportion to the

relative blood supply. The brain and the heart receive the greatest proportion of the amount absorbed (Whiteside and Wildsmith, 2000).

Metabolism

Levobupivacaine is extensively metabolised hepatically through oxidative dealkylation by cytochrome P450, primarily the CYP1A2 and CYP3A4 isoforms (Arias, 2002). The major metabolite of levobupivacaine, 3-hydroxy-levobupivacaine, is further converted to glucuronic and sulphate ester conjugates, with no unchanged levobupivacaine detected in the urine and faeces, so can be deemed to be hepatically cleared. In healthy subjects it was shown that 71% was excreted within 48 hr in the urine and 24% in the faeces (Foster and Markham, 2000).

Elimination

Clearance is the 'volume of blood cleared of a drug per unit of time'. Measured in L/hr, it is the efficiency of irreversible elimination of a drug from the body (Birkett, 1998). Clearance is determined by blood flow, blood binding and the intrinsic function of the eliminating mechanism (Tucker, 1986). The clearance of levobupivacaine was 39 L/hr after 40 mg was administered intravenously in healthy subjects (Table 5). The clearance of levobupivacaine is low which makes it a low hepatic extraction ratio drug. This implies that the hepatic blood flow is not a major parameter in its clearance, but rather its clearance is more determined by hepatic low intrinsic clearance and protein binding. The elimination half-life after intravenous administration in healthy subjects was 1.3 hr after a 40 mg dose (Foster and Markham, 2000). The half-life is a derived parameter proportional to the two primary parameters of distribution volume (V) and clearance (CL), i.e. the half-life = (0.693 x V)/CL, where 0.693 is the elimination rate constant, the natural logarithm of 0.5, therefore the half-life could increase either because of the volume of distribution increasing or the clearance decreasing, or combinations of both.

1.2.3 (b) iii. Toxicity

Apart from allergenic reactions, systemic toxicity typically results from high plasma drug concentrations, overdose or accidental intravascular or intrathecal injection. Toxic effects increase with increasing plasma drug concentrations (Smith, 2007). Adverse effects can be minor at toxicity threshold concentrations or have a more pronounced effect on the central nervous system and cardiovascular system at higher concentrations.

Common side effects observed after administration of levobupivacaine consist of: hypotension, nausea, fever, vomiting, anaemia, pruritus, drowsiness, disorientation, tinnitus, back pain, headache, constipation and dizziness (Burlacu and Buggy, 2008, Arias, 2002). Common side-effects that were noted in 1141 patients (which included patients that were in labour) that were treated with levobupivacaine are displayed in Table 7.

Table 7: Adverse events which occurred in > 5% of patients that were treated with levobupivacaine in Phase II/III studies (n = 1141) (Compiled from (Abbott, 2006)).

Adverse Events	
Hypotension (31%)	Anaemia (12%)
Foetal distress (31%)	Pruritis (9%)
Nausea (21%)	Pain (8%)
Post-operative pain (18%)	Headache (7%)
Fever (17%)	Constipation (7%)
Vomiting (14%)	Dizziness (6%)

The central nervous system is more sensitive to local anaesthetic toxicity than the cardiovascular system, hence symptoms are apparent here first. Central nervous symptoms are due to the blockade of inhibitory central pathways and initial signs include shivering, muscle twitching and tremors, dizziness,

tinnitus, speech disorders and parathesia which can proceed to tonic-clonic seizures (Leone et al., 2008, Casati and Putzu, 2005).

Cardiovascular toxicity occurs after the activation of the sympathetic nervous system during the central nervous system excitatory phase. This leads to postural hypotension, hypertension and tachycardia, which can disguise myocardial depression induced by the local anaesthetic. This is followed by arrhythmias and cardiac depression, resulting in cardiovascular collapse (Leone et al., 2008, Casati and Putzu, 2005).

Although levobupivacaine is considered safer than bupivacaine, as shown throughout the literature mentioned above, nevertheless, care should be taken as cases where the risk of cardiovascular and neurotoxicity symptoms have developed are evident.

1.2.4 Protein Binding

The process of protein binding is reversible and occurs at a rapid rate. In general terms, drugs bind primarily to the plasma proteins albumin, alpha$_1$-acid glycoprotein (AAG) and lipoproteins. The degree to which a drug is bound to protein is exposed as the fraction unbound (Fu) and typically expressed as a percentage (Fu%), which are expressions of the unbound concentration (Cu) in relation to the total concentration (Ct). A lower Fu signifies greater protein binding. Basic drugs, such as levobupivacaine, preferentially bind to AAG which is an acute phase reactant with one binding site. The variation in the plasma AAG concentration is the main basis of variability in the Fu (Tucker, 1986). It is the Fu that is considered pharmacologically active as it is able to pass out of the circulation and exert pharmacological effects in tissues. Protein binding of levobupivacaine in normal healthy volunteers measured *in vitro* was found to be >97% at concentrations between 0.1 and 1 mg/L. The association of levobupivacaine with human blood cells was very low (0 - 2%) over the concentration range 0.01 - 1 mg/L but did increase to 32% at 10 mg/L. Once absorbed from the injection or infusion site into plasma.

It is the concentration of unbound drug that (the 3%), is responsible for the pharmacological actions on other tissues including the un-desirable and toxic side-effects (Arias, 2002). Hence, measuring the total drug concentration in plasma in healthy volunteers or short term clinical studies presumes that the Fu remains constant, ie., that the total drug concentration reflects the active unbound concentration. The unbound concentration is less often determined as it technically more difficult and expensive, and requires a more sensitive assay method.

AAG concentrations have been shown to increase post-operatively as an acute phase reaction and so affect drug binding parameters to a clinically significant extent. Hence, following such acute reaction, although the total drug concentration increases, the Fu reduces as binding to AAG increases, leaving the pharmacologically unbound concentration relatively unchanged (shown in Figure 11). This helps to explain those clinical studies in post-operative patients using 'high' dosages where the total levobupivacaine concentration appears to have exceeded the toxicity threshold established in normal volunteers (with normal protein binding), and yet no toxicity was observed (Burlacu and Buggy, 2008, Berrisford et al., 1993, Blake et al., 1994). Despite this, it should be noted that local anaesthetics bind reversibly to plasma proteins and will still continue to diffuse down concentration gradients. Therefore, protein binding should be utilised as an indicator for relative duration and not toxicity (Whiteside and Wildsmith, 2000). This 'complexity' is primarily relevant for drugs that are highly protein bound, like levobupivacaine, where small changes in protein binding have a marked effect on the total concentration and pharmacologically active fraction.

Changes in protein binding have significant effects on the distribution and clearance of local anaesthetics. The efficacy of levobupivacaine may be affected by its degree of protein binding. Only the unbound fraction of the drug displays pharmacological effects and undergoes metabolism. As the drug disassociates from the protein, more drug undergoes metabolism. Consequently, changes in the concentration of free drug changes the volume of distribution as the unbound faction distributes into the

tissues resulting in a decrease of the plasma drug concentration. Total clearance for drugs with low hepatic extraction ratios (discussed above), like levobupivacaine, is directly proportional to the product of Fu and intrinsic clearance (Cl_{int}). Whereas drugs with high hepatic extraction ratios that undergo rapidly metabolism (high intrinsic clearance CL_{int}), the clearance is proportional to hepatic blood flow (Taheri et al., 2003, Porter et al., 2001, Routledge, 1986, Birkett, 1998).

Changes in protein binding were evident in a pilot study from our unit. Corso (2007b) aimed to assess the safety of the ON-Q PainBuster, a commercial infiltration device, using 0.2 % ropivacaine which was maintained for 96 hr post-operation. The results for the 5 patients studied in detail were: (a) there were no incidences of drug toxicity observed or reported; (b) unbound ropivacaine (being the pharmacologically active moiety) concentrations were well below the threshold for systemic adverse effects reported in the most sensitive patients from the literature; (c) an increase in AAG concentration was observed at 48 hr post-operation (mean 63%, $p< 0.05$); (d) the unbound fraction decreased with the extended infusion. This pilot study demonstrated that if one simply applied the total ropivacaine concentration to toxicity thresholds in 'normal' patients, then one would have under-estimated the safety margin potentially available. The reason for this change in protein binding, as previously reported (Arias, 2002, Tucker, 1986) and discussed above, was that the AAG concentration increases in response to the surgical stress of surgery for at least 2 weeks following surgery. It was confirmed that the AAG concentrations were indeed elevated in 4/5 patients at 48 hr post-op, with the 5^{th} being already elevated pre-operatively for reasons which were not determined.

1.2.5 Serum Cortisol

Surgery produces physiological stress on the body that results in many neuroendocrine and metabolic changes. The concentrations of stress hormones such as cortisol, prolactin, adrenocorticotropic hormone (ACTH) and β-endorphin have been shown to increase in the circulation following surgery (Ilcol et al., 2002, Desborough, 2000). The stimulation of ACTH leads to a rapid increase in cortisol from

the adrenal cortex after the commencement of surgery. The production of cortisol is correlated to the degree of surgical stress (Plumpton et al., 1969, Traynor and Hall, 1981). Baseline values of cortisol are approximately 300 nmol/L, which can increase to a maximum concentration 4 to 6 hr following surgery, where it may exceed 1500 nmol/L. This is dependent on the severity of the surgical procedure (Nicholson et al., 1998).

There is usually a feedback control mechanism in place to inhibit the further secretion of ACTH following increased concentrations of cortisol. However this control mechanism is not functional after surgery so concentrations of cortisol and ACTH remain elevated (Desborough, 2000). Cortisol has many effects on the metabolic system. Cortisol stimulates protein breakdown and gluconeogenesis in the liver which in turn inhibits glucose utilisation by cells thereby increasing blood glucose concentrations. Cortisol is also linked with anti-inflammatory activity as corticosteroids block macrophages and neutrophils from accumulating into areas of inflammation and disrupts the synthesis of inflammatory mediators such as prostaglandins (Desborough, 2000).

Opioids can have an impact on the stress response. In pelvic surgery, when 50 μg/kg fentanyl was administered during the induction of anaesthesia, changes to the concentration of cortisol were suppressed (Hall et al., 1978). However, when 50 μg/kg fentanyl was administered an hour after the start of pelvic surgery there was no major effect on the endocrine system (Lacoumenta et al., 1987). Furthermore, opioids were ineffective in inhibiting the stress response following upper abdominal surgery, although 100 μg/kg fentanyl did completely eliminate hormonal changes, the technique was associated with marked respiratory depression (Klingstedt et al., 1987). Epidural analgesia with local anaesthetic can have a preventative effect on cortisol concentrations. Following hysterectomies, epidural blockade from the dermatomal segment T4 to S5 can prevent increases in cortisol and glucose concentrations (Enquist et al., 1977).

A randomised controlled trial by (Yardeni et al., 2007), compared the impact of three different post-operative pain techniques on serum cortisol concentrations in patients undergoing lower abdominal surgery. Patients received either 50 to 75 mg of pethidine intramuscularly on demand, 1 mg bolus of morphine per demand via a PCA, or 3 mL of 0.1 % bupivacaine plus 2 mg/L of fentanyl per demand, with a continuous infusion of 6 mL/hr through patient-controlled epidural analgesia (PCEA). The patients' receiving the PCEA had reduced serum cortisol concentrations post-operatively compared to the other groups, who only had opioids administered on demand. The PCEA group received local anaesthetics, which reduce the post-operative inflammatory response along with the provision of improved afferent blockade and weakened neurogenic inflammation. Furthermore, these patients also experienced less severe post-operative pain (Yardeni et al., 2007).

1.3 Surgical Techniques

This section on surgical techniques will further elucidate the concept of colorectal surgery including colorectal disease states, colorectal surgical procedures and abdominal incisions through to the novel concept of fast-track surgery.

1.3.1 Colorectal Surgery

1.3.1 (a) Colorectal Disease States

The main colorectal disease states, included in this study are: colorectal cancer, diverticular disease and inflammatory bowel disease.

Colorectal cancer

Colorectal cancer is cancer involving the colon and rectum. It is the third most common fatal malignancy worldwide after lung and breast cancer, accounting for 1.23 million cases (9.4% of total worldwide cancers) (Naef et al., 2010). Colorectal cancer is the most frequently diagnosed cancer in the westernised world, with approximately 608,000 deaths estimated worldwide (8% of all cancer deaths) (Ferlay et al., 2010, Jemal et al., 2007). On a national level, colorectal cancer is the second most common cancer in Australia. The risk of being diagnosed is 1 in 17 for males and 1 in 26 for females, with more than 12,500 new cases diagnosed each year, resulting in 4,372 deaths per year (Cancer Council SA, 2007).

Risk factors include: colorectal polyps, a family history of colorectal cancer in near relatives, a high alcohol consumption, smoking and a low dietary fibre and high fat intake (Kune, 2010). Symptoms of colorectal cancer include a change in bowel habits, gastrointestinal and rectal bleeding, anaemia, blood in the stools, anorexia due to a loss of appetite, weight loss, abdominal pain and bowel obstruction or perforation, which is usually indicative of a poor prognosis. Approximately 70% of all colon cancers are evident below the mid-point of the descending colon, the rest occur in the right, middle and upper descending colon. Curative surgical resection has been possible in more than 80% of cases (Naef et al.,

2010). Surgery is the optimal treatment for colorectal cancer. The staging of colorectal cancer is shown in Table 8. The five-year survival rate of colorectal cancer is approximately 50% and is dependent on the stage of the cancer (Stage-0 > 95%; Stage-I 75-100%; Stage-II 50-75%; Stage-III 30-50% involving lymph nodes; Stage-IV < 10% distant metastases) (Kune, 2010).

Table 8: Stages of colon cancer (Adapted from National Cancer Institute at the National Institute of Health, last modified, 11 March 2011 http://www.cancer.gov/cancertopics/pdq/treatment/colon/Patient/page2#Keypoint9).

Diverticular disease

Diverticula are pockets that develop mainly in the wall of the distal colon, with up to 90% of cases involving the sigmoid colon. Diverticular disease is comprised of either diverticulosis or diverticulitis. Diverticulosis involves the presence of the diverticula pockets. Diverticulosis can be asymptomatic or symptomatic as characterised by pain and bowel irregularity. Haemorrhage is the common complication. Diverticulitis involves necrotising inflammation and complications of the diverticula. Characteristics include microperforation as made apparent by local inflammation or macroperforation, which is manifested by abscess, fistula, peritonitis, obstruction or haemorrhage (Almy and Howell, 1980).

An accurate incidence of the rate of diverticular disease is difficult to predict due to its asymptomatic nature. It is evident that its incidence increases with age as 10% of cases occur in those under 40 and approximately 50 to 66% cases occur in patients over the age of 80 (Stollman and Raskin, 1999). The highest rates occur in Australia, the United States and Europe, whereas it is exceedingly rare in Africa and Asia (Stollman and Raskin, 1999). The incidence of diverticular disease has furthermore increased over the last 100 years as the intake of dietary fibre has decreased (Gear et al., 1979). Interestingly, a study by Gear (1979) showed that diverticular disease was more common in non-vegetarians (33%) compared to vegetarians (12%) which correlated with the mean fibre intake of 21.4 g/day and 41.5 g/day for non-vegetarians and vegetarians, respectively.

Infected diverticular disease is known as diverticulitis and treated by the use of analgesics and antibiotics. Despite the fact that diverticulitis can resolve with these treatments, in some circumstances it can be life-threatening, as 15 to 30% of hospitalised patients require surgery due to abscess or fistula formation, obstruction or perforation. Patients who experience recurrent attacks may need to undergo surgery. In patients that have had surgery symptoms such as bowel dysfunction or lower abdominal cramping may re-occur (Almy and Howell, 1980).

Inflammatory bowel disease

The two main forms of inflammatory bowel disease are Crohn's disease and ulcerative colitis. The increase in the incidence of inflammatory bowel disease has been associated with the 'hygiene hypothesis' which states that a change in lifestyle from high to low microbial exposure can lead to a weaker immune system (Kugathasan and Fiocchi, 2007, Kucharzik et al., 2006). The rate of ulcerative colitis is stable whereas Crohn's disease has increased in frequency. In 10 to 15% of patients differentiation between Crohn's and ulcerative colitis is difficult (Kirsner, 1991). The exact aetiology is not known although it is thought that it is due to immunological, environmental and bacterial causes with a genetic linkage (Kugathasan and Fiocchi, 2007, Kucharzik et al., 2006, Kirsner, 1991). Furthermore, smoking, psychological stress and NSAIDs are thought to exacerbate inflammatory bowel diseases (Ardizzone and Bianchi Porro, 2002).

Patients with inflammatory bowel disease are typically treated with corticosteroids to control inflammation (Ardizzone and Bianchi Porro, 2002). Antibiotics are also administered for bacterial flora and anti-CD4 antibodies are used to manage its immuno-inflammatory aspects. Furthermore, modification of the nutritional and dietary requirements of the patient can aid treatment. In more complicated or advanced cases, surgery is required to treat inflammatory bowel diseases. Surgery usually involves removing the colon and rectum and creating a stoma (Kirsner, 1991).

1.3.1 (b) Colorectal Surgical Procedures

Colorectal surgical interventions are necessary in order to restore normal bowel function when injury, obstruction, ischaemia or perforation has occurred to the bowel. Although colorectal surgical techniques are used in other disorders such as anal fissures, haemorrhoids, rectal prolapse and bowel incontinence, etc, the focus of this thesis, is on major colorectal surgical procedures for the disease states mentioned above in Section 1.3.1 (a).

Major colorectal surgical procedures consist of colorectal resections, where the diseased portion of the bowel and in some circumstances rectum or anus, is removed. Some colorectal surgical procedures may involve the creation of a stoma. Common stomas in colorectal procedures are colostomies and ileostomies. A colostomy, involves taking a portion of the large intestine through the abdominal wall and creating a stoma (opening) so that faeces can be emptied into a pouch. An ileostomy is created when the ileum, the lower end of the small intestine is brought out through the abdominal wall to form the stoma. Colostomies and ileostomies can be permanent or temporary with other surgical procedures required to restore intestinal patency.

Until 1990, all colorectal surgical procedures were performed via large abdominal incisions. The introduction and implementing of laparoscopic surgical techniques have some advantages over conventional open surgery and is an evolving field.

Hewett and colleagues (2008) conducted the Australian Laparoscopic Colon Cancer Surgical trial (ALCCaS), a randomised controlled study in order to compare clinical outcomes of 298 patients undergoing open laparotomy to 294 patients undergoing a laparoscopic colonic resection for colorectal cancer. It was identified that laparoscopic surgery had a significantly more rapid return of gastrointestinal function (4.4 ± 2.1 versus 4.9 ± 2.2, p= 0.011) and shorter length of hospitalisation (9.5 ± 7.4 versus 10.6 ± 7.2, p= 0.068) than open surgery. However, no significant difference was noted

between post-operative complications, re-operation rates and peri-operative mortality. Similarly, a study conducted by Braga (2002) compared the 30-day post-operative morbidity of 269 patients that were randomly assigned to either laparoscopic or open surgery. It was shown that the laparoscopic group had a lower rate of post-operative morbidity (20.6% compared with 38.3%; p= 0.003), post-operative infection (15 patients compared to 31; p = 0.01) and length of hospitalisation (10.4 ± 2.9 days compared with 12.5 ± 4.1 days) compared to the open group, thereby highlighting the advantages of laparoscopic surgery. The Braga study may appear to have seemingly better outcomes than the ALCCaS study as it was conducted in a more controlled manner in one institution by four surgeons. The ALCCaS study was a multi-institutional study which included a much larger number of surgeons with varying degrees of expertise and therefore less controlled, so arguably more realistic and representative of a 'real world' experience.

Furthermore, other studies have proposed that laparoscopic surgery is advantageous as it reduces the severity of post-operative pain, blood loss, wound complications, post-operative ileus and the length of hospitalisation, whilst providing faster recovery by reducing surgical trauma and increasing post-operative nutrition (Tekkis et al., 2005, Roig et al., 2009).

However, despite the benefits of laparoscopic surgery, there are associated drawbacks such as longer operative time, increased costs of laparoscopic instruments and devices and an increased mental strain on surgeons (Berguer et al., 2001). Furthermore, despite the proven benefits of laparoscopic surgery compared to open surgery, its uptake in elective cases for colorectal surgery has been slow in Australia and world-wide (Abraham, 2011).

Complications of Surgery

Complications from surgery usually arise while the patient is in hospital. Surgical site infections are the most common type of hospital acquired infections and account for 38% of all post-operative infections.

Surgical site infections can potentially lead to increased lengths of hospitalisation and medical costs or even death (Kobayashi et al., 2008).

Other complications that may be present following colorectal surgery include: wound infections, wound dehiscence, excessive bleeding, intra-abdominal abscess, paralytic ileus, thrombo-embolic events, pulmonary embolisms, mechanical bowel obstruction, anastomotic leakage, bleeding, pneumonia, myocardial infarction, cardiac arrhythmia, renal impairment, urinary tract infection, hypoxaemia and allergic reactions to anaesthesia and medications (Stottmeier et al., 2010).

1.3.1 (c) Abdominal Incisions

Choice of Incision

A well-planned abdominal incision is essential in surgical procedures. Factors that comprise a good-quality incision are displayed below in Table 9.

Table 9: Factors that determine the choice of surgical incision. (Adapted from (Grantcharov and Rosenberg, 2001, Donati et al., 2002, Reidel et al., 2003, Burger et al., 2002)).

Choice of incision
• Made quickly • Time taken to open and close the abdomen • Provides good exposure of intra-abdominal viscera • Can be extended if required • Associated with less post-operative complications, post-operative pain, incisional hernia, wound dehiscence and infection • Duration of the operation and length of hospitalisation • Nature of the operation- whether it is an elective or emergency case • Personal choice of the surgeon

Types of incisions

During abdominal surgery, the abdominal cavity can either be opened vertically (midline incision) or transversely (Reidel et al., 2003).

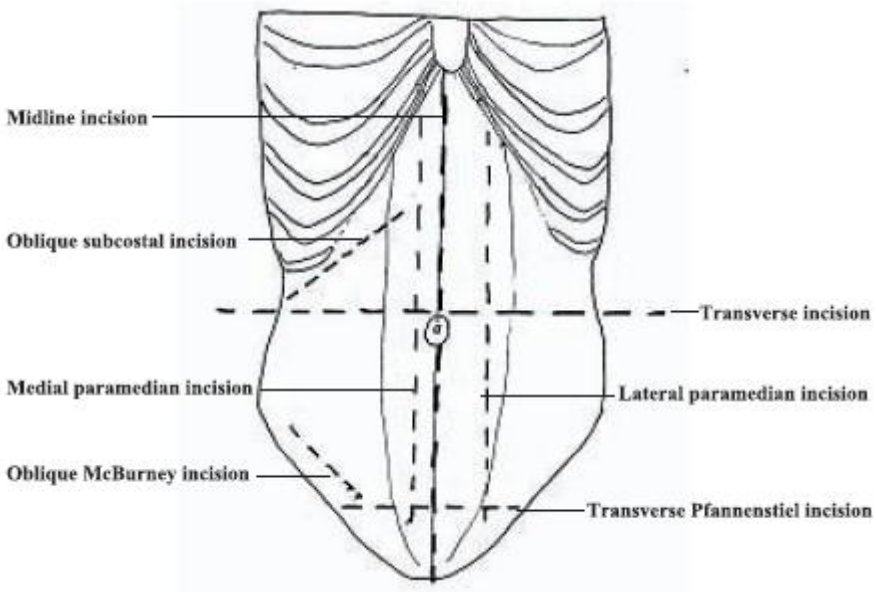

Figure 16: Diagram of the abdomen, displaying common abdominal incisions (Source: (Burger et al., 2002))

Common abdominal incisions, as shown in Figure 16, include: midline; paramedian; transverse; pfannenstiel and oblique. These abdominal incisions are further discussed.

A midline incision entails a vertical cut through the skin, subcutaneous fat, linea alba and peritoneum. The majority of the fibres which cross the linea alba are cut transversely. The advantages of the midline incision is that it is easy to carry out, there is minimal blood loss (due to the avascular nature of the linea alba), the incision can be performed rapidly (average 7 min), there is good exposure of the abdomen, allowing for extensions to be made when required thereby allowing for complete access to the entire abdomen (Burger et al., 2002). Although the midline incision is simple and rapid, it is associated with a high incidence of incisional herniae and wound complications (Burger et al., 2002).

The paramedian incision is an alternative to the midline incision. It offers better exposure of the abdomen on the side of the incision and reduces the likelihood of impaired wound healing, as the technique does not involve the avascular linea alba. The technique is more complicated than the midline incision, the opening time is longer at an average of 13 min and the potential need to extend the incision are limited due to the costal margin (Burger et al., 2002)

The transverse incision provides good exposure of the upper abdomen, although extension of the incision is difficult. A transverse incision results in the partial split of the oblique muscles, the split of the transverse muscle along the direction of its fibres, a horizontal split to the linea alba and the rectus abdominus muscle fibres are split perpendicular to their direction. In contrast to the midline incision, the transverse incision takes longer to perform (average 13 min) (Burger et al., 2002).

During the pfannenstiel incision, blood vessels and nerves are spared from dissection as the abdominal wall is cut in the same plane as the skin incision. Some surgeons, open the abdominal cavity vertically, combining the transverse and vertical technique (Burger et al., 2002).

The oblique incision splits the external oblique, transverse muscle and rectus abdominus muscle parallel to the direction of their fibres, as well as dissecting blood vessels and nerves. The loss of blood and the time taken to perform the oblique incision are similar to the transverse incision (Burger et al., 2002).

Midline versus transverse Incisions

Although midline incisions provide greater access to all parts of the abdomen, transverse incisions improve healing and cosmesis. Many studies have been conducted to show the difference between these two types of incisions.

Seiler and colleagues (2009) designed a randomised controlled trial in order to compare the differences between the midline or transverse approach in 200 patients requiring major elective abdominal surgery. Post-operative pain, complications and the incidence of incisional herniae were compared between the two groups. Seiler (2009) concluded that there were no significant differences detected between levels of post-operative pain, incisional herniae, pulmonary complications and median length of stay. Therefore, the type of incision should be determined by the choice of the surgeon with consideration of the best outcome for the patient.

A study by Donati (2002) retrospectively analysed the post-operative parameters of 61 patients with midline incisions to 62 patients with transverse incisions who underwent surgery for right-sided colonic cancer. The wound incision length (median, 20 cm versus 10 cm; $p< 0.0005$) and duration of surgery (median, 60 min versus 45 min; $p< 0.0005$) were significantly longer in the midline group. In addition, the transverse incision group had a significantly earlier return of bowel function ($p< 0.0005$), a shorter time to oral fluid intake ($p< 0.001$) and duration of hospitalisation ($p< 0.0005$). However, there were no differences in terms of opioid consumption between the two groups. Hence Donati and colleagues concluded that the transverse incision was of a similar standard but with improved post-operative recovery outcomes when compared with midline incisions.

Similarly, Grantcharov and Rosenberg (2001) analysed 18 randomised controlled trials that compared midline to transverse laparotomy incisions in patients undergoing open abdominal surgery. They came to the conclusion that transverse incisions should be recommended in surgical practice as they are

associated with fewer complications such as pain, burst abdomen, pulmonary morbidity and incisional herniae. However, despite this, Grantcharov and Rosenberg deduced a midline incision is preferred in situations such as trauma (which may require rapid intra-abdominal entry) as it is quicker and can be extended more easily and in circumstances where the pre-operative diagnosis is unknown (Grantcharov and Rosenberg, 2001).

In summary, advantages of the transverse abdominal over the midline incision include: less post-operative pain; less sedation; decreased incidence of nausea; earlier oral feeding; decreased incidence of pulmonary complications; earlier ambulation; more rapid convalescence; decreased incidence of dehiscence and a decreased incidence of incisional herniae (Silvis, 1955, Gatt et al., 2005).

1.3.2 Fast Track Surgery

This section on fast-track surgery will present traditional peri-operative care techniques as compared to the novel evidence-based concept of fast-track surgery.

1.3.2 (a) Traditional Post-Operative Care

Pre-operative and post-operative care in colorectal surgery has largely been directed by traditional methods and attitudes. Traditional care includes techniques such as fluid and dietary restrictions, mechanical colon cleansing, the use of drains and tubes and delayed solid oral intake following surgery (Roig et al., 2009). Many surgeons are sceptical about changing established methods and reluctant to adapt more innovative techniques and so the potential benefits that this will have on their patients may represent as a missed opportunity (Roig et al., 2009).

Traditionally, colorectal surgery has been associated with significant morbidity and extended hospitalisation. Traditional care has been associated with morbidity rates of 20 to 30% and an average length of hospitalisation of 7 to 12 days, with an average stay of 10 days (Abraham and Albayati, 2011, Carli et al., 2009). Complication rates following colorectal surgery is between 15 to 20 %, which can prolong hospitalisation by 6 to 10 days (Gouvas et al., 2009).

Conventionally, patients may be placed on a restricted diet pre-operatively for several days. A liquid diet is common the day before surgery, with nothing by mouth after midnight. Bowel cleansing solutions are taken in order to empty the bowel of stool. Furthermore, oral antibiotics may be prescribed to decrease bacterial infection in the bowel and prevent post-operative infection. Fluids are administered intravenously and the patient commences on a liquid diet before resuming solid foods. Post-operatively, all patients have a nasogastric tube maintained until there is evidence of return of bowel function (occurrence of flatus or faeces). Interestingly, as a historical perspective, medical doctor Mayo said “it is more important for a surgeon to carry a nasogastric tube in his pocket than a stethoscope” (Sands and

Wexner, 1999). Traditionally dietary requirements were accomplished with clear liquids, then full liquids before resuming a regular diet. As a result, it was predictable that many patients lost between 5 to 10% of their initial weight following surgery (Sands and Wexner, 1999).

Aspects that delay a patient's discharge from hospital include pain, nausea, vomiting, ileus, stress-induced organ dysfunction, intravenous fluids, a lack of mobility and mechanical factors for example the use of catheters and drains (Delaney et al., 2001, Fearon et al., 2005)

Patients may have their non-urgent surgery delayed due to the lack of bed space in the full hospital, and patients admitted for urgent medical reasons often occupy beds allocated for surgical patients. The occupancy rate at The Queen Elizabeth Hospital, the site of the study, is typically 98%, notably an occupancy rate over 85% is deemed 'unsafe' (Shephertd, 2008). This supports the need for change and a more efficient peri-operative care protocol.

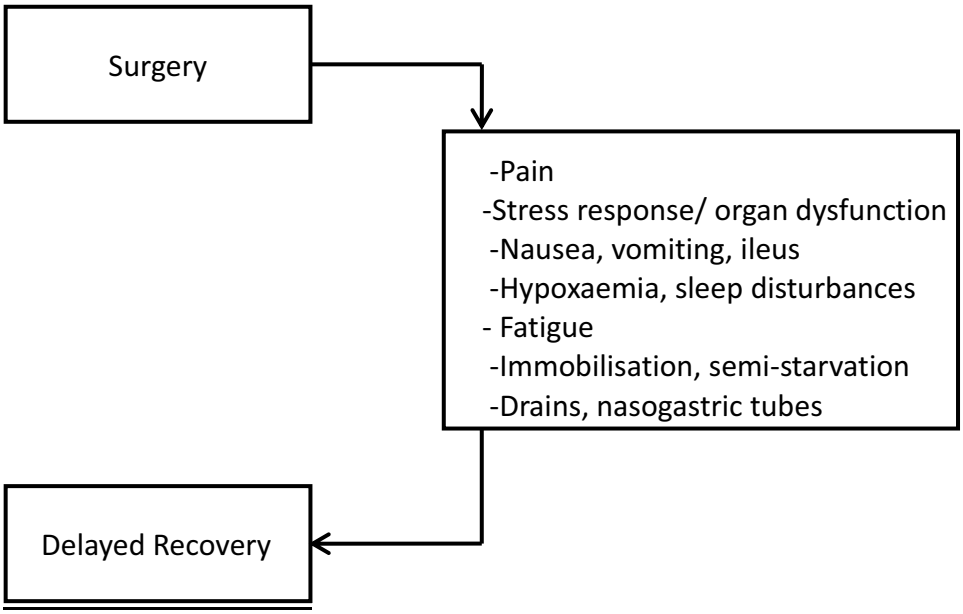

Figure 17: Factors contributing to post-operative morbidity. Based on (Wilmore and Kehlet, 2001).

These negative outcomes of traditional peri-operative care were noted by Professor Henrik Kehlet, a Danish gastrointestinal surgeon, who was alarmed at the length of hospitalisation, post-operative complications and post-operative pain in patients following surgery. Kehlet subsequently pioneered an innovative approach to enhance recovery following elective surgery; this was termed 'fast-track surgery'.

1.3.2 (b) What is Fast Track Surgery?

Fast-track surgery is a novel approach to elective surgery, which is comprised of an evidence-based, multi-modal recovery protocol that is designed to optimise patient outcomes by reducing the length of hospitalisation, post-operative pain, morbidity and complications whilst accelerating patient recovery (Counihan and Favuzza, 2009, Kehlet, 2008, Delaney et al., 2001, Polle et al., 2007).

The aim of fast-track surgery is to reduce the physiological and psychological stresses associated with surgery. This consists of: reducing the duration of post-operative ileus; reducing the surgical stress response and organ dysfunction; improving muscle strength, maintaining oral energy and protein intake and decreasing hospitalisation, cardiopulmonary morbidity and post-operative convalescence without jeopardising patient safety (Kehlet, 2008, Roig et al., 2009, Gouvas et al., 2009, Carli et al., 2009, Scatizzi et al., 2010, Donohoe et al., 2011). There are many advantages associated with a decreased length of hospitalisation. Earlier discharge translates to a less complicated post-operative course with lower utilisation of resources with associated direct and indirect cost benefits. Furthermore, it may decrease the onset of chronic pain syndromes thus decreasing long-term care costs This can lead to a decreased capacity of the institution, impact upon surgical waiting lists, a reduction in morbidity related to opioid use, an increase in patient satisfaction due to less time away from their family, normal daily activities and return to productive work (Zimberg, 2003).

The cost balance equation for a fast track surgical approach is complex. Whilst superficially it would seem that a successful earlier discharge would reduce the cost of the admission and so save money.

However, one need also account for readmission rates between traditional models of care and fast-track approaches. Furthermore, it is clear that the early days of a given admission are more expensive (e.g., the surgery and immediate post-operative care), versus the later stage of an admission that are less expensive recovery days. If a hospital that has a surgical waiting list and is normally near capacity, earlier discharge and higher throughput could mean that more patient days are spent in the more expensive phase of treatment and fewer days are spent in the lower cost recovery phase, so overall this could result in a cost increase. However, if the funding model of the hospital is based on a set reimbursement per procedure that includes a average number of admission days, then if a surgical unit is able to discharge earlier than this set number and admit another patient in this bed, then there is a positive financial gain to that hospital through efficiency.

The protocols utilised in a fast-track surgery recovery are displayed in Figure 18, with certain components to be further discussed in the following section.

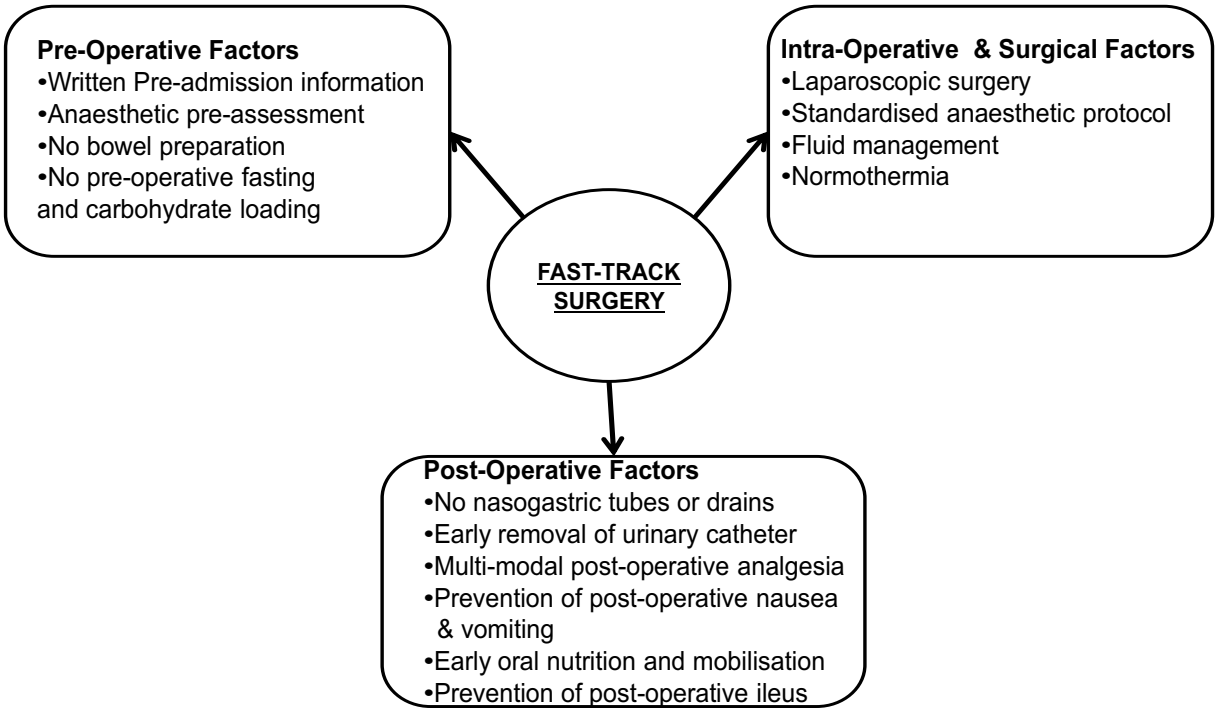

Figure 18: An overview of the techniques involved in fast- track surgery, including its pre-operative, intra-operative and post-operative factors.

1.3.2 (c) Evidence Supporting Fast Track Surgery

Evidence supporting the concept of fast-track surgery can be shown through pre-operative, intra-operative and post-operative factors.

1.3.2 (c) i. Pre-operative Factors

Examples of pre-operative factors supporting the concept of fast-track surgery include: pre-operative information, no pre-operative fasting, carbohydrate loading and the avoidance of a pre-operative bowel preparation.

Pre-Operative Information

Written pre-operative information is associated with a reduction in patient anxiety and better patient compliance with the fast-track surgery recovery protocol (Gatt et al., 2005).

Pre-Operative Fasting and Carbohydrate loading

The intended purpose of fasting prior to general anaesthesia is to reduce the volume and acidity of stomach contents thereby reducing the risk of aspiration. However, a systemic review of 38 randomised trials by Brady and colleagues (2003) concluded that a reduced fluid fast did not increase the risk of aspiration or associated morbidity in comparison to the traditional 'nil by mouth' fasting policy. Therefore, the deletion of pre-operative fasting has been implemented in fast-track protocols as it avoids the symptoms associated with prolonged fasting such as thirst, hunger, light-headedness and irritability. Despite this evidence, anaesthetists are quite resistant to limiting the fasting of liquids to only 2 to 3 hr prior to surgery (Roig et al., 2009).

The basis of pre-operative carbohydrate administration is to reduce post-operative insulin resistance. Insulin resistance is an element of the metabolic response following surgery and hence a predictor of the length of hospitalisation (Kehlet, 2008, Gatt et al., 2005, Nygren et al., 1998). This was supported by

Nygren and colleagues (1998) who compared 7 patients that had received 800 mL of an iso-osmolar carbohydrate drink the evening before their operation and 400 mL of the drink 2 hr prior to surgery, to 7 patients that were fasted overnight before surgery. The whole body glucose depletion was more marked in the fasted group (-49 +/- 6% versus -26 +/- 8%, $p < 0.05$) and glucose oxidation decreased post-operatively only in the fasted group ($p<0.05$).

Studies have shown pre-operative carbohydrate drinks to be beneficial and result in reduced nausea, vomiting, immune-depression, hunger, anxiety and length of hospitalisation (Hausel et al., 2001, Nygren et al., 1998, Breuer et al., 2006). In addition an increase in muscle strength and well-being has been noted (Melis et al., 2006).

In essence, it is recommended by the American Society of Anesthesiologists that drinking clear fluids two hours pre-operatively is safe for healthy patients undergoing elective surgery although the guidelines advised caution against conditions that may affect gastric emptying, fluid volume (such as obesity, diabetes, hiatus hernia, gastroesophageal reflux disease, bowel obstruction or the need for enteral tube feeding) or patients with a difficult airway (Anonymous, 2011).

Pre-Operative Bowel Preparation

The avoidance of pre-operative bowel preparations have been implemented as an intervention of fast-track surgery as it is associated with less patient stress and the prevention of electrolyte imbalances or dehydration (Gatt et al., 2005) A meta-analysis by Wille-Jorgensen and colleagues (2005) established that pre-operative bowel preparations were not beneficial and in some circumstances were associated with increased wound infection and anastomotic dehiscence rates. This finding was supported by Pena-Soria and colleagues (2007) who assessed surgical site infection and anastomotic failure in patients that had received bowel preparations in comparison to patients that had no pre-operative bowel treatment. The complication rate was 27.1% compared to 16.3% in the no treatment group, while the

rate of anastomotic failure was 8.3% and 4.1% in the bowel preparation and no bowel preparation groups, respectively. This therefore suggests that the use of pre-operative bowel preparation provides no advantage over the use of no bowel preparation but may potentially increase detrimental effects.

1.3.2 (c) ii. Intra-Operative Factors

Examples of intra-operative interventions that are favourable components of a fast-track protocol include maintaining normothermia and fluid management.

Normothermia

It is known that patients lose body heat during surgery, which can have adverse effects. The maintenance of patient normothermia has become a standard of care (Counihan and Favuzza, 2009). Intra-operative hypothermia can lead to a susceptibility to infections as a consequence of vasoconstriction, hence maintaining normothermia can lead to a reduction in wound complications (Sessel, 1997, Roig et al., 2009). Normothermia is less harmful to organs and systemic function thereby leading to less post-operative complications. Normothermia also has an effect on blood coagulation. In the absence of normothermia, hypothermia-induced coagulation abnormalities consisting of platelet dysfunction, increased fibrinolytic activity and the slowing of enzymatic activity required for clotting are apparent. Hence maintaining normothermia is important in the prevention of bleeding-related complications (Schubert, 1995).

Fluid Management

The liberal use of fluids during surgery has been the basis of care of colorectal surgical patients. It was thought that fluid loading was necessary to counteract pre-operative bowel preparations, overnight fasting, and a potential reduction in urine output and blood pressure. However, this approach leads to a 3 to 6 kg increase in weight with a potential hindrance to gastrointestinal function and hence increase in complications (Counihan and Favuzza, 2009). Studies on fluid management in patients undergoing

colectomy have been contradictory. Studies by Nisanevich et al. (2005) and Brandstrup et al. (2003) have shown that patients benefit from fluid restriction although this has not been confirmed by other studies (Holte et al., 2007). As the optimal fluid regimen has not been developed for patients undergoing colorectal surgery, there has been a trend towards goal-directed fluid therapy (Counihan and Favuzza, 2009). The aim of fluid management is to diminish the surgical stress response thus optimising physiological recovery post-operatively. Patients differ in terms of their fluid requirements, and standardised protocols need to take this into account, hence this is termed 'goal-directed' fluid administration (Donohoe et al., 2011, Counihan and Favuzza, 2009).

1.3.2 (c) iii. Post-Operative Factors

In conjunction with the post-operative components of a fast-track protocol that are mentioned in Figure 18, the fast-track components of nasogastric tubes, drains, urinary catheters, early oral nutrition, early mobilisation and the importance of a collaborative team are presented below.

Nasogastric tubes

Evidence supporting the avoidance of nasogastric tubes has been favourable. The nasogastric tube was thought to decrease the incidence of ileus, wound complications and protect anastomoses. However, a prospective analysis involving the insertion of a nasogastric tube was found to be found to be unnecessary and inconvenient in 90% of patients. Furthermore, patients displayed less psychological trauma with the absence of the nasogastric tube and were able to eat independently as desired (Sands and Wexner, 1999).

Drains

Traditionally, drainage of the abdomen was considered standard practice due to its ability to remove fluids, which are potential sources of infection and the possibility that it might allow for the early detection of anastomotic leaks or haemorrhage. However, its use has been controversial due to the

increased risk of infection, the ineffectiveness of most drains within 24 hr and the risk that it may induce an anastomotic leak. The unwarranted use of drains was supported by Merad and colleagues (1999) who found no significant difference (14.9% drainage group versus 12.2% no drainage group; $p > 0.05$) in post-operative complications between 248 patients who had drains inserted post-operatively to 246 patients that had no drainage following elective rectal or anal anastomosis in the pelvis. Hence the avoidance of drains is fundamental aspect of a fast-track surgery recovery protocol.

Removal of urinary catheter

Approximately 15 to 20% of all hospitalised patients have indwelling urinary catheters. The main purpose of these catheters is to monitor urine output following surgery and treat urinary retention (Griffiths and Fernandez, 2007). The early removal of urinary catheters decreases the time of first mobilisation and length of hospitalisation (Alessandri et al., 2006). Although inconclusive, evidence suggests there may be benefits associated with early catheter removal. Furthermore, although the placement of indwelling catheters do not increase morbidity for the first 24 hr following surgery, its use is generally unnecessary (Summitt et al., 1994, Griffiths and Fernandez, 2007).

Early oral nutrition

Approximately half of all surgical patients experience protein and calorie malnutrition (Sands and Wexner, 1999), hence early oral nutrition has been adapted as a component of fast-track surgery. It is a safe intervention and it enhances immune function and reduces the risk of post-operative infections (Kraft et al., 2005, Gatt et al., 2005). Advantages of early oral nutrition include the maintenance of the absorptive integrity of the bowel, an increase in the collagen content in the anastomosis, a reduction in insulin resistance and assistance in wound healing thereby decreasing the risk of sepsis (Roig et al., 2009, Sands and Wexner, 1999).

Early mobilisation

Early mobilisation is beneficial as it prevents pulmonary and thrombo-embolitic complications while sustaining muscle mass and function. It is also associated with less post-operative ileus, fewer post-operative complications and a shorter length of hospitalisation (Roig et al., 2009, Gatt et al., 2005).

Collaborative team

In order for peri-operative care to be successful, a team approach is required to ensure satisfactory care has been taken from the pre-operative assessment and management, to the safe administration of intra-operative anaesthesia to effective post-operative pain management (Pasero, 2003a, Kehlet, 2008). Members that should be involved for the successful implementation of fast-track recovery are displayed in Table 10.

Table 10: Team involved in a fast-track surgery protocol (Adapted from Counihan and Favuzza, 2009).

1.3.2 (d) Fast-Track Surgery Studies

Over the past decade, the concept of fast-track surgery has been a growing research area of interest; therefore literature is evident which supports its utilisation in comparison to traditional peri-operative care.

Tsikitis and colleagues (2010) compared the length of hospitalisation and rate of complications after laparoscopic right hemicolectomy in patients that were fast-tracked through their surgery to patients that had a traditional care protocol. Tsikitis found that the length of hospitalisation was on average 1 day

shorter in the fast-tracked group with a mean of 3 days (range, 3 to 4 days) versus a mean of 4 days (range, 3 to 6 days) respectively. Furthermore, the fast-tracked group had a significantly lower complication rate (29% versus 56%), thereby, supporting the advantages of a fast-track multi-modal surgical protocol. These findings were supported by research carried out by Wang and colleagues. Wang (2011) compared hospital stay, gastrointestinal function and post-operative complications in 106 patients who underwent a multi-modal fast-track protocol to 104 patients undergoing standard care post-operatively. Wang (2011) concluded that gastrointestinal function recovered significantly faster after fast-track rehabilitation (2.1 days versus 3.2 days, $p< 0.01$). Fewer patients developed complications (13.2% versus 26.9%, $p< 0.05$) in the 30 days after surgery in the fast-track group. Furthermore, length of hospitalisation was shorter (5 days versus 7 days, $p<0.01$), highlighting the benefits of fast-track rehabilitation in comparison to standard care following surgery.

Furthermore, a meta-analysis and Cochrane review analysing the differences between fast-track recovery and traditional care following surgery was undertaken. A meta-analysis by Gouvas (2009) analysed 11 studies, involving 1,021 patients to compare the difference in hospitalisation, morbidity and re-admission rates in patients that had been fast-tracked to those who has standard care. It was concluded that the length of hospitalisation (weighted mean difference -2.46 days, 95% CI -3.43 to -1.48 days, $p< 0.00001$) was significantly lower in patients that had been fast-tracked. There was also a trend towards lower morbidity in patients that had been fast-tracked; however, there was no difference in re-admission rates. A Cochrane review, conducted by Spanjersberg (2011) investigated the efficacy and safety of 119 patients who completed a fast-track surgery recovery protocol with 118 patients who received traditional care following colorectal surgery. There was a significant risk reduction for all complications in the fast-tracked group (risk ratio 0.50; 95% CI 0.35 to 0.72), although the reduction was not a result of a reduction in major complications. In addition, the fast-tracked group had a significant reduction in the length of hospitalisation (mean difference -2.94 days; 95% CI -3.69 to -2.19), although there were no differences in re-admission rates between the two groups. Spanjersberg concluded that

although a fast-track recovery protocol is safe, it should not be implemented as the standard of care until more quality trials are conducted. Furthermore, it was noted that compliance of fast-track protocols, is an issue that requires further investigation.

1.3.2 (e) Issues of Fast-Track Surgery

Despite evidence-based positive benefits of the implementation of a fast-track surgery protocol, there are negative aspects associated with its use which may impede its widespread utilisation. Issues present in fast-track surgery can be attributed to the attitudes of the medical staff, the patient re-admission rate and the poor compliance to the protocol.

Wilmore and Kehlet (2001) suggested that a limiting factor for the general introduction of fast track surgery is that surgeons remain unconvinced about the advantages offered and techniques involved given that in many ways it is a radical departure from 'traditional' practice. However, Rusby and colleagues (2005) disagree with this. Rusby believes that the surgeons are motivated and ambitious in initiating this change, but the large number of other health care professionals together with shift work makes this difficult. For example, anaesthetists allocated to a surgical list often change; there is a high turnover of nursing and junior medical staff and the cross-over between day-time and night-time staff makes the compliance of a fast track protocol complex. Furthermore it is difficult to guarantee full compliance with all health care professionals to achieve the interventions of the protocol to a consistent standard as they have been previously taught (Rusby et al., 2005) Hence the creation of a 'fast-track' team approach is fundamental. Another reason for not implementing a fast-track protocol is that many institutions have integrated certain aspects of fast-track protocols into their traditional care protocols such as encouraging early mobilisation after surgery (Gouvas et al., 2009).

The re-admission rate of fast-tracked patients has been a problem. However; this has been overcome by planning discharge at a slightly later stage (Kehlet, 2008). For example, Andersen (2007) found that

re-admission rates fell from 20.1% to 11.3% when planned hospital discharge was increased from 2 to 3 days respectively. To minimise re-admission, protocols must also be fixed with stringent discharge criteria (Gouvas et al., 2009).

Poor protocol compliance has been a further issue of fast-track surgery. In a meta-analysis by Gouvas (2009) the rate of compliance to fast-track protocol interventions were analysed. In these 10 studies, a total of 17 individual fast-track interventions were applied, with a mean of 8.5 interventions. The most widely used interventions consisted of pre-operative counselling, the absence of nasogastric tubes, early mobilisation and oral nutrition (Gouvas et al., 2009). The met-analysis revealed that a mean of only 7.4 interventions out of a possible 13 were actually implemented. However, despite this, it did not affect the clinical benefits of fast-track surgery protocol. Low compliance can be attributed to a lack of collaboration and communication between, surgeons, anaesthetists and nurses in clinical practice.

In summary, despite the benefits of fast-track surgery, the peri-operative care and treatment of colorectal surgical patients have been bound by regimented tradition with attitudes and practices that are slow and difficult to change. This is evident as fast-track protocols are not extensively implemented in clinical practice. This is due to: insufficient multi-disciplinary collaboration between surgeons, anaesthetists and nurses; a lack of evidence-based research; non-acceptance of published data; reluctance at the institutional capabilities of being able to carry out a fast-track protocol; time limitations; unavailability of data; lack of experience from staff and liability issues (Kehlet, 2008). This is supported by Gouvas (2009) who emphasises the importance of having a sound organisation and structure prior to the implementation of a fast-track protocol.

1.4 Research Objectives

Based on the review of the current literature as shown above, it is still evident that post-operative pain continues to be under-managed and consequently under-treated, hence negatively impacting on patient outcomes and recovery following colorectal surgery. Therefore, this present research endeavours to enhance the pre-existing knowledge available in the treatment of post-operative pain and recovery following surgery.

Primary Aim

The primary aim of this study is to test whether a continuous local anaesthetic infiltration of 0.5% levobupivacaine using a commercial infiltration device, the ON-Q Painbuster®, can minimise, or eliminate, the need for opioid analgesia following open or laparoscopic abdominal surgery. Novel aspects of this study include:

- The placement of the soaker catheter in the deeper muscle layers of the abdomen adjacent to the sensory nerve fibres most affected rather than the superficial, subcutaneous layers that requires diffusion of the drug to this site of action
- The higher concentration of the local anaesthetic infiltrated at the surgical incision site
- The longer duration of post-operative local anaesthetic infiltration to 96 hr from the recommended practice of 48 hr post-operatively

Secondary Aim

The secondary aim of this study is to test whether the implementation of a fast-track surgery protocol will enhance recovery of the patient, including earlier mobilisation and a shorter length of hospitalisation.

Rationale of the Study

The purpose of this study is to investigate the benefits this local anaesthetic approach may provide to the patient such as:

- Earlier mobilisation
- A decrease in opioid requirements and its related side-effects such as gut motility problems, nausea and vomiting and respiratory depression
- A shorter length of hospitalisation
- A decrease in post-operative complications
- An improvement in patient pain management

If this approach proves to be efficacious then this should improve care delivery, which is potentially a win-win situation for patient and health-care system.

In order to fulfil the aims of this study, a double-blind, placebo-controlled clinical trial was undertaken using the ON-Q Painbuster® primed with levobupivacaine (or saline for controls) to treat post-operative pain following open or laparoscopic abdominal surgery under a multi-modal fast-track recovery protocol. All patients were provided with a patient-controlled analgesia (PCA) option to relieve pain, as required. Measurements of PCA usage, pain scores, plasma concentrations of levobupivacaine, binding protein changes by measuring AAG, cortisol, as well as patient outcome measures and morbidity were also conducted. This is further explained in detail in the following chapter entitled “Research Methodology”.

CHAPTER 2: RESEARCH METHODOLOGY

CHAPTER 2: RESEARCH METHODOLOGY

The background, aims and rationale of this thesis provide an insight into the pertinent research methodology required to investigate the efficacy of local anaesthetic infiltrated at the incision site in order to minimise or eliminate post-operative pain following abdominal surgery. Hence, this chapter will elucidate the clinical, laboratory and statistical methods utilised to achieve this.

2.1. Clinical Studies

The clinical component of the research methodology section is comprised of the trial design, the inclusion/ exclusion criteria of the trial patients, the determination of sample size, the randomisation sequence and allocation of the patients, trial interventions administered and the primary and secondary outcome measures. The methods of the clinical component are based on the Consolidated Standards of Reporting Trials (CONSORT), a website (http://www.consort-statement.org/home/), which consists of evidence based recommendations for the reporting of randomised clinical trials. CONSORT is a widely accepted method adopted by many journals and editorial groups in respect to improving the quality of research reports.

2.1.1 Trial Design and Setting

This was a single centre, with imbalanced randomisation (2:1, active: placebo), double-blinded, placebo-controlled, surgical in-patient trial conducted at The Queen Elizabeth Hospital (TQEH), Woodville, South Australia, Australia, with recruitment phase from September 2007 to October 2009. The Queen Elizabeth Hospital is a 350 bed public teaching hospital, which services a population of approximately 250,000 people, predominantly living in the western community of Adelaide, South Australia (The Queen Elizabeth Hospital, http://www.tqeh.sa.gov.au/public/content/, updated June 2009).

Approval (ethics application number #2008006) to conduct this trial entitled ”Efficacy of 96 hr duration local anaesthesia (levobupivacaine) infused at the incision site compared with saline controls for post-

operative pain management following open or laparoscopic abdominal surgery. An application to fast track surgery" (Appendix 1) was obtained from the Central Northern Adelaide Health Service Ethics of Human Research Committee.

2.1.2 Patients

The majority of patients were recruited into the trial in the Pre-Admission Clinic (PAC) or less commonly at the Day of Surgery Admission (DOSA) rooms at The Queen Elizabeth Hospital. Selected patients on the Colorectal Unit (Department of Surgery, University of Adelaide, TQEH) surgical theatre (elective not emergency) list that required either laparoscopic or open abdominal surgery for colorectal cancer, diverticular disease, Crohns disease or ulcerative colitis were assessed against the inclusion/exclusion criteria as potential subjects for participation in this trial.

Patients were included in the trial if they were:

- Able to sign an informed consent
- Over 18 and under 90 years of age
- Had an American Society of Anesthesiologists (ASA) physical status classification of I (a normal, healthy patient), II (a patient with mild systemic disease) or III (a patient with severe systemic disease) (Keats, 1978)
- Had normal to mildly (< 20% above upper limit) elevated biochemical indices of renal and/or hepatic function
- Considered to be mentally stable

Notably, smokers were admissible in this trial and patients were allowed to continue their current medication(s), unless contraindicated on the basis of their surgery. Certain specified drugs were deemed aspects of the exclusion criteria (below).

Conversely, patients were excluded from the trial if they:

- Failed to provide written informed consent
- Were under 18 or over 90 years of age
- Were pregnant
- Had an ASA score of IV (a patient with a systemic disease that is a constant threat to life) or V (a patient near-death that is not expected to survive without the operation) (Keats, 1978)
- Had moderate to severely (> 20% above the normal range) elevated indices of renal and/or hepatic function
- Were taking medications that were known to influence the pharmacokinetics of levobupivacaine, such as CYP1A2 or CYP3A inhibitors and/or inducers, e.g., phenytoin, phenobarbitone, rifampicin, ketoconazole, ritonivir, macrolide antibiotics, erythromycin, verapamil and clarithromycin: or medications that had an effect on pain perception, such as narcotic analgesics, tricyclic antidepressants, chronic pain killers and anti-epileptic drugs used in pain therapy
- Were receiving epidural analgesia or
- Had a known allergy to levobupivacaine, fentanyl or oxycodone

There was a predicament evident in the exclusion criteria. Initially, omeprazole, a proton pump inhibitor used to treat gastro-oesophageal reflux disease, was listed as an excluded drug. However, due to the high frequency of patients prescribed this medication and presenting for this surgery, it caused a significant inhibition to patient recruitment. A study conducted by Dowd et al (1997) showed that there were no significant differences in plasma bupivacaine concentrations in patients that had been administered 40 mg of omeprazole in comparison to those who had not, suggesting that it was not likely to impact on the study of the pharmacokinetics of levobupivacaine. Subsequently the ethics protocol

was revised and resubmitted to the Ethics Committee as a change in protocol and was approved (Appendix 2).

Patients who fulfilled these inclusion/exclusion criteria were considered eligible for the trial. Additionally all patients were free to withdraw their consent any time prior to, or during the extent of the study.

2.1.3 Sample Size

This trial planned to test the effect of a local anaesthetic infusion, at the incision site following abdominal surgery. Patients recruited underwent either open or laparoscopic abdominal surgery. Within the different types of operation group, two thirds of patients received levobupivacaine in the Painbuster, while the remaining third received a saline infiltration in the Painbuster. The efficacy of the Painbuster was primarily assessed by the amount of opioid PCA consumed by the patient and the patients pain score as a rating of pain on a VNRS.

The sample size calculation was determined by: the variability in patient VNRS and PCA, the significance level, the power of the study and the treatment allocation. Firstly, the variability in the VNRS and PCA was based on a study conducted by Baig and colleagues (1997) which provided information on the variability of VAS (Baig used VAS compared to VNRS) and daily opioid consumption in a similar trial. The Baig (2006) study had mean ± SD VAS scores of 3.48 ± 2.34 for the control group and 4.01 ± 2.46 for the active treatment group giving a coefficient of variation (CV= standard deviation (sd) /mean) of approximately 67%. Similar information on the variability in daily narcotic requirement showed that the CV was approximately 100% (control group of 33.7 ± 32 mg; and active treatment group of 60.1 ± 62 mg). The significance level of this trial was 0.05 or 5% based on the assumption that a real difference actually existed and the power of the study was 80%. Based on the plan of two-thirds of the patients receiving a local anaesthetic infusion, the size of the difference that the trial can be detected as significant was calculated. This is shown below.

Table 11: This table shows that when the operation groups are combined, giving 80 patients, if two-thirds of patients (53 patients receive) receive the local anaesthetic treatment and one-third (27 patients) receive the placebo, then a difference of 68% or more in PCA will be detected as significant at the 5% level, with 80% power. Likewise, a difference of 46% in VAS will be detectable as significant.

Group	n_1	n_2	Detectable difference	
			PCA	VAS
Both open and laparoscopic operations combined	53	27	68%	46%

Based on the variability in the Baig (2006) study, 144 (96:48), or 60 (40:20) patients in the 50% and 80% groups, respectively would be required. Hence the 80 patients proposed was in the right general number range. It may be possible that be our study has lower variability than Baig et al (2006) observed, as one of our hypotheses is that previous studies have not necessarily located the catheter soaker tip in deeper tissue layers close enough to the pain nerve fibres, therefore, the clinical outcome was less predictable, resulting in greater variability in their data. This is shown in Table 12.

Table 12: This table shows the 1:2 placebo: active treatment split. It displays how many patients would be required to show either a 50% or 80% difference in PCA usage between groups as indicators of clinical significance.

Ratio of sample size	n_1	n_2	Detectable difference	
			PCA	VNRS
1:2	10	20	115 %	80 %
	20	40	80 %	52 %
	22	44	75 %	50 %
	48	96	50 %	33 %

Therefore, to reiterate, the sample size was 81 patients. It was 81 patients instead of 80, so there could be an equal three-way distribution to account for the imbalanced randomisation (2:1) This trial consisted of two study groups, a treatment (active) group, which received an infiltration of the local anaesthetic, levobupivacaine in the Painbuster and a control (placebo) group, which received a saline infiltration in the Painbuster. The ratio between the active and placebo group was 2:1, hence 54 patients recruited were on the treatment and the remaining 27 patients were control subjects.

Further, the plan was also to reassess the study power by having the bio-statistician (only) un-blinded after 40 patients had been investigated, and consider study power based on our data.

2.1.4 Randomisation and Blinding

Patient randomisation was conducted by independent pharmacists from the Clinical Trials Division, of the Queen Elizabeth Hospital Pharmacy. The randomisation allocation was generated by using a table of random permutations of 20 numbers. Patients were randomised, in permuted blocks of 9, to either the treatment group or control group (2:1). The pharmacists dispensed either 0.5% or 0.25% (depending on whether the operation was open or laparoscopic) levobupivacaine (Chirocaine®) or a 0.9% normal saline solution into the Painbuster, according to a randomisation list, once the patient had been recruited into the trial.

Patients, investigators and medical, surgical and nursing staff were blinded to the treatment allocation in order to reduce selection bias which is particularly important when subjective outcomes are assessed, as in the case of this trial. The study plan allowed for un-blinding and removal from the trial, in the circumstance of a serious adverse event or medical emergency, in which case the treatment allocation could be revealed by the trial pharmacists, who held the code.

2.1.5 Trial Interventions

This section will elucidate the pre-operative process, surgical techniques, and the insertion of the Painbuster catheter(s), the fast track surgery recovery protocol and the post-operative care of trial patients.

2.1.5 (a) Pre-Operative Process

Patients were approached in the Pre-admission clinic and less frequently in the DOSA rooms in order to assess their eligibility for recruitment into the study. Patients were given a Patient Information Sheet with the Consent Form (Appendix 3). The procedures of the trial, what was required and expected from the patient and any potential risks or side-effects were explained to the patient. In the chance of language barrier issues, the patient was accompanied with a language translator, if required. Patients had an opportunity to discuss this with family or friends if necessary. A pre-operative carbohydrate drink, Nutricia Preop®, as per fast track surgery protocol (Section 2.1.5.3) was given to the patient. A blood sample was taken before surgery for the plasma levobupivacaine concentration, AAG concentration and cortisol concentration determination (i.e., a pre-dose blood sample).

The Painbuster (ON-Q PainBuster® Surgical Synergies, I-Flow Corp, USA) was filled under sterile conditions in the Pharmacy, the day before the surgery. The protective cap was removed from the pump and a syringe filled with either 0.5% (or diluted to 0.25% in open cases) levobupivacaine or 0.9% saline (placebo), was attached to the fill port, where it was injected into the pump for the 96 hr duration of infusion. Once this was complete, the protective cap was closed and the pump was labelled with the appropriate patient details. Prior to the connection of the Painbuster to the soaker catheter, the pump clamp was removed in order to prime the Painbuster.

2.1.5 (b) Surgical Techniques

All abdominal surgical resections were performed under general anaesthesia. Surgical procedures were classified to be either open or laparoscopic. Open surgical procedures consisted of; high anterior resections, ultra-low anterior resections, right hemicolectomies, sub-total colectomies, Hartmann's procedure, abdomino-perineal resections, left hemi-colectomies, laparotomies, low anterior resections and protectomies. Laparoscopic cases consisted of: right hemicolectomies, extended right hemi-colectomies, high anterior resections, extended high anterior resections, ultra-low anterior resections, low anterior resections and left hemi-colectomies.

The type of surgical procedure, whether it was open or laparoscopic, was not randomised (unlike treatment type) and was assigned according to the consultant surgeon's clinical assessment.

Open procedures consisted of a lateral transverse dermatome incision, crossing 1-2 dermatomes (primarily the right hand side, but could also be the left hand side). The Painbuster soaker catheter was placed in between the internal oblique and transverses muscle layers (the neuromuscular layer of T7-12) in the abdominal wall. This was lateral to the wound and extended along the incision in order to continuously infiltrate in the levobupivacaine, or saline in the case of controls. Other open abdominal surgical procedures consisted of midline incisions (crossing 8-10 dermatomes) or Pfannenstiel incisions. A dual Painbuster catheter was located on either side of the incision and lateral to the mid-line incision, in order to block the transmission of both right and left side pain fibres.

Laparoscopic procedures involving bowel resections included Hand Assisted Laparoscopy (HAL) procedures. The Painbuster catheter was used for post-operative pain management at the largest port site, possibly including HAL ports which sometimes require larger (5 cm) incisions. Like open surgical procedures the soaker catheter was located lateral to the incision site and the anatomical location of the nerve fibres in this area.

In open and laparoscopic cases, the tissue location of the soaker catheter was dependent on the particular course of the nerve fibre(s) as relevant to the incision site. This was between the internal oblique and transversus abdominus muscle layers for thoracic nerves T7-T12. For lower abdominal incisions, the soaker catheter was inserted between the internal and external oblique layers for lumbar L-1 nerves. Hence the dermal location of the catheter was in the deeper muscle layers that were more highly vascular, thereby providing a more direct nerve fibre and dermatome infiltration to maximise the local anaesthetic effects. As shown in Figure 5, the catheter was inserted lateral to the incision site.

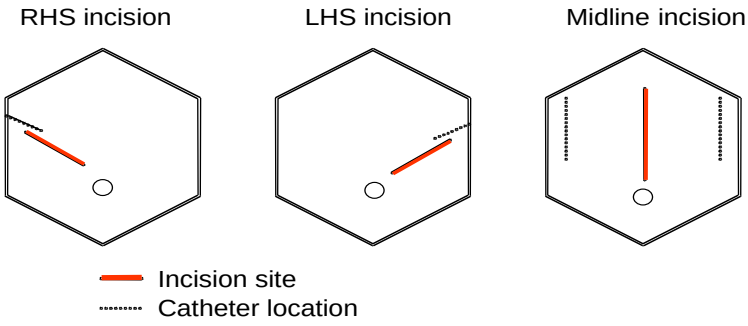

Figure 19: Shows 3 diagrammatic representations of abdominal surgical incisions (solid line) and the location of the Painbuster soaker catheters (broken lines). It is important to note that the two soaker catheters for the midline incision cover both nerves from right and left sides. (RHS= right hand side; LHS= left hand side).

At the conclusion of both laparoscopic and open procedures, a bolus dose of 20 to 30 mL of 0.5% levobupivacaine (dependant on the weight of the patient) was injected along the surgical incision and the actual volume was recorded. This occurred in all patients regardless of their treatment group so as to avert un-blinding. The time of the administration of the bolus dose was the start time for subsequent blood collections. This dosage was based on the clinical experiences of the surgeon investigators, and data from the pilot study conducted by Corso and colleagues (2007).

Painbuster Insertion

The Painbuster (ON-Q PainBuster® Surgical Synergies, I-Flow Corp, USA): is an elastomeric infusion pump delivers the local anaesthetic, levobupivacaine, continuously to the surgical site, through a soaker catheter that is designed to infiltrate the drug along the length of the terminal catheter. The pump consists of a multi-layer membrane that has a protective PVC cover. The pump consists of three layers: the inner layer, which is a synthetic elastomer that contains the drug; a middle layer that is composed of natural rubber latex and an outer PVC protective layer. All the fluid contact materials are biocompatible. It works as the exertion of the elastomeric membrane gives a positive pressure of about 10 PSI. The flow rate is controlled by a capillary orifice. The delivery accuracy of the flow device is ± 20% of the labelled infusion rate of levobupivacaine. As the flow restrictor of the Painbuster pump is calibrated to be at skin temperature, it should not be placed near any cold therapy to avoid the levobupivacaine infusing slower than the expected flow rate. There are certain processes that can be used to prevent infection in patients. These include:

- Inserting the catheter 3.5 cm away from the wound site
- Covering the catheter site with an occlusive dressing separate from the surgical site
- Protecting the catheter site from water
- Removing the catheter as soon as the infiltration is complete ensuring the catheter does not stay inserted in the patient for any longer than 5 days post-operation.

The risk of infection is furthermore reduced with the use of an ON-Q SilverSoaker anti-microbial catheter (only recently available in Australia). The catheters are coated with silver nanoparticles which have anti-microbial properties.

For laparoscopic cases, a single catheter Painbuster was used (Figure 20). The infusion rate was 5 mL/hr (0.5% levobupivacaine solution or normal saline). This was maintained for 48 hr, followed by a

flow-rate reduction to 2 mL/hr (0.5% levobupivacaine solution or normal saline) from the 48 to 96 hr time-point.

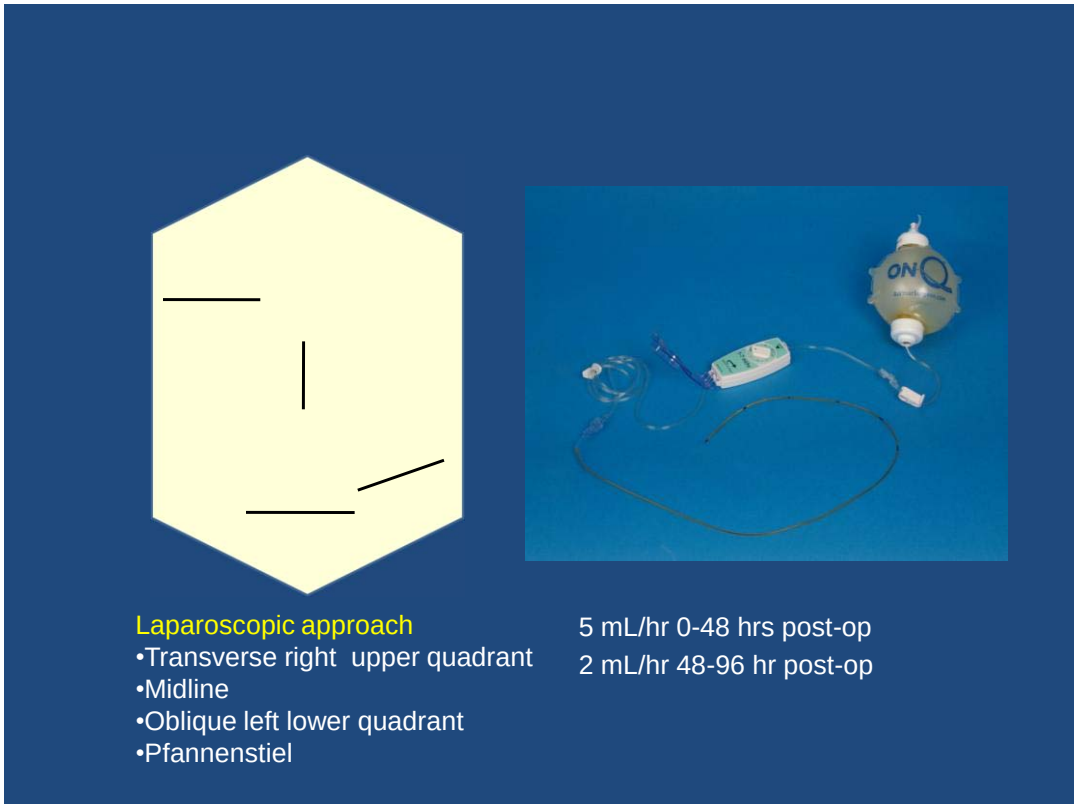

Figure 20: This figure depicts a single catheter Painbuster used for laparoscopic procedures. It consists of a soaker catheter, an adjustable flow rate (to the left of the figure) and an elastomeric infusion pump (in its inflated form, to the right of the figure).

For open midline or Pfannenstiel incisions, a dual catheter Painbuster (Figure 21) was used to cover left and right side pain fibres. The infusion flow rate was 10 mL/hr of 0.25% levobupivacaine (or saline) for the first 48 hr. This was reduced to 5 mL/hr from the 48 to 96 hr time-point post-operation. Given that dual catheters were used, delivering the drug at 5 mL/hr each, the dosage was reduced to 0.25% levobupivacaine to keep the total levobupivacaine dosage at the same level as the single catheter patients and thereby reducing the potential of any risks.

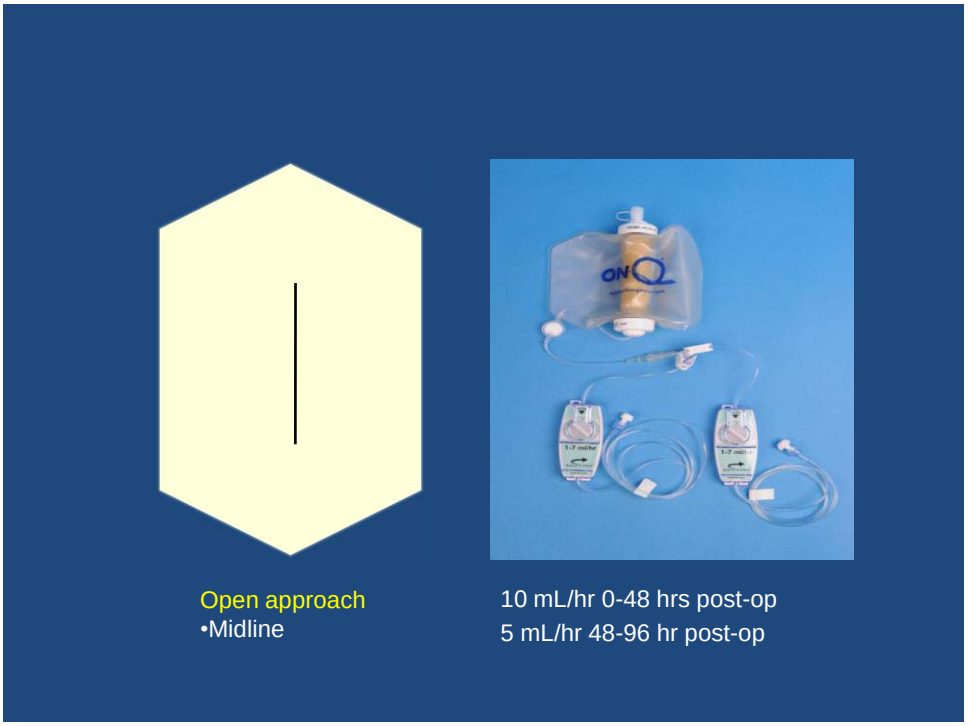

Figure 21: This figure depicts the dual catheter Painbuster. It consists of two adjustable flow rates and an elastomeric infusion pump (in its deflated form).

The Painbuster was maintained for 96 hr post-operation with the potential that it will result in appropriate pain control without the associated undesirable effects of opioid analgesia.

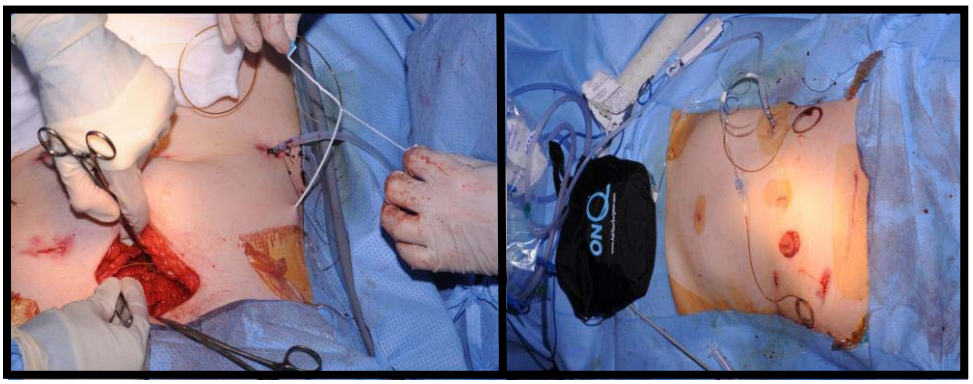

Figure 22: The catheter insertion in the pre-peritoneal layer (left); and the Painbuster, in the black bag in place post-surgery (right).

2.1.5 (c) Fast-Track Surgery Recovery Protocol

As mentioned above, the local anaesthetic protocol forms a strategic element of the aim of implementing a high-throughput surgical protocol, as is increasingly popular internationally. The aim being to expedite patient recovery by using minimally invasive surgical techniques where possible, at the same time as supporting measures that facilitate, patient well-being and early mobilisation. Such approaches have been shown to deliver less morbidity and reduced length of hospitalisation than "traditional" surgical protocols. The fast track surgery protocol that was applied in this study was based on the methods of Kehlet (2007a) and Wilmore (2006). The interventions of the fast track surgery protocol are outlined below in Table 13. Each intervention was marked as "yes" or "no" in relation to whether it was completed or not.

However, after anaesthetic consultation, restrictions were put into place in patients that were considered medically unfit to receive certain fast track surgical protocol interventions. The interventions of concern were the administration of a pre-operative carbohydrate drink (Nutricia Preop®), and the use of post-operative NSAIDs. The carbohydrate drink was not given to patients with the following risk factors: obesity (body mass index BMI >30); hiatus hernia and a history of reflux; diabetes; renal impairment; sepsis; difficult airway and conditions that may delay gastric emptying. Patients were also reviewed with respect to their NSAID profile. Certain patients were excluded from NSAID use due to their risk of adverse effects from NSAIDs as follows: asthma (precipitates bronchospasm), renal side effects (impairs renal function, oedema, hyperkalaemia, interstitial nephritis, papillary necrosis) anti-platelet effects (increased bleeding time) and gastro-intestinal toxicity (nausea, dyspepsia, ulcer formation, perforation, direct irritation to gastro-intestinal tract, prostaglandin inhibition).

Table 13 Fast Track Surgery Protocol

	YES	NO
PRE-OP DAY 1		
BMI Measurement		
No Bowel Preparation (except patients undergoing low anterior resection needing ileostomy)		
No pre-medication		
400 mL of carbohydrate drink (Nutricia Preop®)		
DAY OF SURGERY		
200 mL of carbohydrate drink 2 hr prior to surgery		
In Theatre		
No nasogastric tube		
Intravenous fluids to maintain normovolaemia		
Analgesia: • Levobupivacaine + Painbuster (start 5 mL/hr) • Parenteral Paracetamol & NSAID (parecoxib) • PCA as required		
On Ward		
Clear fluids as tolerated (aim for 1 L)		
IV fluid 1 L Hartmann's solution/ 12 hr		
Urine output ideally 30 mL/hr		
Analgesia: • Paracetamol 1 g q.i.d. • PCA as required		
DAY 1 POST-OP		
Catheter out		
Free fluids + Energy drink X2		
3-4 hr out of bed		
Walk: 20 m twice daily		
Stop IV fluids		
1 sachet movicol		
Analgesia: • Painbuster continues at 5 mL/hr • Regular paracetamol 1 g q.i.d., ibuprofen 400 mg tds		
DAY 2 POST-OP ONWARDS		
Ward diet		
Walk 40 m twice daily		
HOME		
Mobilising safely		
Tolerating full diet and passing flatus		

2.1.5 (d) Post-Operative Care

At the conclusion of the operation, before admittance into the High Dependency Unit (HDU) or surgical inpatient wards, patients were taken to the Recovery area, where their PCA was commenced. All patients received PCA for breakthrough pain regardless of their treatment group. Initially patients received an iv PCA of fentanyl (20 μg/mL, frequency/ PCA lockout of 3 to 5 min). However, this caused a logistical problem as there was an aspect of the fentanyl iv PCA use that conflicted with the trial protocol. The fast track protocol aimed for early discharge, whereas, it was a requirement that the iv PCA was maintained for the 96 hr, to comply with the duration of the local anaesthetic infusion. This was problematic as patients could not be sent home with the iv PCA. Therefore, the fentanyl PCA was replaced with oxycodone (Endone®), which after an iv PCA infusion (1 mg. Frequency/PCA lockout 5 min) could be converted to an oral PCA (PCAO), hence not hindering early patient discharge before the conclusion of the 96 hr infusion period.

Patients commenced the PCAO with oxycodone once they no longer required oxycodone via the iv PCA. Oxycodone was readily available in a locked draw at the patient's locker for use at their discretion under nursing supervision (with upper safety limits applied). A diary and treatment record forms of usage and outcomes were maintained by nursing staff. This PCA therapy was in addition to the continuous levobupivacaine or saline infusion in the Painbuster. The dose of the PCAO was 5-10 mg, depending on patient's age. If the patient did not receive any relief from pain for 4 hr following PCAO, then treatment with PCA was re-commenced, and reviewed by the Acute Pain Service (APS) team. All PCA orders were under the responsibility of the APS team and reviewed at least once a day until the prescription required changing. The PCAO usage (demands for medication and actual consumption) was recorded as an index of efficacy of the continuous levobupivacaine or saline infusion (Appendix 4).

Pain scores, at rest and movement, were taken prior to the operation and 6, 12, 24, 48, 72 and 96 hr after the administration of the bolus dose of 0.5% levobupivacaine. Pain scores were verbally assessed by asking the patient the perception of the level of their pain. A score of "0" indicated no pain through to a score of "10" indicating that they were experiencing the worst pain imaginable. Subsequent to the recording of pain scores, blood samples were taken via venipuncture at the above time-points to assess the patient's plasma levobupivacaine, AAG and cortisol concentrations (Section 2.2).

While on the surgical ward, patients were also monitored for their return of bowel function, their time to mobilisation, abdominal wound complications, the length of hospitalisation and any side-effects related to the use of levobupivacaine during the 96 hr infusion period. In addition, the interventions of the fast track surgery recovery protocol (Section 2.1.5 (c)) were adhered to, where applicable throughout the trial period and adjuvant analgesia was administered if required.

At the conclusion of the 96 hr infiltration period, patients were assessed for hospital discharge. If patients were not medically capable for discharge, they were under the normal clinical care of their treating surgeon until ready. In the circumstance that patients were eligible for discharge, as per fast track surgery protocol, before the completion of the 96 hr infusion period, they were sent home with the Painbuster (due to the portability of this device in comparison to PCA infusion machines) and requisite blood sampling for the trial was conducted by The Queen Elizabeth Hospital's, hospital-at-home team.

In the event of a patient withdrawal from the study, their attending surgeon and/or anaesthetist determined the form of the patient's on-going pain management. This included continuing with the PCA or reverting to existing pain management protocols, such as the use of NSAIDs and/or low dose ketamine infusions.

Furthermore, patient costing data from TQEH database records included parameters such as: nursing costs, pathology costs, pharmacy costs, ICU costs, and surgical and anaesthetic costs were recorded for each patient.

2.1.6 Post-Operative Clinical Outcome Indices

The primary clinical outcome indices consisted of PCA usage, which comprised of the demands for opioid analgesia and the actual doses delivered (µg/ mL, Fentanyl; mg, oxycodone- although the fentanyl was converted to the oxycodone (mg) equivalence for analysis) and pain scores at rest and movement, scaled from 0-10 using the VNRS.

The secondary clinical outcomes comprised: the patient's return of bowel function (day(s) to first occurrence); their time to mobilisation (day(s) to first movement), the length of hospitalisation (days), re-admission rates, surgical complications and any side-effects related to the use of levobupivacaine during the 96 hr infiltration period. The outcome of the adherence with the fast track surgery recovery protocol and costing data was also assessed.

2.2 Laboratory Studies

To enhance the methodology used in the clinical setting, laboratory testing was conducted in order to support the utilisation of levobupivacaine as a safe and efficacious local anaesthetic for the provision of pain relief. Assays used to determine this comprised of a total plasma levobupivacaine concentration assay, an alpha$_1$-acid glycoprotein (AAG) assay and an assay used to determine the cortisol concentration of the patient.

2.2.1 Total Plasma Levobupivacaine Concentrations

The methodology for the total plasma levobupivacaine concentration assay was adapted from the works of Corso et al (2007), Tanaka et al (2006) and Karatassas (1992).

2.2.1 (a) Blood Sampling

Venous blood samples were collected in order to determine the plasma levobupivacaine concentration, AAG concentration and the patient's cortisol concentration. Blood was collected into a 10 mL, lithium heparin Vacutainer® blood tube via venipuncture. The sampling times were pre-dose (prior to surgery) and 1, 6, 12, 24, 48, 72 and 96 hr after the administration of the bolus dose of 0.5% levobupivacaine along the length of the surgical incision at the conclusion of the surgery. Samples were subsequently centrifuged at a speed of 3000 rpm for 5 min at 4°C. Once spun down, the plasma was equally divided into two separate, uniquely labelled, 5 mL polypropylene tubes, and stored at -20°C until further analysis.

2.2.1 (b) Extraction Procedure

Prior to analysis by high performance liquid chromatography (HPLC) patient plasma samples went through an extraction process so that a pure form of the drug of interest, levobupivacaine could be recovered from the patients' blood. The extraction process firstly consisted of the addition of 100 µL of

the internal standard, ropivacaine (AstraZeneca Pharmaceuticals, Sydney, Australia) to 0.5 mL aliquots of patient plasma samples, quality control (QC) samples (0.5- 5.0 mg/L) and calibration standards (0.2-5.0 mg/L). Consequently, 100 µL of acetonitrile (Merck, Lichrosolv grade, Melbourne, Australia) and 3 mL of tert-butyl methyl ether (Sigma-Aldrich, Chromasolv, St. Louis, USA) were added to this mixture. After 60 s of vigorous vortex mixing, the tubes were centrifuged (Jouan, CR412, France) at 3000 rpm for 5 min at 4°C. The different phases were then separated by snap-freezing the aqueous acid layer in a dry ice/ ethanol bath and decanting the organic layer. Samples were then dried by a centrifugal vacuum evaporation unit, which consisted of a freeze drier (Dynavac, Australia) and a centrifugal vacuum evaporation unit (Savant, Speed Vac Concentrator, Thermo Fisher Scientific, Australia). Once dried, 200 µL of mobile phase (below, Section 2.2.1.3 was added to each tube before it was vortex mixed for a further 60 s. This mixture was transferred into the HPLC auto-sampler tubes from which, 50 µL of this extract was injected for chromatographic separation.

2.2.1 (c) Method of Plasma Levobupivacaine Analysis

The high performance liquid chromatographic system comprised of a mobile phase that consisted of 0.04 mol/L NaH_2PO_4, pH 5.6 (Ajax Firechem, Sydney Australia), acetonitrile (Merck, Lichrosolv grade, Melbourne, Australia) and methanol (Fisher Scientific, HPLC grade, Leicestershire, UK) (65: 25: 10, v: v: v). The mobile phase was pumped (Waters Model 510, Waters/Millipore, Milford, M.A.) at 1 mL/min via an auto sampler (Ultrawisp 715, Waters/Millipore, Milford, M.A.) through a 200 x 4 mm 5 µm C8, column (RP-Select B, LiChrosphere 60, Darmstadt, Germany). UV absorbance (Spectra Physics, UV2000) at 210 nm, with an attenuation of 0.05 to 0.01 AUFS, detected the peaks that were separated by this system. In order to quantify the results, peak height ratios (PHR) of levobupivacaine to the internal standard, ropivacaine, were used.

This assay was calibrated using blank human plasma standard samples that were spiked to final concentrations of 1.0, 2.5 and 5.0 mg/L of levobupivacaine (levobupivacaine hydrochloride, Abbott

Laboratories, North Chicago, USA). Quality Control (QC) samples were extracted in parallel using aliquots from levobupivacaine-spiked aliquots of a plasma pool (stored at -20°C) at 5 mg/L, 2.5 mg/L and 1.0 mg/L to assess the analytical accuracy in each analytical run. Repeated measurements at concentrations of 1.0, 2.5 and 5.0 mg/L were conducted in order to test the precision of the assay within a single run. The QC samples were prepared from a different levobupivacaine stock solution to that used for the preparation of the calibration standards to avert potential error in weighing. The target coefficients of variation (CV%) for precision and bias within and between runs were set at less than 15%, and 20 % as the lower limit of quantification (LLOQ) (Shah et al., 2000).

2.2.2 Alpha$_1$-Acid Glycoprotein (AAG) Assay

The AAG assay (NOR Partigen®, Siemens, Marburg, Germany, 2003), was used to determine changes in protein binding. It was analysed by radial immuno-diffusion, an in vitro diagnostic technique. Five µL of the patients undiluted plasma sample (at pre-dose, 12 hr and 48 hr time-points) was dispensed with a 10 µL pipette into an empty well in the 12-well NOR Partigen® plate. After samples were diffused into the agarose gel in the NOR Partigen® plate, the lid was closed and it was kept at room temperature (15 to 25°C) for 2 days. Each plate contained a control sample. The diameter of the precipitin ring was measured after 2 days, using a ruler that was accurate to 0.1 mm under lateral lighting. The diameter was correlated to a calibration table provided in the kit comparing the readings to the corresponding AAG concentration. According to the manufacturer's claim, the intra-assay precision of the kit was CV 3.0% and inter-assay precision was CV 2.4%.

2.2.3 Cortisol Concentration

As mentioned in Section 1.2.5, serum cortisol concentrations were measured as an index of each patient's stress levels in response to surgery. An aliquot of the patient's plasma samples were sent to the Institute of Medical and Veterinary Sciences (IMVS), an accredited independent laboratory, for analysis of their cortisol levels as an existing part of this laboratory's routine biochemistry testing. This

was analysed, as described by the manufacturer, by using the ADVIA Centaur® System, which is a competitive immunoassay that uses direct chemiluminescent technology. The procedure of this assay is outlined in Appendix 5. The ADVIA Centaur Cortisol assay was highly specific for cortisol and the sensitivity and range of the assay was 5.5- 2069 nmol/L.

2.3 Statistical Analyses

All data are presented as mean ± SEM unless otherwise stated. The rationale for this is based on published work by Cumming and colleagues (2007). Results are considered to be significant when $p < 0.05$.

The clinical data was analysed under direction of Biostatistician, Dr John Field, using the "R" software program (R Development Core Team, 2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/). The patients demographic and surgical data were analysed by one-way analysis of variance followed where necessary by Tukey's test. Frequencies, which were given for all count data, were analysed by Fisher's exact test.

Opioid consumption and demand, and pain scores at rest and movement along with the co-variates were analysed by an analysis of variance. When significance was apparent, Tukey's test was used to detect differences between individual groups. A repeated measures analysis of variance using a Greenhouse-Geisser adjustment was used to detect for significant interactions between the treatment types over time with the presence of the co-variates. Furthermore a partial R^2 plot for regression was used to show the contribution of each of the co-variates of treatment, age, stoma, gender, drain and BMI on opioid consumption.

An analysis of variance was used to determine significance in the length of hospitalisation, re-admission rates, the return of bowel function, time to mobilisation and catheter fall-outs between the four treatment

groups, with Tukey's test applied in order to compare individual treatments, if shown to be significant. Furthermore, an un-paired t-test was used to analyse the costing differences between laparoscopic and open procedures and the active and placebo treatments.

A Mann-Whitney test, using the Prism 5 software (GraphPad, La Jolla, CA, USA, 2010) was used to detect for differences in the AAG concentration from before surgery to 12 hr and 48 hr post-operation. A one-way analysis of variance was used to detect for differences in cortisol concentrations between the laparoscopic active, laparoscopic placebo, open active and open placebo groups. In addition, an un-paired t-test also using the Prism 5 software was used to detect for differences in cortisol concentrations between laparoscopic and open procedures.

CHAPTER 3: PATIENT RECRUITMENT, DEMOGRAPHICS & PRIMARY CLINICAL RESULTS

CHAPTER 3: PATIENT RECRUITMENT, DEMOGRAPHICS & PRIMARY CLINICAL RESULTS

3.1 Patient Recruitment Flow

One hundred and twenty patients were approached and considered for recruitment into this study at the Pre-Admission Clinic and less commonly the Day of Surgery Admission rooms. Twenty-nine of these patients were excluded before proceeding to the trial randomisation for the following reasons: unwillingness to sign the Informed Consent and participate in the trial (14 patients); currently using medications that were on the excluded criteria list (8 patients); difficulties with English (2 patients); inadequate mental status (2 patients); a drug allergy to oxycodone (1 patient); an ASA score of 4 (1 patient); and 1 patient who was over the age of 90. A further 9 patients were excluded after randomisation due to: a change of incision type from the abdomen to the rectum (2 patients); patient pulling out of the Painbuster catheter on the night of operation (2 patients); infection during the operation (1 patient); trial protocol violations by the attending anaesthetists including epidural drug administration (2 patients); morphine or ketamine administered in the PCA (2 patients). Therefore, for these reasons, 38 potential patients were not included in the final analyses.

Hence 81 randomised patients were administered either the active drug treatment in the Painbuster which contained 0.5% or 0.25% levobupivacaine, or the placebo treatment with 0.9% saline in the Painbuster. Thirty-one patients in the active group underwent laparoscopic surgery and 24 patients had open surgery; whereas in the placebo group, 20 patients underwent laparoscopic surgery and 6 patients had open surgery (Figure 23). The prospectively planned allocation ratio between the active to placebo treatment types was 2:1, but without further randomisation by type of surgery proposed.

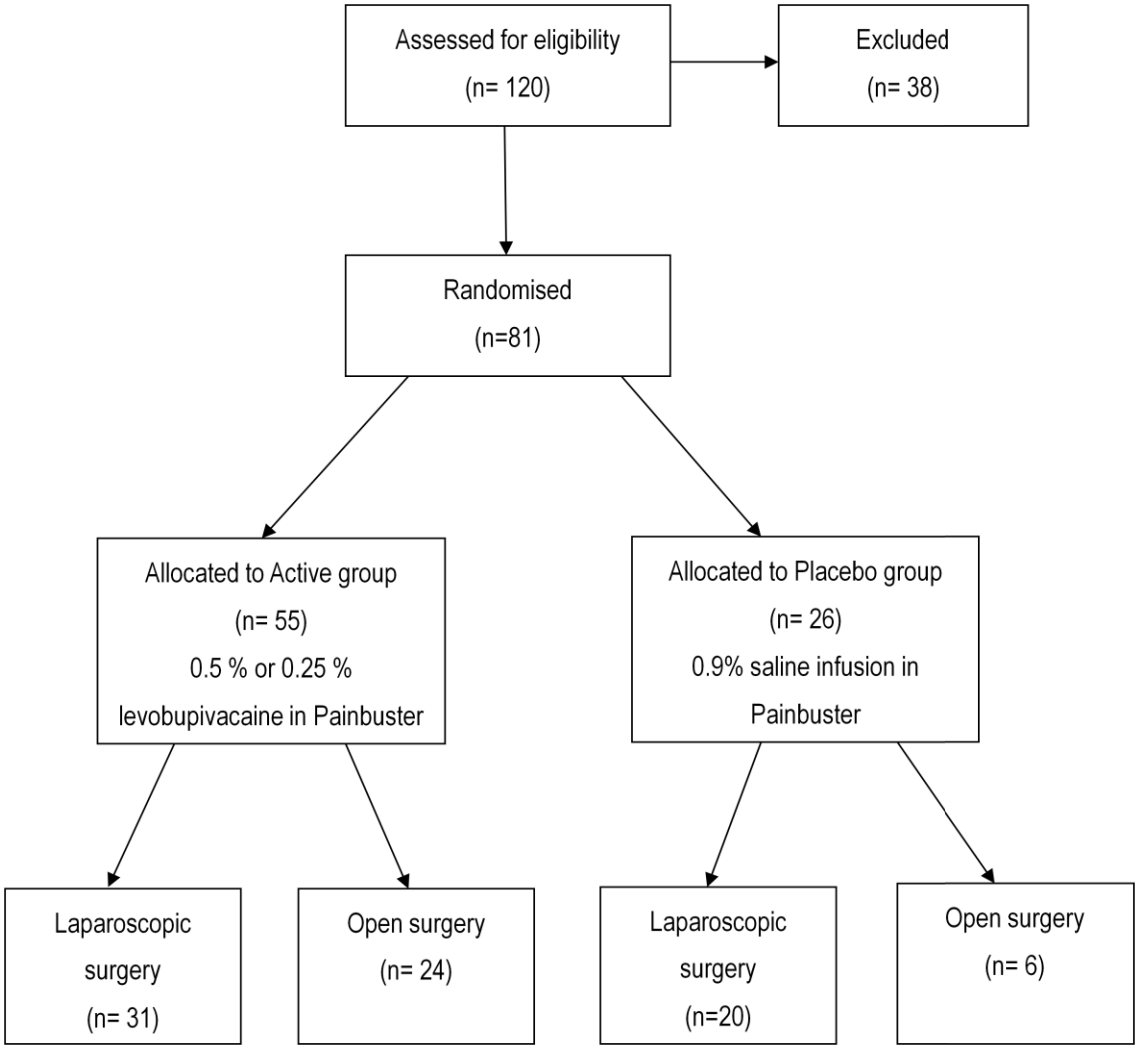

Figure 23: Patient recruitment flow.

3.2 Demographic Data

The basic demographic data of the patients are displayed in Table 14. The variables of age, gender and body mass index (BMI) were similar between the laparoscopic active, laparoscopic placebo, open active and open placebo groups, hence there were no significant differences evident between these treatment groups for age, gender and BMI (one-way ANOVA).

Table 14: Patient Demographics.

Variable	Treatment Group				Significance
	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n=6)	
Age, years (mean)	65.6	63.8	65.5	64.5	P= 0.96
Gender F (%)	14 (45%)	10 (50%)	10 (42%)	2 (33%)	P= 0.91
BMI, kg/m^2 (mean)	27.9	27.7	29.3	27.8	P= 0.71

3.3 Diagnosis and Co-morbidities

The patients' diagnosis prior to surgery and existing co-morbidities are detailed in Table 15. The majority of patients (81% laparoscopic active; 90% laparoscopic placebo; 88% open active and 83% open placebo) were diagnosed with colorectal cancer (sigmoid carcinoma, rectosigmoid adenocarcinoma, caecal carcinoma or ascending colon carcinoma) before surgery. Less common diagnoses consisted of benign polyps that required surgical removal, diverticular disease, Crohn's disease and ulcerative colitis. Hypertension was the most common co-morbidity noted in the laparoscopic active (42%) and open active (58%) groups, whereas hypercholesterolaemia was the most prevalent co-morbidity in the laparoscopic active group (30%). 'Other co-morbidities' were the

most common in the open placebo group and consisted of conditions such as: cystitis, hyperthyroidism, haemorrhoids, gastritis, diverticulitis, skin cancers, glandular fever and alcohol abuse,

3.4 Surgical Procedures

Table 16 details the types of surgery involved between the four different treatment groups. Ten per-cent of patients in the laparoscopic active group (3/31 patients) and laparoscopic placebo group (2/20 patients) had conversions from laparoscopic to open surgery as a clinical decision during the surgical procedure. Twenty-six per cent of patients in the laparoscopic active group (8/31 patients) had stoma formation compared to 5% (1/20 patients) in the laparoscopic placebo group, whereas half of all patients who had open surgery in the actively-treated (12/24 patients) and placebo groups (3/6 patients) had stoma formation. In patients that had laparoscopic surgery, 19% (6/31 patients) of active patients had drains in comparison to 10% (2/20 patients) in the placebo group, whereas 46% (11/24 patients) of the open active group had drains in comparison to 83% (5/6 patients) of the open placebo group.

Table 15: Patient diagnosis and co-morbidities. Data presented as number (%).

	Lap-Active (n =31)	Lap-Placebo (n =20)	Open Active (n =24)	Open Placebo (n= 6)
Diagnosis				
Cancer	25 (81%)	18 (90%)	21 (88%)	5 (83%)
Benign Polyps	2 (6%)	0 (0%)	0 (0%)	0 (0%)
Diverticular Disease	4 (13%)	2 (10%)	1 (4%)	0 (0%)
Crohn's Disease	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Ulcerative Colitis	0 (0%)	0 (0%)	1 (4%)	1 (17%)
Co-morbidities				
Hypertension	13 (42%)	5 (25%)	14 (58%)	0 (0%)
Hypercholesterolaemia	7 (23%)	6 (30%)	9 (38%)	0 (0%)
Hyperlipidaemia	1 (3%)	0 (0%)	0 (0%)	1 (17%)
GORD	6 (19%)	3 (15%)	3 (13%)	1 (17%)
IBS	2 (6%)	1 (5%)	0 (0%)	0 (0%)
Type 2 Diabetes Mellitus	3 (10%)	5 (25%)	5 (21%)	1 (17%)
Ischaemic Heart Disease	3 (10%)	2 (10%)	1 (4%)	1 (17%)
Osteoarthritis/ Osteoporosis	4 (12%)	0 (0%)	4 (17%)	0 (0%)
Anxiety/ Depression	2 (6%)	0 (0%)	2 (8%)	0 (0%)
COAD	3(10%)	1 (5%)	2 (8%)	0 (0%)
Other	6 (19%)	8 (40%)	6 (25%)	4 (67%)

Abbreviations: lap=laparoscopic; GORD= gastro-oesophageal reflux disease; IBS= irritable bowel syndrome; COAD= chronic obstructive airway disease.

Table 16: The patients' surgical procedures including conversion from laparoscopic to open surgery, stoma formation, the presence of drains and extra-operations.

	Lap - active (n=31)	Lap - placebo (n=20)	Open - active (n=24)	Open - placebo (n=6)
Surgery				
Ileocaecal resection	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Right hemicolectomy	11 (35%)	10 (50%)	3 (13%)	0 (0%)
Left hemicolectomy	1 (3%)	0 (0%)	1 (4%)	0 (0%)
Subtotal colectomy	0 (0%)	0 (0%)	3 (13%)	0 (0%)
High anterior resection	10 (32%)	7 (33%)	7 (29%)	0 (0%)
Low anterior resection	2 (6%)	2 (10%)	0 (0%)	1 (17%)
Ultra-low anterior resection	5 (16%)	1 (5%)	5 (21%)	2 (33%)
Abdomino-perineal resection	1 (3%)	0 (0%)	2 (8%)	1 (17%)
Hartmann's procedure	1 (3%)	0 (0%)	1 (4%)	1 (17%)
Reversal of Hartmann's	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Proctectomy/ileo-anal pouch	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Conversion	3 (10%)	2 (10%)	N/A	N/A
Stoma				
Ileostomy	6 (19%)	1 (5%)	9 (38%)	1 (17%)
Colostomy	2 (3%)	0 (0%)	3 (13%)	2 (33%)
Drains	6 (19%)	2 (10%)	11 (46%)	5 (83%)
Extra-operations				
Cholecystectomy	1 (3%)	0 (0%)	0 (0%)	1 (17%)
Hernia repair	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Oophorectomy	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Partial cystectomy	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Partial gastrectomy	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Closure of ileostomy	0 (0%)	0 (0%)	1 (4%)	0 (0%)

3.5 Surgical Data

The patients' ASA scores, duration of surgery, incision length and type of abdominal incision that was utilised in their surgery are presented in Table 17. There was a significant difference evident between the four treatment groups and the ASA scores of 1, 2 and 3 (p= 0.004; one-way ANOVA) and duration of surgery, which was recorded from the induction of anaesthesia to the time the patient left the operating theatre (p= 0.04; one-way ANOVA). Although there was no difference in incision length between treatment type within surgical groups, an expected significant difference was evident, as expected between laparoscopic and open cases (p< 0.001; one-way ANOVA). Laparoscopic procedures consisted of midline, transverse, pfannenstiel and oblique incisions, whereas open cases predominantly had midline incisions.

Table 17: Patient surgical details.

Variable	Treatment Group				Significance
	Lap Active (n= 31)	Lap Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n=6)	
ASA Score					
1	3	2	1	2	
2	21	14	10	0	
3	7	4	13	4	p= 0.004
Duration of Surgery	246.0	219.8	213.9	284.2	p = 0.04
Incision Length	7.8	8.4	24.0	28.9	p< 0.001
Incision Type					
Midline	9	3	23	6	
Transverse	5	8	1	0	
Pfannenstiel	7	1	0	0	
LIF/Oblique	9	8	0	0	p< 0.001

Notes: abbreviation LIF= left iliac fossa**; ASA**: laparoscopic vs open p= 0.003; laparoscopic: active vs placebo p= 1.00; open: active vs placebo p= 0.04. **Operation duration**: while the one-way ANOVA shows significances, Tukey's test shows no pair-wise comparisons significant at p= 0.05. **Incision length**: laparoscopic: active vs placebo p= 0.98; open: active vs placebo p=0.31 **Incision type:** laparoscopic: active vs placebo p= 0.09; open: active vs placebo p= 1.00

CHAPTER 4: OPIOID CONSUMPTION & DEMAND RESULTS

CHAPTER 4: OPIOID CONSUMPTION & DEMAND RESULTS

The total and daily opioid consumption and opioid demand results for the patients are presented in this Chapter. In addition the effects of the co-variates on each of the above clinical indices are further analysed.

4.1 Fentanyl to Oxycodone Conversion

Initially patients received intravenous fentanyl (n= 27) but due to a clinical decision to further enhance early ambulation (as per the fast-track surgery strategy), a protocol change was made for the remaining patients who received intravenous and/or oral oxycodone (n= 54). Therefore, fentanyl usage was converted to the oxycodone equivalence for all the resulting analyses. Based on the fact that 1000 µg of oxycodone is equivalent to 20 µg of fentanyl, it was possible to convert fentanyl to the equivalent mg of oxycodone by dividing the fentanyl values by 20 (50/1000). Hence opioid consumption data displayed throughout this section are expressed in mg of oxycodone or oxycodone-equivalent. Fentanyl consumption was compared to oxycodone consumption in Figure 24 and shown to be equivalent.

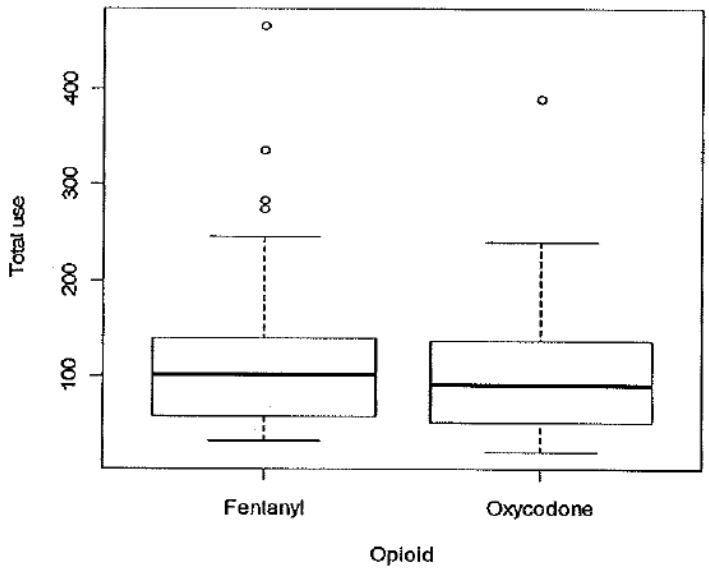

Figure 24: Shows a comparison of the total dose (mg) of fentanyl expressed as the oxycodone equivalent dose) (n= 27) compared to oxycodone (n= 54) (p= ns).

4.2 Total and Daily Opioid Consumption

Total Opioid Consumption

Patients in the laparoscopic active group consumed more opioids than patients in the laparoscopic placebo group, while patients in the open active group consumed less opioid than that of the open placebo patients. This is shown in Table 18. Although the effect was significantly different (p= 0.0024; analysis of variance), it can be attributed to the low numbers in the placebo group, which will be considered below. (Note: although there are 6 patients in the open placebo group, opioid consumption and demand data are only shown in 5 patients due to a missing PCA chart of 1 patient in this group).

Table 18: The mean ± SEM total opioid consumption (mg) of the four treatment groups over the 96 hr levobupivacaine (or saline) infiltration.

	Laparoscopic Active (n= 31)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 5)**
Total Opioid Consumption (mg)	99.0 ± 12.3	83.8 ± 10.6	120.7 ± 20.4	196.6 ± 55.2
Range (mg)	22.0- 274.5	25.0- 183.5	26- 465.5	109- 388.8

Daily Opioid Consumption

The patients' daily opioid consumption is displayed in Table 19. Across the four treatment groups, opioid consumption decreased with time. The daily opioid consumption in the laparoscopic active group was higher (surprisingly) than the laparoscopic placebo group on all days except post-operative day 4, whereas the open active group had a lower mean daily consumption compared to the open placebo group at all time-points. Significant differences were evident on all days between the four treatment groups, although the small numbers in the open placebo group needs to be taken into consideration. This is further explored in the next section.

Table 19: The mean (±SEM) daily opioid consumption (range) by the four treatment groups.

Daily Opioid Consumption (mg)	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 5)	Significance
Day 1	61.4 ± 5.69 (22.0- 124.5	49.6 ± 7.16 (0.0- 116.3)	66.7 ± 7.06 (21.0- 137.6)	78.8 ± 21.29 (63.0- 176.5)	p= 0.05
Day 2	22.2 ± 4.03 (0.0- 85.0)	17.1 ± 2.81 (0.0- 40.0)	26.8 ± 4.88 (4.0- 90.50)	53.6 ± 17.31 (20.0- 111.7)	P= 0.0008
Day 3	11.4 ± 2.921 (0.0- 57.0)	11.3 ± 3.46 (0.0- 44.0)	15.9 ± 5.74 (0.0- 127.5)	37.7 ± 12.38 (0.0- 88.0)	P= 0.012
Day 4	4.0 ± 1.47 (0.0- 30.0)	5.8 ± 2.44 (0.0- 40.0)	11.2 ± 5.56 (0.0- 127.5)	26.6 ± 16.17 (10- 96.10)	P= 0.02

4.3 The Effects of the Co-Variates on Total and Daily Opioid Consumption

Further ancillary analyses were performed in order to determine if the following variables of: stoma, drain, gender, age, BMI, incision length and the duration of surgery had an effect on opioid consumption. The results of these are outlined below. (Note: in the following figures LA= laparoscopic active; LP= laparoscopic placebo; OA= open active; OP= open placebo; Y= yes; N= no; M= males; F= females).

4.3.1 The Effect of the Stoma

The effect of the stoma on total opioid consumption and daily opioid consumption are presented below.

Total Opioid Consumption

The effect of the stoma on total opioid consumption and daily opioid consumption were further analysed. The mean total opioid consumption over the 96 hr levobupivacaine (or saline) infiltration period is shown in Table 20. In relation to the active treatments there are sufficient numbers in each group, however, for the placebo groups, the number of patients with stomas is small making analysis difficult.

Table 20: The mean total opioid consumption (mg) by treatment type and presence of stoma.

Stoma	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo
Stoma Absent	90.1 (n= 23)	85.3 (n= 19)	103.0 (n= 13)	54.5 (n= 1)
Stoma Present	124.6 (n= 8)	56.0 (n=1)	141.6 (n= 11)	267.7 (n= 4)

This data is also displayed in Figure 25. In regards to the two active groups, there is little difference between opioid consumption with or without the presence of stomas. Comparison is difficult in the two placebo groups due to the small numbers.

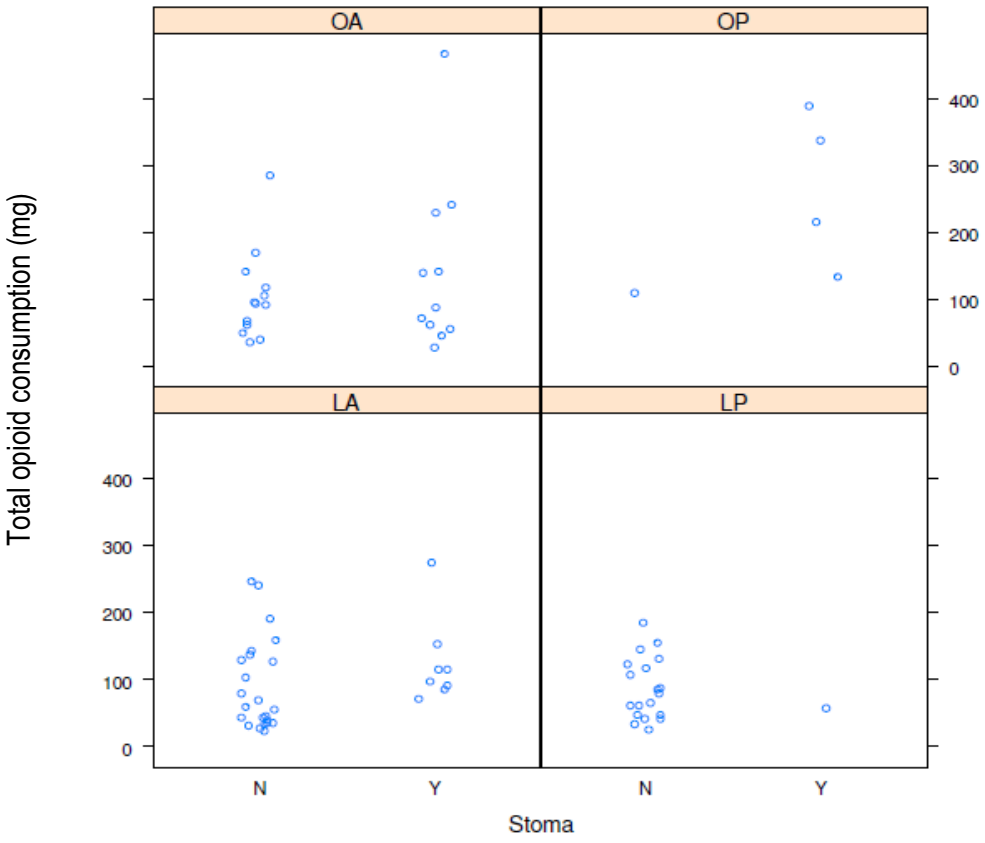

Figure 25: Total opioid consumption (mg) by presence of stoma.
(Note: Abbreviations for this figure and subsequent figures are explained on page 137)

Although an analysis of variance did not show any significant difference between the four treatment types (p= 0.16), there was a trend towards increased opioid consumption between treatment type and stoma interaction (p= 0.07). This suggests that the four treatments affect total opioid consumption differently depending on the presence or absence of a stoma. In the presence of this interaction, the significant stoma effect (p= 0.02) is not important. However, if the open placebo group is omitted from the analysis, then neither the treatment type, stoma or their interaction are significant.

Daily Opioid Consumption

Figure 26 shows the patients' opioid consumption by day. The left hand side of the figure shows patients without a stoma (n= 57), and the right hand side depicts patients with a stoma (n =24). Clearly, there is a consistent reduction in opioid usage from day 1 to day 4 post-operation regardless of treatment group or stoma. In the open placebo group, opioid consumption by day appears higher for the patients with a stoma than for those without one. However, the number of patients is very small for these open placebo groups: no stoma group (n= 1) and stoma group (n= 4). There is not much difference between the other groups, although there is only one patient with a stoma in the laparoscopic placebo group.

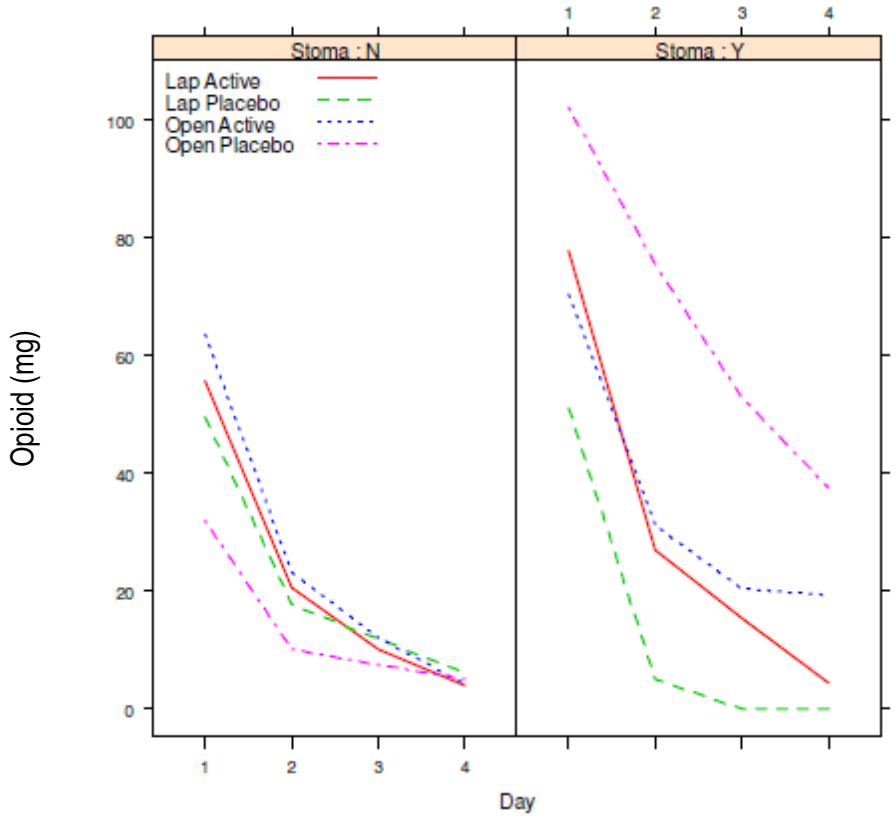

Figure 26: Opioid consumption by day (post-operative) by stoma presence. (Stoma N = no stoma present; n= 57; Stoma Y = stoma present; n= 24).

The small patient numbers were an anticipated problem when drilling the database down into smaller and smaller sub-group analyses. Repeated measures analyses of variance using a Greenhouse-Geisser adjustment (separate analyses for stoma and no stoma groups) showed no significant difference between the 4 treatments and additionally there were no significant treatment type and day post-operative interactions (Table 21).

Table 21: Significance levels for repeated measurements analyses of variance.

Effect	No Stoma	Stoma
Treatments	p= 0.72	p= 0.15
Treatment and Day	p= 0.54	p= 0.63

Table 22 shows treatment means and significance levels for analysis of variance at up to post-operative day 4, for patients with and without stomas.

Table 22: The mean daily opioid consumption (mg) in patients with and without stomas.

No Stoma					
Day	**Laparoscopic Active (n= 23)**	**Laparoscopic Placebo (n= 19)**	**Open Active (n= 13)**	**Open Placebo (n= 1)**	**Significance**
1	55.6	49.5	63.5	32.0	p= 0.47
2	20.6	17.7	23.2	10.0	p= 0.77
3	10.0	11.9	12.1	7.5	p= 0.96
4	3.9	6.1	4.2	5.0	p= 0.56
Stoma Present					
Day	**Laparoscopic Active (n= 8)**	**Laparoscopic Placebo (n= 1)**	**Open Active (n= 1)**	**Open Placebo (n= 4)**	**Significance**
1	77.9	51.0	70.5	102.1	p= 0.48
2	26.9	5.0	31.2	75.4	p= 0.02
3	15.4	0	20.5	52.8	p= 0.21
4	4.4	0	19.4	37.4	p= 0.38

The only significant difference evident was in the stoma group at post-operative day 3, where opioid use for the open placebo group is significantly higher (p= 0.02) than the other three treatment groups.

This data was further investigated by various other analyses. This included:

- Analyses as displayed in Table 22 but included age, gender and BMI as co-variates. None of the non-stoma analyses showed any significance, however there were significant treatment effects at day 2 (p= 0.01), day 3 (p= 0.01) and day 4 (p= 0.047) for the stoma group. In these regressions, age was close to significance at day 2 (p= 0.055) and day 3 (p= 0.066) and was significant at day 4 (p= 0.02).

- Additional co-variates such as incision length, duration of surgery and presence/absence of drains were included; however, there were no significant treatment or co-variate effects at any day.

4.3.2 Drain

Total opioid consumption

The effects of the drain on opioid consumption are displayed in Table 23 and Figure 27.

Table 23: Total opioid consumption (mg) by presence of drain.

Drain	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo
Drain Absent	97.3 (n=25)	86.4 (n=18)	124.5 (n=13)	0 (n=0)
Drain Present	106.0 (n=6)	60.5 (n=2)	116.1 (n=11)	236.0 (n=5)

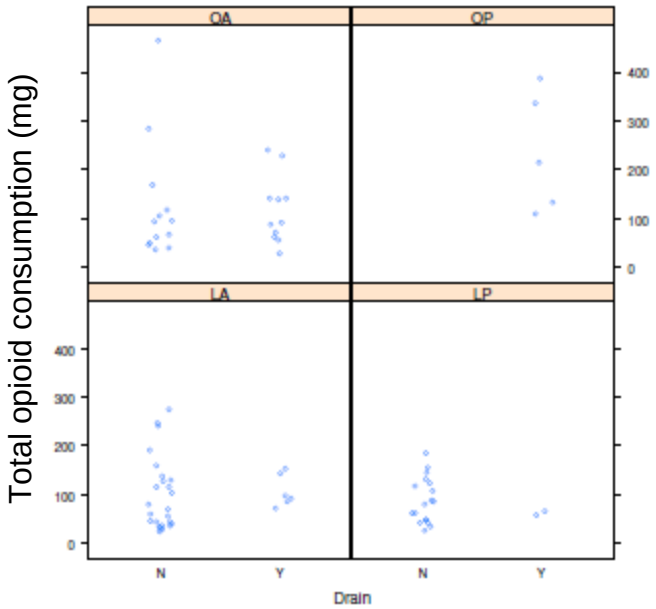

Figure 27: Total opioid consumption by presence of drain.

There is a trend close to significance (p= 0.07; analysis of variance) between treatment type and drain interaction. This implies that the presence or absence of a drain may impact on opioid consumption differently for different treatments, as apparent from Table 23 and Figure 27, as shown above. However, once again, if the open placebo group is omitted from the analysis, there is no indication of significance either for treatment type or drain presence.

Daily Opioid Consumption

The opioid consumption for each of the treatment types over time are shown in Figure 28.

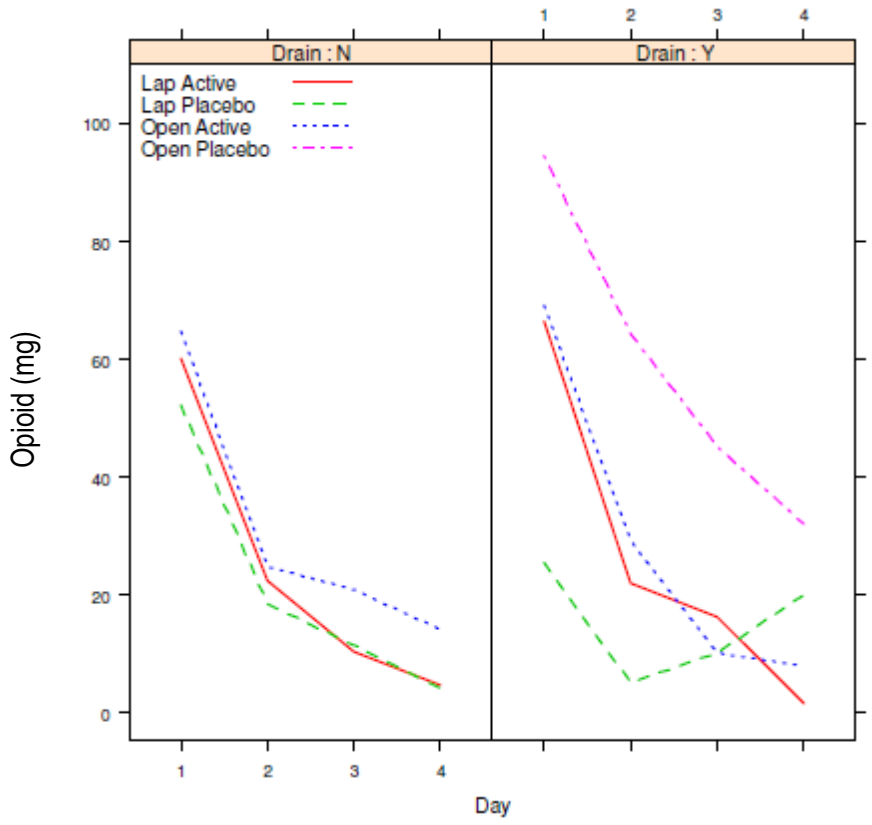

Figure 28: Opioid consumption by day (post-operative) by drain presence. (Drain N = no drain present; n= 57; Drain Y = drain present; n= 24).

In Figure 28, all 5 patients in the open placebo group had drains. While opioid consumption was similar between the laparoscopic active and open active groups with and without the presence of drains, more variability was evident in the laparoscopic placebo group, however there were only two patients in this group.

The significance levels from repeated measurements analyses of variance for each group are shown in Table 24. There were no significant treatment effects for patients without drains, whereas patients with drains in the open placebo group had significantly higher opioid consumption than the other three groups.

Table 24: Significance levels for repeated measurements analyses of variance

Effect	**No Drain**	**Drain**
Treatments	p= 0.37	p= 0.02
Treatment Type and Day	p= 0.40	p= 0.29

Table 25 shows the results of the analyses from post-operative day 1 to 4. There were no significant effects in the patients without a drain. However, in the patients who had a drain, there were significant effects at day 2 (p= 0.01) and day 3 (p= 0.005) post-operation and an effect trending towards significance on post-operative day 4 (p= 0.10). These differences were due to the open placebo group.

The data was further analysed with the same method of analyses and the significance between treatment types and the use of drains did not change if age, gender and BMI were included as co-variates, although the treatment effect did become slightly stronger on post-operative day 4 (p= 0.057).

Table 25: The mean daily opioid consumption (mg) between the four treatment groups with and without the presence of drains.

No drain					
Day	**Laparoscopic Active (n= 25)**	**Laparoscopic Placebo (n= 18)**	**Open Active (n=13)**	**Open Placebo. (n= 0)**	**Significance**
1	60.2	52.3	64.8	0	P=0.24
2	22.3	18.5	24.9	0	P=0.66
3	10.3	11.5	20.8	0	P=0.51
4	4.6	4.2	14.0	0	P=0.41
Drain					
Day	**Laparoscopic Active (n= 6)**	**Laparoscopic Placebo (n= 2)**	**Open Active (n= 11)**	**Open Placebo. (n= 5)**	**Significance**
1	66.5	25.5	69.0	94.5	P=0.18
2	21.8	5.0	29.1	64.3	P=0.01
3	16.2	10.0	10.1	45.2	P=0.005
4	1.5	20.0	7.8	31.9	P=0.10

4.3.3 Gender

Total Opioid Consumption

The effect of gender on total opioid consumption is shown in Table 26 and Figure 29. In the laparoscopic active and open placebo groups males consumed more opioids than females, whereas total opioid consumption was similar between bother genders in the laparoscopic placebo and open active groups. An analysis of variance shows a significant treatment effect (p= 0.036) averaged over treatments that males consumed more opioids than females. However, this is likewise influenced by the open placebo group with small numbers. If this group is omitted from the analysis, there are no treatment effects (p= 0.30). It is acknowledged that there is a small number in the open placebo group. This is dealt with in the Discussion Chapter (Chapter 8).

Table 26: Total opioid consumption (mg) by gender.

Gender	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo
Female	83.0 (n=14)	85.3 (n=10)	114.3 (n=10)	120.5 (n=2)
Male	112.1 (n=17)	82.3 (n=10)	125.2 (n=14)	234.7 (n=3)

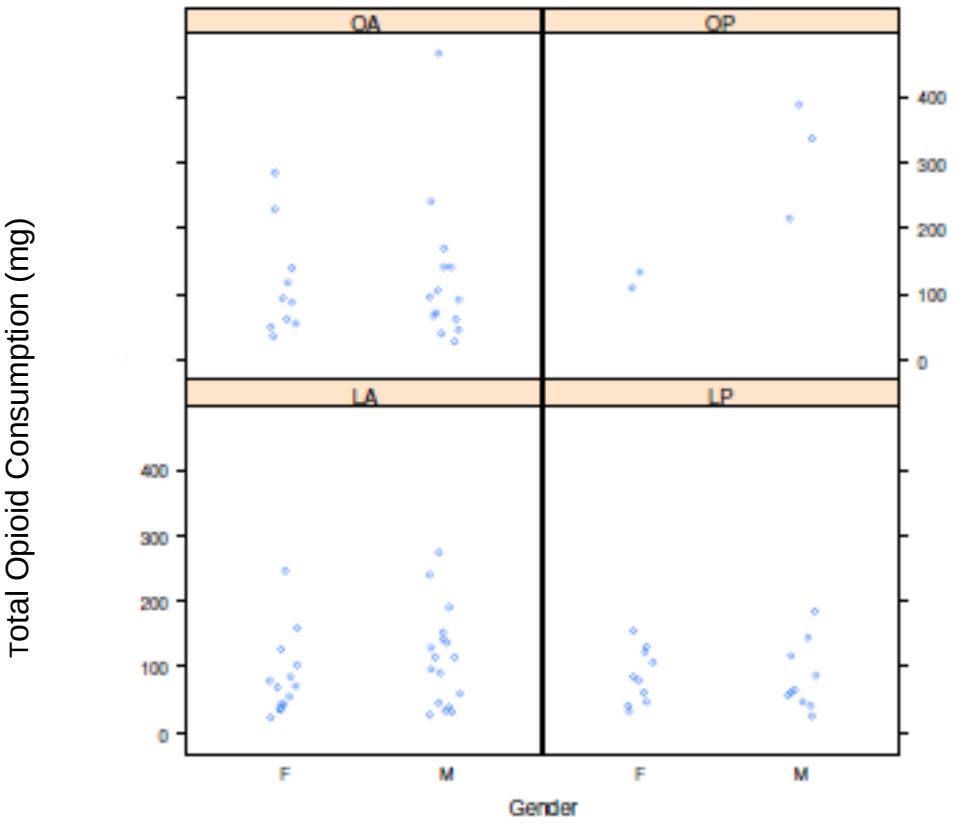

Figure 29: Total opioid consumption (mg) by gender

Daily Opioid Consumption

The opioid consumption by gender is shown in Figure 30. Opioid consumption was the highest on day 1 post-operation and the lowest on day 4 post-operation among all treatment types and both genders. The male open placebo group had a higher opioid consumption than the other treatment groups of both gender.

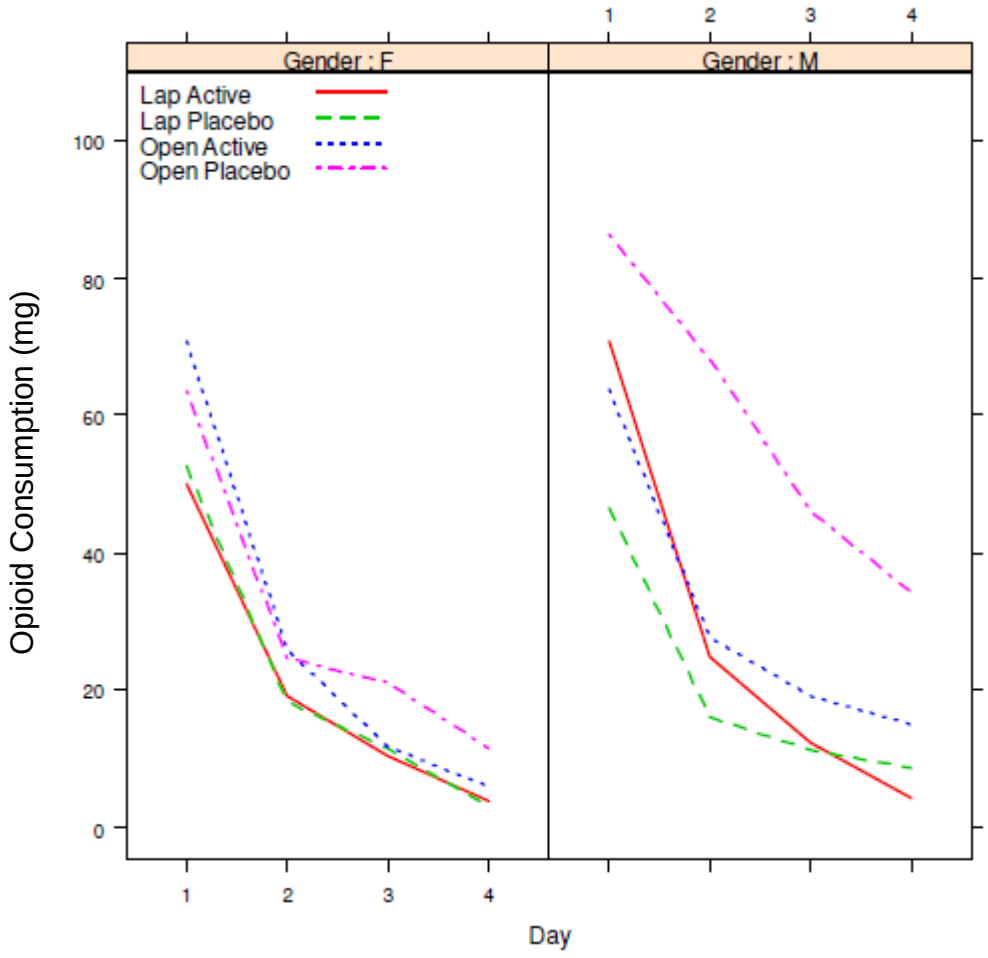

Figure 30: Opioid consumption (mg) over time by gender.

Repeated measures analyses of variance are displayed in Table 27. There were no significant differences evident in treatment type and day post-operation in female patients however, there is trend approaching significant treatment differences in male patients.

Table 27: Significance levels for repeated measurements analyses of variances by gender.

Effect	**Female**	**Male**
Treatment	p= 0.57	p= 0.07
Treatment Type and Day	p= 0.49	p= 0.26

The analyses of variance results at each day are presented in Table 28. There were no significant differences for females. Males in the open placebo group consumed significantly more opioids in relation to the other treatment groups.

This data was further analysed to determine significance with the addition of the existing co-variates. With age and BMI as co-variates, there were significant treatment differences for males at day 2 (p= 0.0002), day 3 (p= 0.001) and day 4 (p= 0.004). These treatment effects (males, days 2, 3 and 4) were still significant if operation duration, incision length, the presence or absence of stomas and drains were included as co-variates.

Table 28: Mean daily opioid consumption (mg) by gender.

Female					
Day	**Laparoscopic Active (n= 14)**	**Laparoscopic Placebo (n= 10)**	**Open Active (n= 10)**	**Open Placebo (n= 2)**	**Significance**
1	49.9	52.6	70.9	63.5	P=0.37
2	19.0	18.2	25.9	24.5	P=0.79
3	10.3	11.4	11.6	21.0	P=0.85
4	3.8	3.1	6.0	11.5	P=0.56
Male					
Day	**Laparoscopic Active (n= 17)**	**Laparoscopic Placebo (n= 10)**	**Open Active (n= 14)**	**Open Placebo (n= 3)**	**Significance**
1	70.8	46.6	63.7	86.4	P=0.27
2	24.8	16.0	27.5	68.2	P=0.01
3	12.3	11.3	19.0	46.0	P=0.10
4	4.2	8.5	14.9	34.2	P=0.15

4.3.4 Age

Total Opioid Consumption

The effect of age on total opioid consumption is presented as linear regressions in Figure 31. In all four of the treatment types, opioid consumption decreases with increasing age. A regression of total opioid consumption on treatment and age shows significant effects for treatments, age and their interaction. Hence the relationship between opioid consumption and age varies with treatment, although if the open placebo group is omitted, there is a significant effect with age but it does not vary with treatment. For the laparoscopic active, laparoscopic placebo and open active groups opioid consumption decreases by 2.29 ± 0.75 mg for every extra year of age.

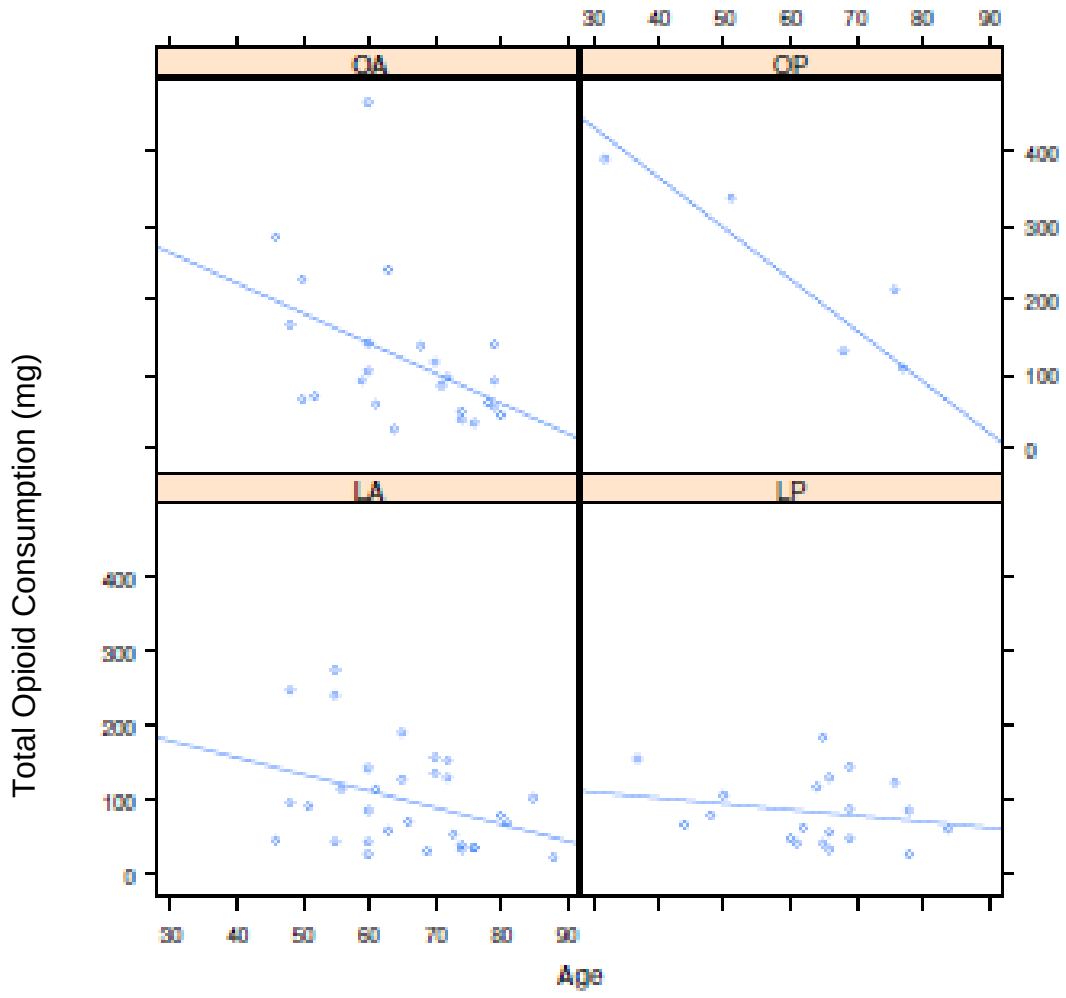

Figure 31: The effect of age by treatment group on total opioid consumption.

Daily Opioid Consumption

Figure 32 shows the effect of age on daily opioid consumption between the treatment groups when the patients were split into the four different age groups of approximate equal size. There were no differences between treatment type in the 61 to 68, 68 to 76 and 76 to 88 age groups although it was only apparent in the 32 to 61 age group that the open placebo group was different to the others.

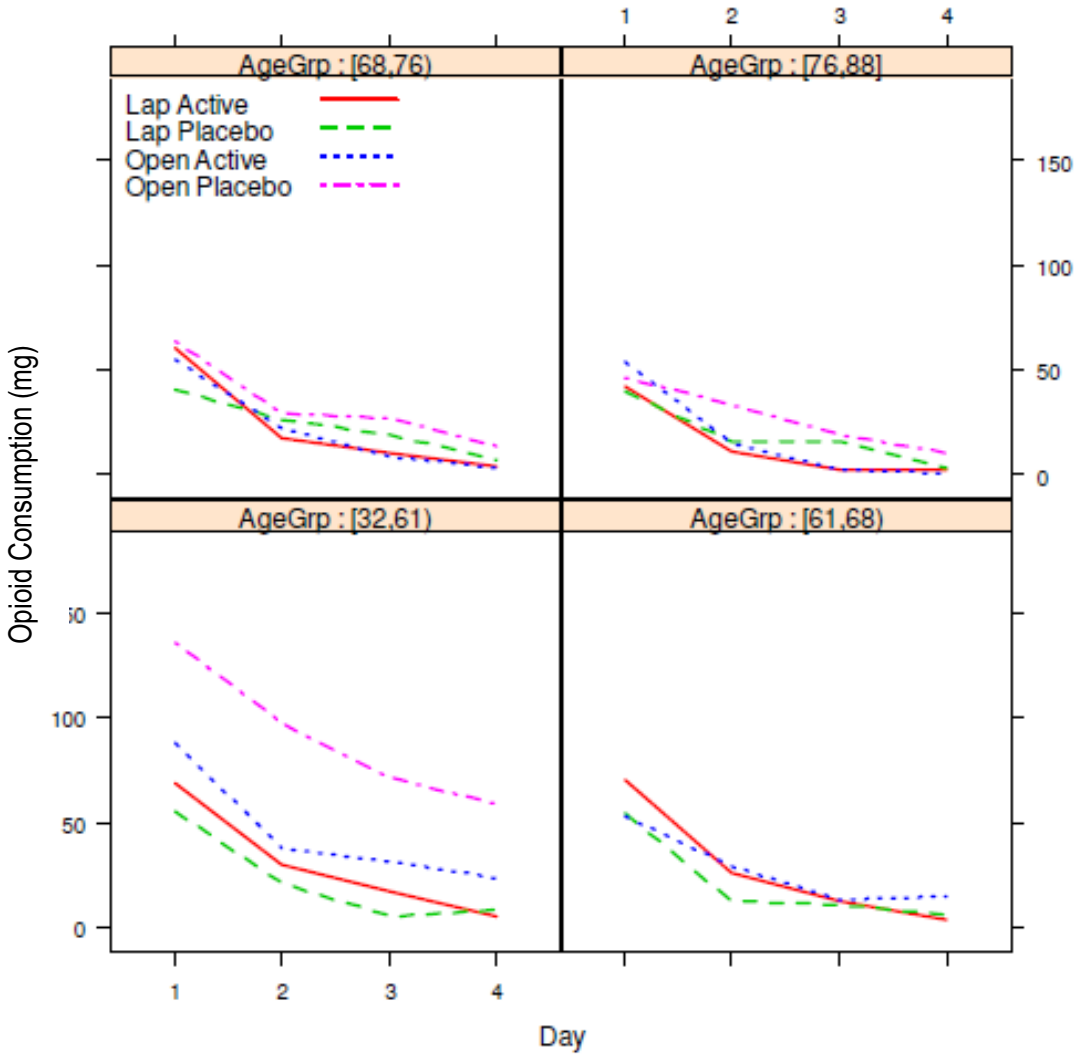

Figure 32: Opioid consumption by day by age group. (Note: The notation [32, 61] indicates that the interval is 'closed' at the lower end but 'open' at the upper end, so it includes ages 32.0 up to 60.99. The next interval [61, 68] includes ages 61.0 to 67.99 and so on. The final interval [76, 88] is closed at both ends, so includes 76.0 to 88.0)

4.3.5 BMI

Total Opioid Consumption

Figure 33 displays the relationship between total opioid consumption and BMI. The relationship between total opioid consumption and BMI was similar between the two laparoscopic and open active groups; however this was not the case in the open placebo group. When this group was excluded from the analysis, there was no significant relationship between opioid consumption and BMI.

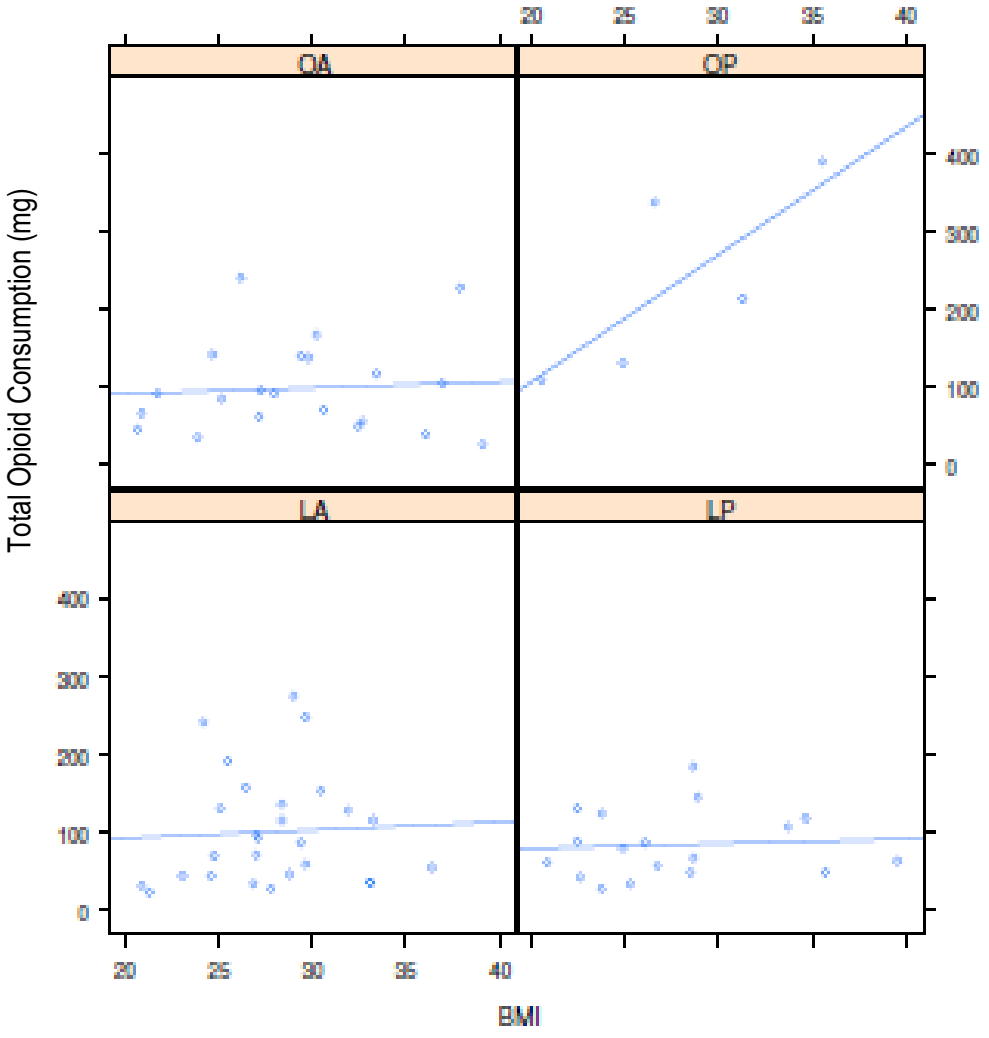

Figure 33: The relationship between total opioid consumption and BMI of the treatment groups.

4.3.6 Incision Length

The relationship between incision length and total opioid consumption between the treatment groups is shown in Figure 34. The mean incision length for laparoscopic operations is 8.1 cm whereas open operations had a mean incision length of 24.9 cm ($p < 0.001$). There was no significant difference between incision length for the active and placebo treatment for either the laparoscopic or open procedures.

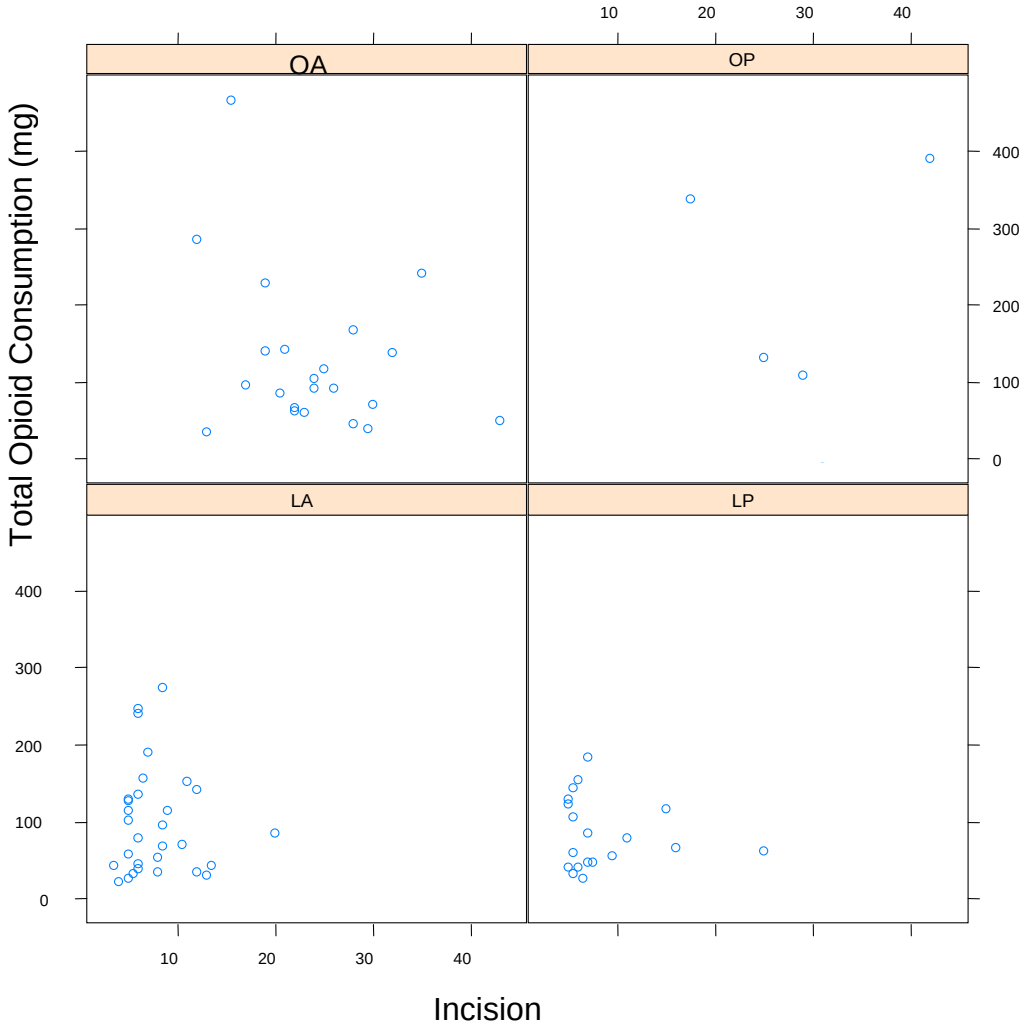

Figure 34: The relationship between total opioid consumption and incison length. (Note: incision length data missing from one patient in the open placebo group).

4.3.7 Duration

The relationship between the duration of surgery and total opioid consumption between the four groups is shown in Figure 35. A significant relationship was evident between the total opioid consumption and the duration of surgery only in the laparoscopic active group.

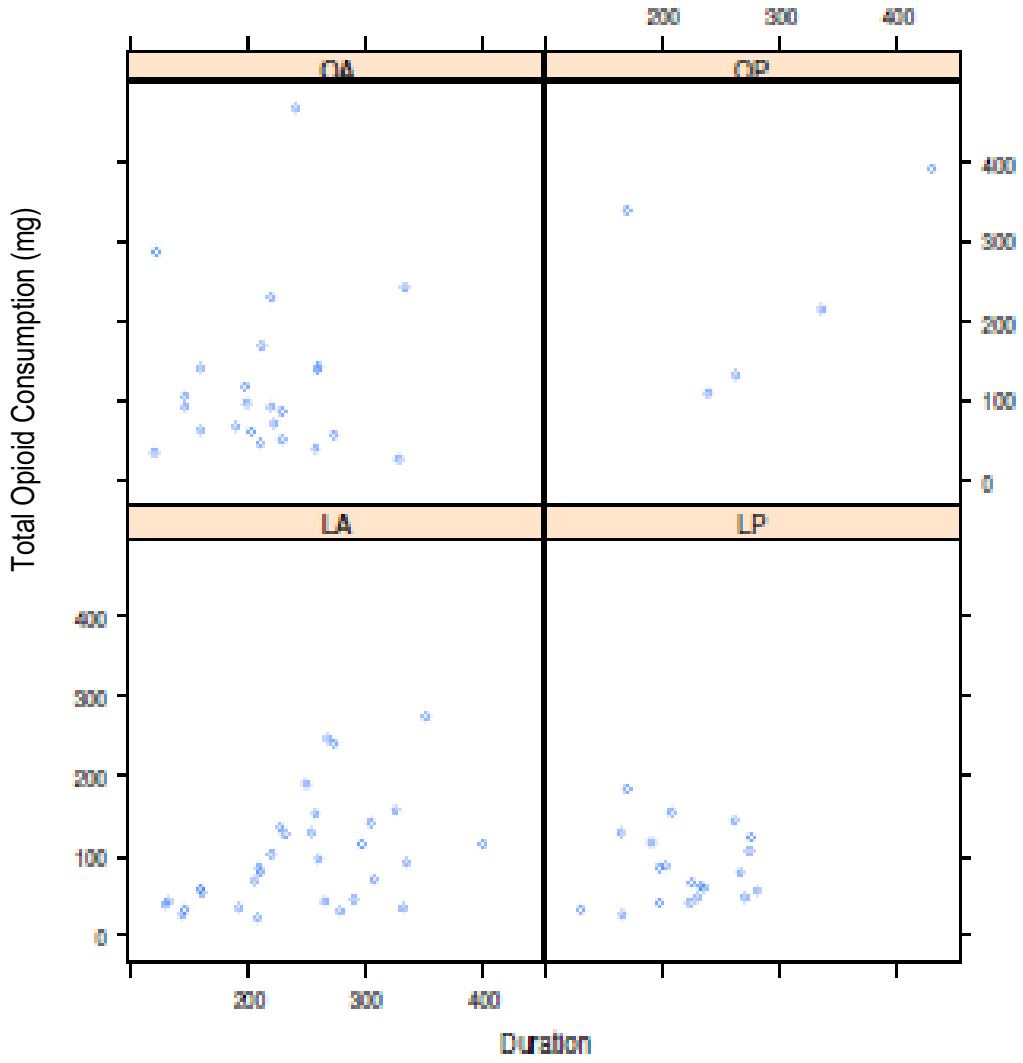

Figure 35: The relationship between total opioid consumption and duration of surgery.

4.3.8 Summary

A model can be fitted to the total opioid consumption using the four treatment groups and the various co-variates, although due to missing values several of the variables with small numbers can't be used. Therefore, the incision length and duration of surgery were omitted from the model. Hence, treatment, age, gender, BMI, stoma and drain were used as co-variates. The resulting regression accounted for 41% of the variation in total opioid consumption. When the numbers of variables that have been fitted were considered, an adjusted R^2 of 33.6% was evident. Significant effects were apparent for treatments and age. The treatment effect was due to the difference of the open placebo group from the other treatments, however if this group was omitted and the model refitted, the significant treatment effect disappears. The partial R^2 values which show the contribution of each variable in the model is presented in Figure 36.

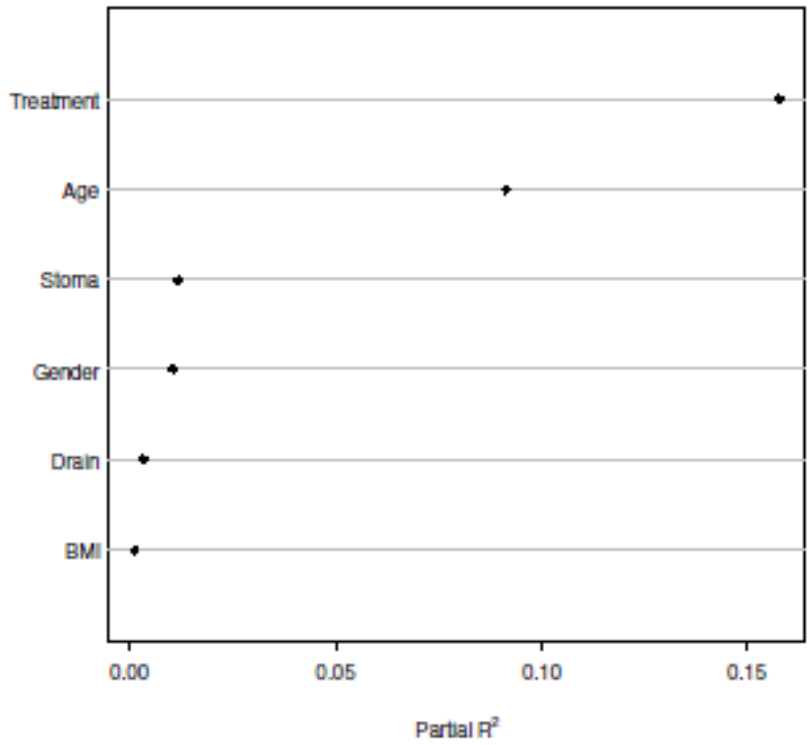

Figure 36: Partial R^2 plot for regression of total opioid consumption.

It is evident that treatment type and age are the main contributing factors. Figure 37 displays the R^2 plot when the open placebo group is omitted.

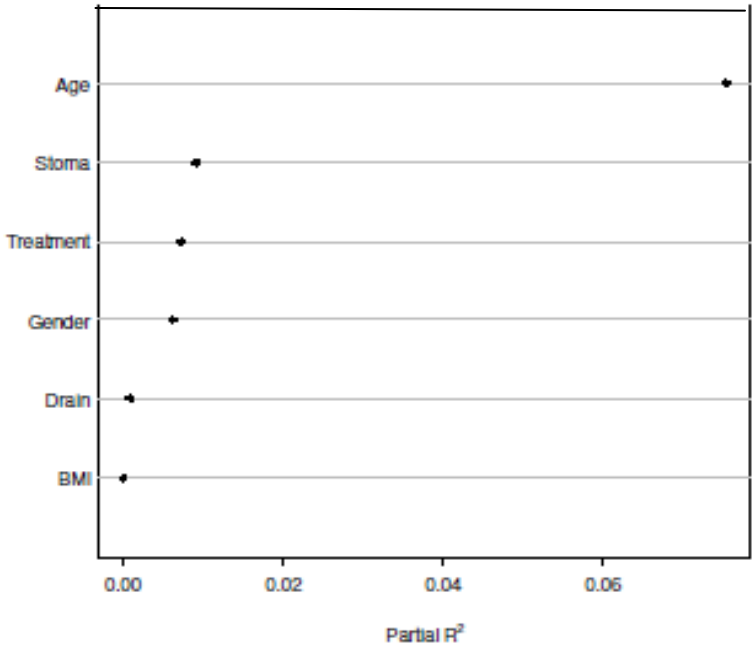

Figure 37: Partial R^2 plot when the open placebo group is omitted.

Similar results were applied to the daily opioid consumption as shown in Table 29. There were no other significant effects present in any other regressions.

Table 29: Significance levels for treatment and age in regressions with and without the open placebo group.

Opioid Consumption	All 4 treatments		Omitting Open Placebo	
	Treatment effect	Age effect	Treatment effect	Age effect
Total	P=0.002	P=0.003	P=0.78	p=0.03
Day 1	P=0.16	P=0.04	P=0.39	p=0.06
Day 2	P=0.003	P=0.01	P=0.75	p=0.04
Day 3	P=0.001	P=0.04	P=0.82	p=0.24
Day 4	P=0.004	P=0.003	P=0.69	p=0.06

In essence, once age was adjusted for, there was no significant difference in opioid consumption between the laparoscopic active, laparoscopic placebo and open active groups. The open placebo group, which only had data for 5 patients, was different.

4.4 Opioid Demand

Total Opioid Demand

The total opioid demands, i.e. the number of times the patient pressed the PCA button and/or requested oral oxycodone are displayed in Table 30. The lowest demand for opioids was in the laparoscopic placebo group while the open placebo group had the highest demand for opioids. An analysis of variance showed a significant difference (p= 0.012) between the four treatment groups.

Table 30: Total opioid demand of the four treatment groups.

	Laparoscopic Active (n= 31)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 5)**
Total Opioid Consumption	137.7 ± 21.23	91.35 ± 18.12	157.5 ± 27.82	286.0 ± 87.12
Range	28- 433	5- 315	15- 534	0- 580

Table 31: Total effective demand of the four treatment groups.

	Laparoscopic Active (n= 31)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 5)**
Total Effective Demand	79	70	108	139
% Difference Between Doses Demanded and Received	42%	23%	31%	51%

The total effective demand, i.e. the doses actually delivered to the patients in response to their demand is shown in Table 31. The percentage of unsuccessful demands, with no dose administered was 42% in the laparoscopic active group, 23% in the laparoscopic group, 31% in the open active group and 51% in the open placebo group.

Daily Opioid Demand

Table 32 displays the daily opioid demand data for the patients by treatment group. Opioid demand decreases over time in all the four treatment groups. The laparoscopic placebo group had a lower daily demand for opioids compared to the laparoscopic active group on all days apart from post-operative day 4, where the demand was the same. The open placebo group had a higher demand for opioids on all days in comparison to the open active group.

Table 32: The mean daily opioid consumption by the four treatment groups.

Daily Opioid Consumption	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 5)	Significance
Day 1	97.48 ± 14.49 (25- 308)	59.20 ± 10.91 (0.0- 177)	101.6 ± 16.03 (14- 385)	131.6 ± 19.24 (99- 207)	p= 0.1082
Day 2	26.00 ± 5.93 (0.0- 121)	23.95 ± 9.51 (0.0- 190)	29.04 ± 6.18 (0- 102)	103.2 ± 29.57 (35- 195)	p= 0.0005
Day 3	11.4 ± 3.91 (0.0- 82)	6.05 ± 2.21 (0- 41)	14.50 ± 5.58 (0- 125)	65.00 ± 19.28 (0- 117)	P< 0.0001
Day 4	2.48 ± 1.01 (0- 24)	2.15 ± 1.18 (0- 23)	12.92 ± 8.29 (0- 193)	43.40 ± 26.66 (2- 147)	p= 0.0106

The reason for the significant difference was due to the small sample size in the open placebo group and the demand for the open placebo group being greater than the other three treatment groups. This is further analysed by looking at the effects of the stoma, gender and age.

4.5 The Effects of the Co-Variates on Total Opioid Demand

The total and daily opioid demand data and its effect on stoma, gender, age and incision length are further explored.

4.5.1 Stoma

Total Opioid Demand

The patients mean opioid demand by the presence of stoma is displayed in Table 33 and shown in Figure 38. All patients who had stomas, apart from the laparoscopic placebo group had a higher demand for opioids compared to patients who did not have stomas. A significant difference was apparent in patients that had stomas in the four treatment groups (p= 0.048; analysis of variance).

Table 33: The average total opioid demand by the four treatment groups with the presence of a stoma.

Stoma	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo	Significance
No	128.5 (n=23)	92.8 (n=19)	148.5 (n=13)	69.5 (n=1)	P=0.47
Yes	164.3 (n=8)	64.0 (n=1)	168.2 (n=11)	394.3 (n=4)	P=0.048

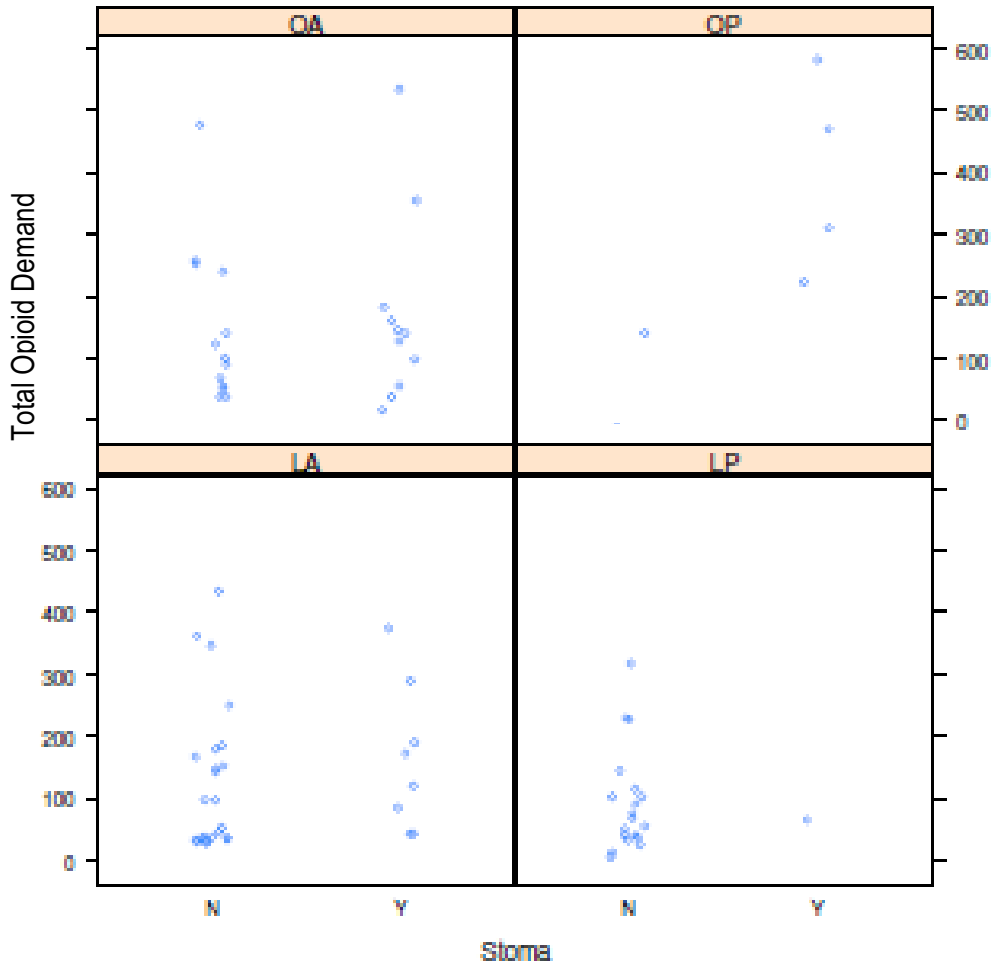

Figure 38: Total opioid demand by the presence of a stoma amongst the four treatment groups.

Daily Opioid Demand

Figure 39 displays the daily opioid demand over the 96 hr period in patients with and without a stoma in the four treatment groups. The opioid demand is similar between the laparoscopic active, laparoscopic placebo and open active patients regardless if they have a stoma or not. However, patients in the open placebo group who had stomas had a much higher demand for opioids than those without stomas. A repeated measures analyses of variance using a Greenhouse-Geisser adjustment (separate analyses for stoma and no stoma groups) displayed no significant interaction between the four treatment groups over time (p= 0.26; no stoma patients, p= 0.30; stoma patients). There was a

significant treatment effect for the stoma group (p= 0.048) that was not apparent in patients in the no-stoma group (p= 0.47).

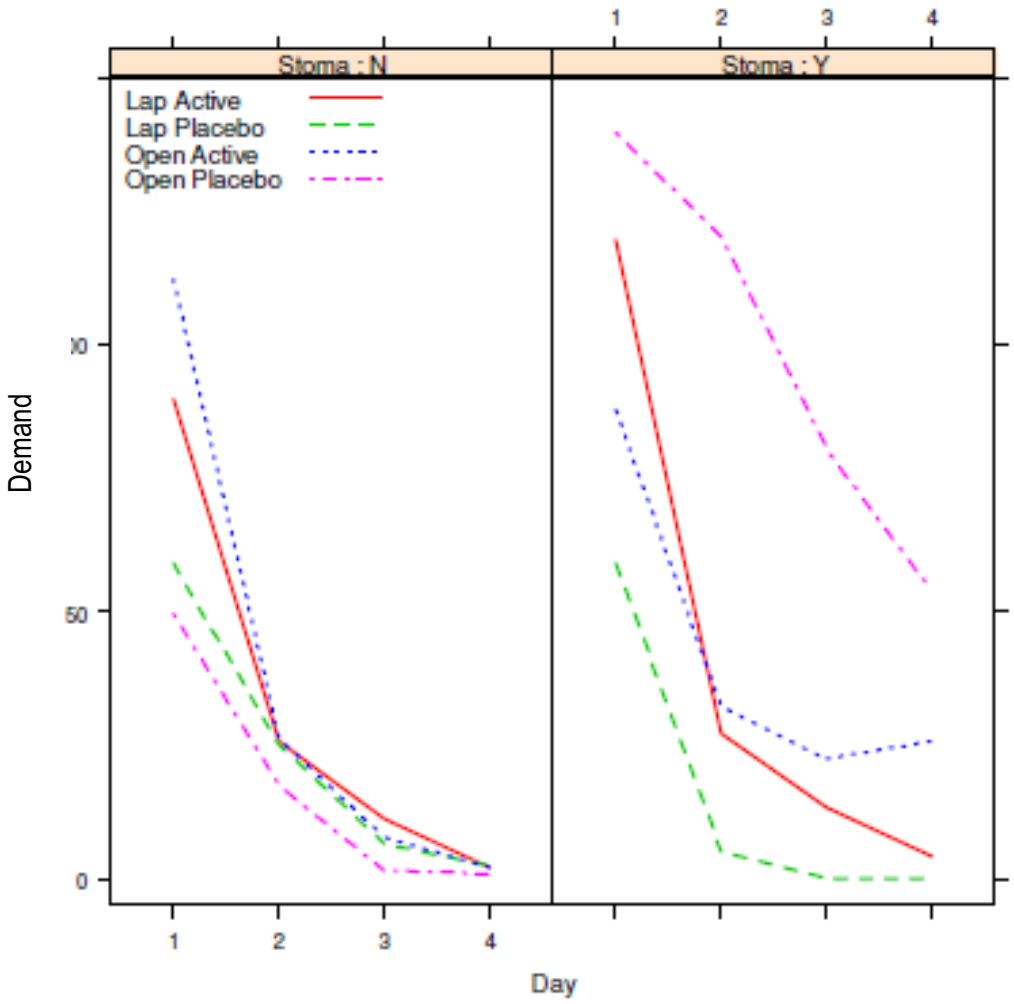

Figure 39: Opioid demand over time by stoma presence.

The means and the significance levels for the analysis of variance at each time-point of the four treatment groups are displayed in Table 34. Significant differences were evident in the stoma group on day 2 and 3 post-operation, where the demand for opioids was much higher in the open placebo group compared to the other three groups.

Table 34: The mean daily opioid demand by stoma presence amongst the four treatment groups.

No stoma					
Day	**Laparoscopic Active (n= 23)**	**Laparoscopic Placebo (n= 19)**	**Open Active (n= 13)**	**Open Placebo (n= 1)**	**Significance**
1	89.8	59.2	112.3	49.5	P=0.24
2	25.6	24.9	26.3	17.5	P=0.99
3	11.2	6.4	7.8	1.5	P=0.72
4	1.9	2.3	2.1	1.0	P=0.98
Stoma					
Day	**Laparoscopic Active (n= 8)**	**Laparoscopic Placebo (n= 1)**	**Open Active (n= 11)**	**Open Placebo (n= 4)**	**Significance**
1	119.6	59.0	87.7	139.8	P=0.39
2	27.1	5.0	32.3	120.3	P=0.004
3	13.4	0	22.5	80.5	P=0.01
4	4.1	0	25.7	53.8	P=0.40

4.5.2 Gender

Total Opioid Demand

Male patients had a higher demand for opioids compared to female patients across all four treatment groups. This is shown in Table 35 and Figure 40. An analysis of variance including treatment and gender showed a significant treatment effect (p= 0.06). However, this was driven by the open placebo group. If this group was omitted from the analysis, no significant treatment effect was present (p= 0.20).

Table 35: Mean total opioid demand by gender.

Gender	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo	Significance
Female	104.0 (n=14)	87.9 (n=10)	134.1 (n=10)	180.0 (n=2)	P=0.45
Male	165.5 (n=17)	94.8 (n=10)	174.2 (n=14)	339.0 (n=3)	P=0.06

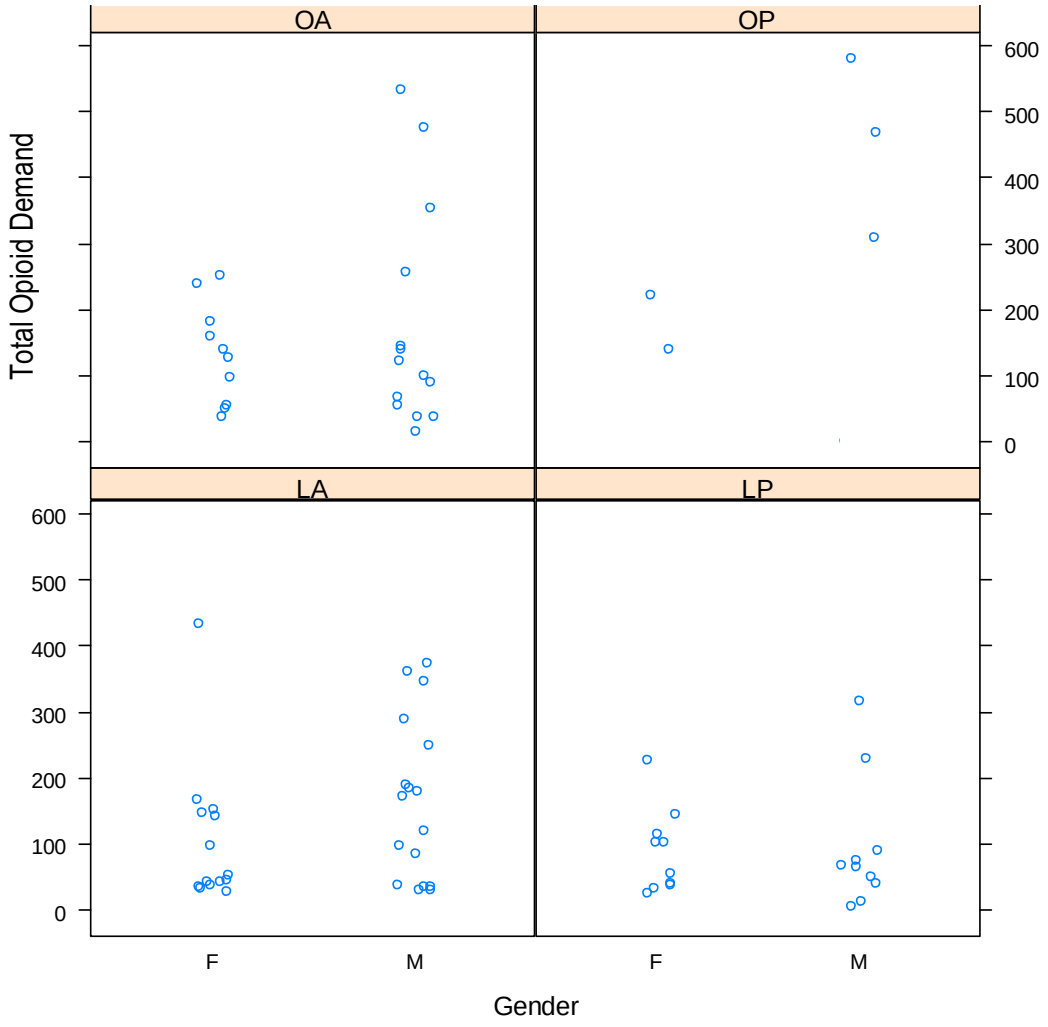

Figure 40: Total opioid demand by gender.

Daily Opioid Demand

The daily opioid demand by gender and the four treatment groups are displayed in Figure 41. Daily opioid demand was similar between gender among the laparoscopic active, laparoscopic placebo and open active groups however males in the open placebo group appear to demand more opioids across the 4 days. A repeated measures analysis of variance showed that there was a near significant treatment difference in male patients (p= 0.06), which was not apparent in female patients (p= 0.45).

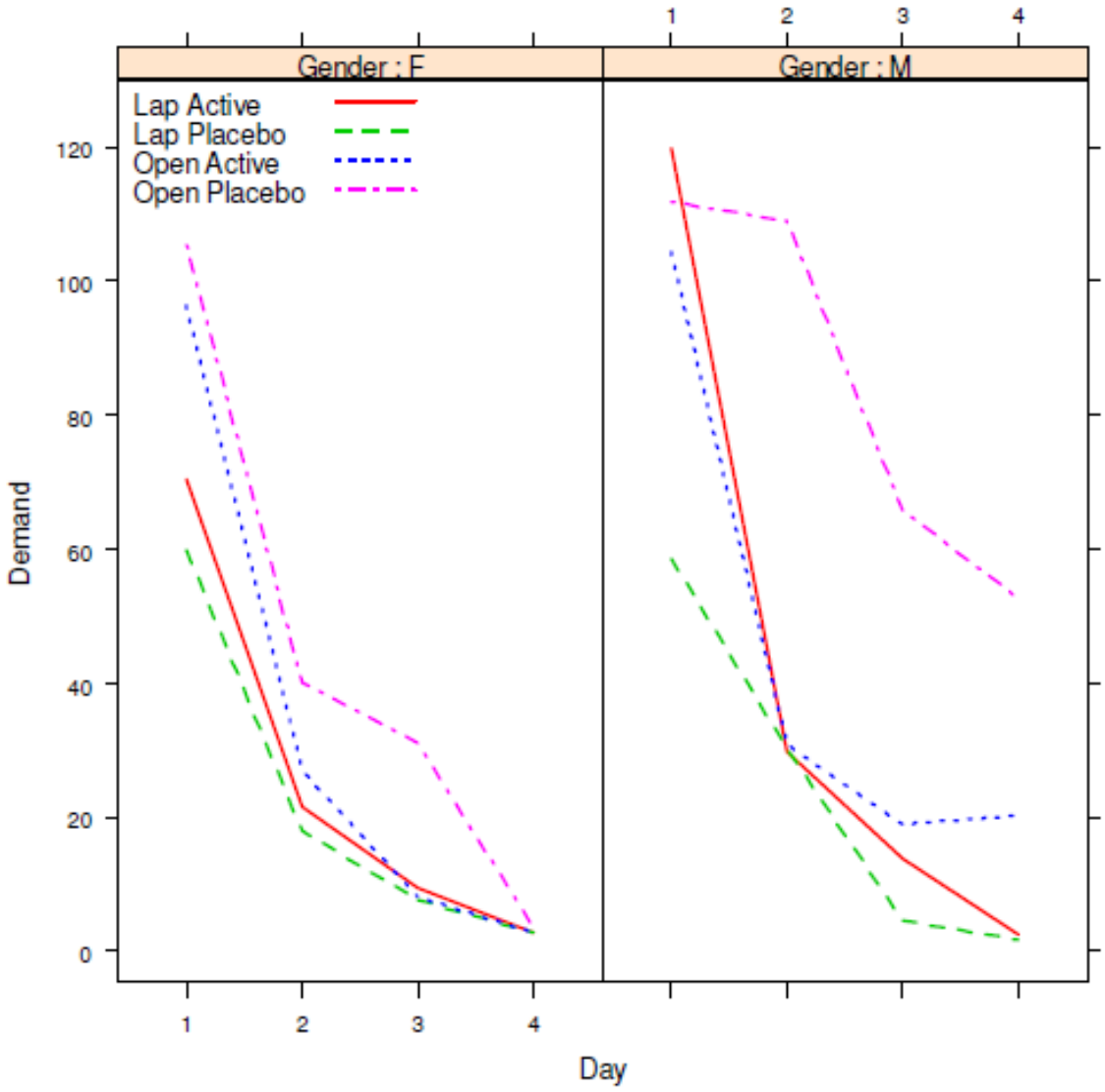

Figure 41: Opioid demand over time by gender.

Table 36 displays the analyses of variance results for each day. There were no significant differences present in female patients across the four treatment groups, although on post-operative day 2 and 3 males in the open placebo group requested significantly more opioids.

Table 36: Mean daily opioid demand by gender.

Female					
Day	**Laparoscopic Active (n= 14)**	**Laparoscopic Placebo (n= 10)**	**Open Active (n= 10)**	**Open Placebo (n= 2)**	**Significance**
1	70.4	59.8	96.3	105.5	P=0.36
2	21.6	17.8	26.8	40.0	P=0.67
3	9.4	7.6	8.2	31.0	P=0.32
4	2.6	2.7	2.8	3.5	P=1.00
Male					
Day	**Laparoscopic Active (n= 17)**	**Laparoscopic Placebo (n= 10)**	**Open Active (n= 14)**	**Open Placebo (n= 3)**	**Significance**
1	119.8	56.8	104.4	111.8	P=0.35
2	29.6	30.1	30.6	109.0	P=0.02
3	13.6	4.5	19.0	65.8	P=0.007
4	2.4	1.6	20.1	52.5	P=0.051

4.5.3 Age

Total Opioid Demand

It was apparent that total opioid demand decreases with increasing age. This effect of age on opioid demand is presented as linear regressions in Figure 42. The relationship between opioid demand and age varies with treatment. However, if the open placebo group was omitted from the analysis, the effect of age no longer varies with treatment. A regression of demand on age for the these three treatments show that demand is reduced by 3.5 ± 1.2 pushes of the PCA button/ requests for oral oxycodone for every year of age.

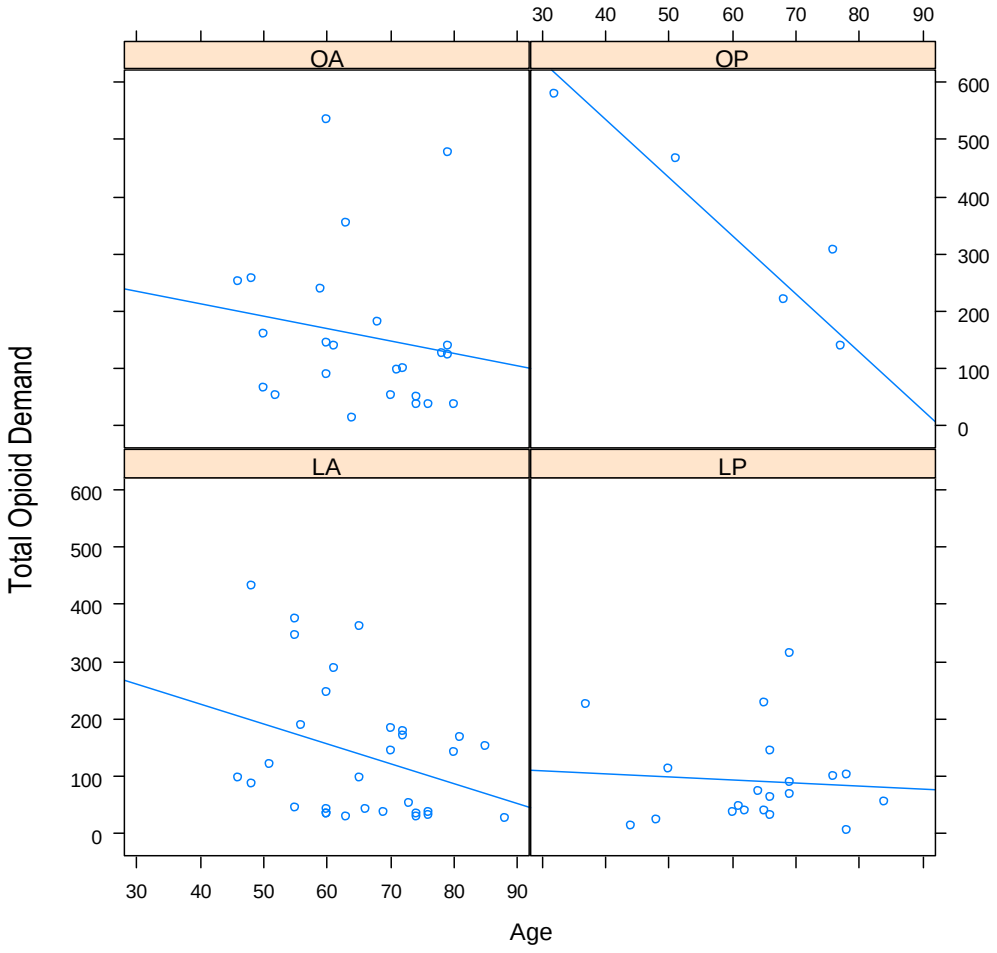

Figure 42: The effect of age on total opioid demand.

Daily Opioid Demand

Daily opioid demand by age is presented in Figure 43. On post-operative day 1 there was no significant relationship between opioid demand and age. On day 2, 3 and 4 post-operation the regression for the open placebo group was significant although this is not the case for the other three treatment groups.

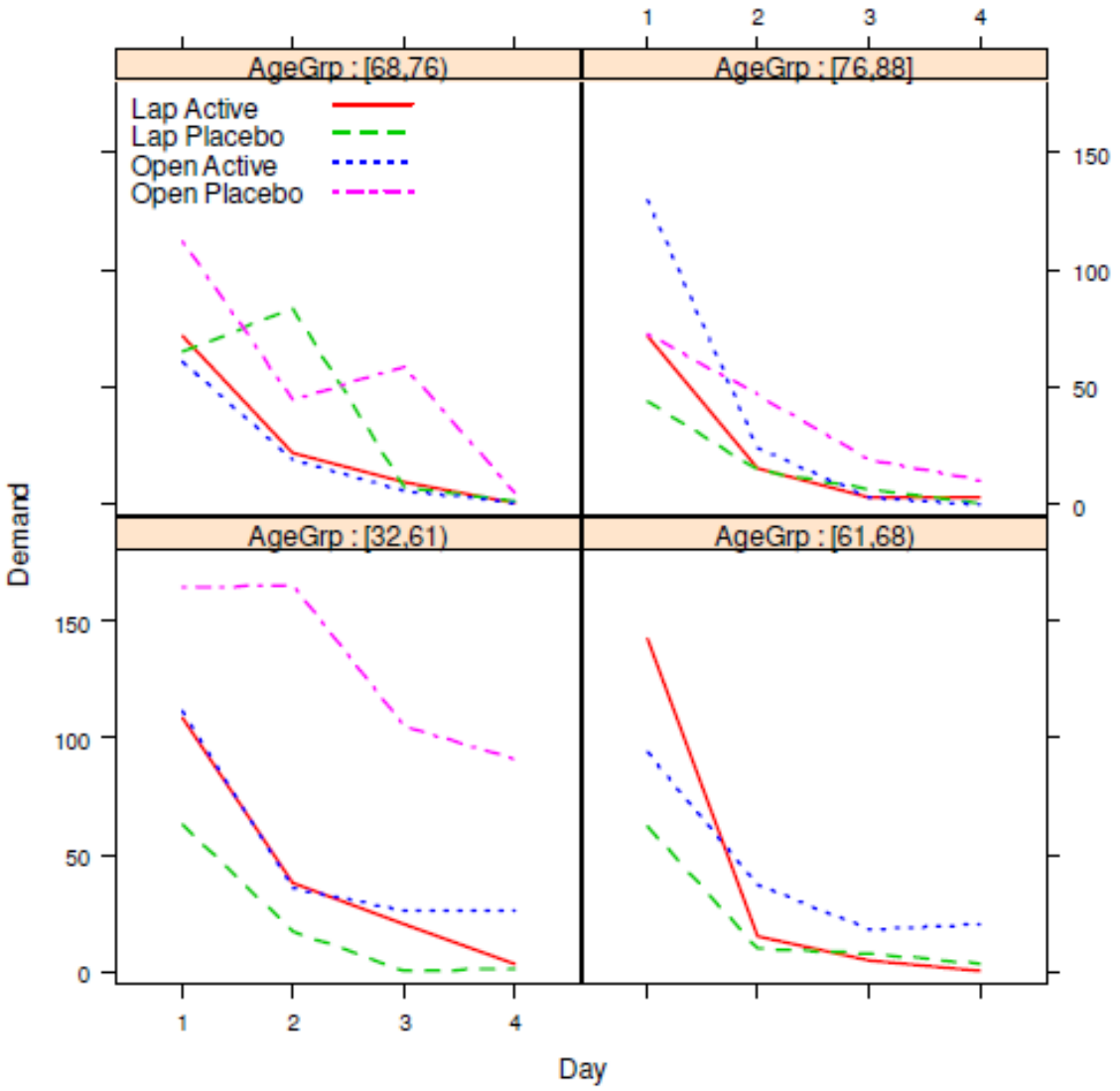

Figure 43: Opioid demand by day and age, with fitted regression lines. (Note: The notation [32, 61] indicates that the interval is 'closed' at the lower end but 'open' at the upper end, so it includes ages 32.0 up to 60.99. The next interval [61,68] includes ages 61.0 to 67.99 and so on. The final interval [76.88] is closed at both ends, so includes 76.0 to 88.0).

4.5.4 Incision Length

The relationship between incision length and total opioid demand is presented in Figure 44. There was no significant relationship evident between total opioid demand and incision length for either laparoscopic or open surgery.

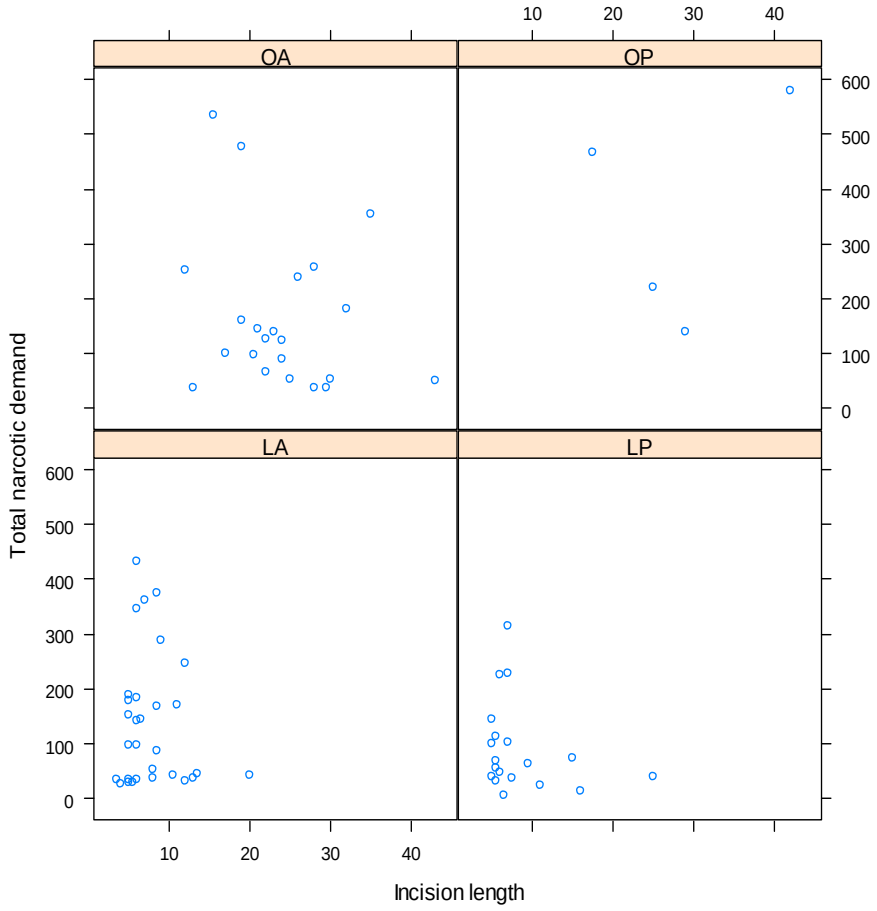

Figure 44: Total opioid demand and incision length (note: only four values in open placebo group due to missing incision length data in one patient).

4.5.5 Summary

A model can be fitted to the total opioid demand using the treatments and co-variates. The resulting regression accounts for 26% of the variation in total opioid demand. If the number of variables that have been fitted are taken into account, there was an adjusted R^2 of 20%. Significant effects of treatment and age were evident, although the treatment effect was due to the difference of the open placebo group from the other three treatment groups. The significant treatment effect disappears once the open placebo group was excluded. The partial R^2 values, which show the contribution of each variable in the model, are displayed in Figure 45.

In relation to daily opioid demand, similar results are applicable. The significance levels for age and treatment are displayed in Table 37. Gender and stoma presence were not significant in any regression.

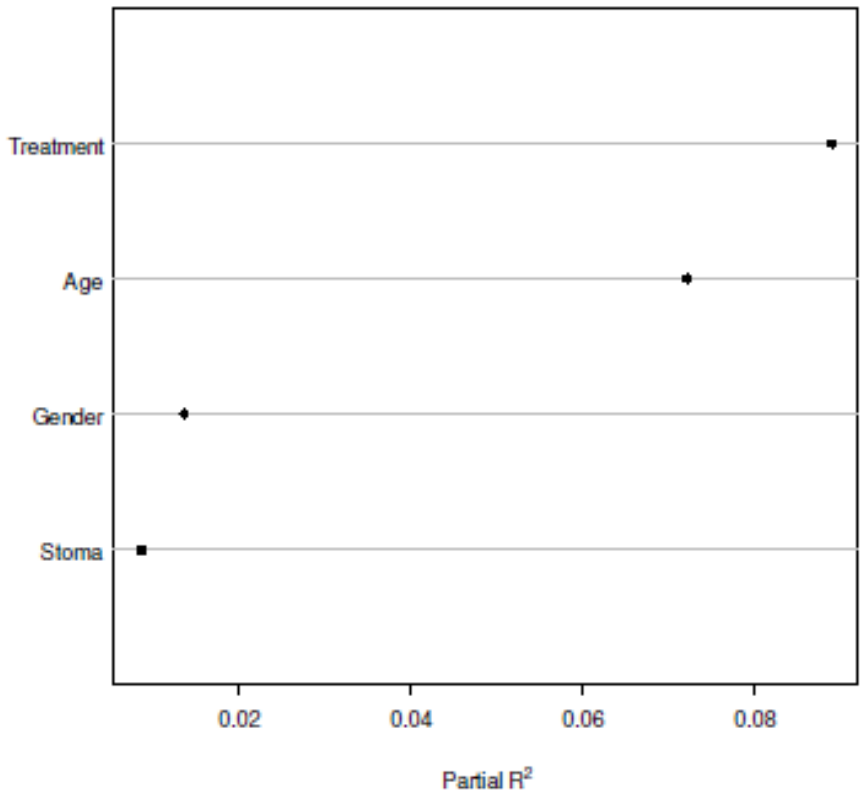

Figure 45: Partial R^2 plot for regression of total opioid demand.

Table 37: Significance levels for the four treatment types and age in opioid demand regressions.

Opioid Demand	All Four treatments		Omitting Open Placebo Group	
	Treatment effect	**Age effect**	**Treatment effect**	**Age effect**
Total	P=0.04	P=0.009	P=0.24	P=0.12
Day 1	P=0.23	P=0.08	P=0.12	P=0.15
Day 2	P=0.01	P=0.03	P=0.90	P=0.34
Day 3	P=0.003	P=0.01	P=0.63	P=0.19
Day 4	P=0.13	P=0.06	P=0.45	P=0.62

CHAPTER 5: PAIN SCORE RESULTS

CHAPTER 5: PAIN SCORE RESULTS

This Chapter presents the results for the patients' pain scores at rest, the effect of the stoma, patient gender and age on the pain scores at rest and pain scores with movement over the 96 hr infiltration period. The ethical basis of this trial was that no patient would be subjected to additional pain by virtue of consenting to participate, as established PCA practices were available to all, whether in the active or placebo arms of either surgical technique (open or laparoscopic).

5.1 Pain Scores at Rest

The pain scores at rest are displayed in Table 38. Across all time-points, except for the 6 hr time-point, the open placebo group had the highest mean pain score. The laparoscopic active group had a higher mean pain score compared to the laparoscopic placebo group at the 6, 12, 48 and 72 hr time-points, whereas the open active group had lower levels of pain compared to the open placebo group across all time-points. The only significant difference is at the at the 24 hr mark, where the mean pain score for the open placebo group is significantly greater than the laparoscopic active group (p= 0.015; Tukey's test).

Table 38: Pain scores at rest (number of patients) by the four treatment groups.

Hour Post-Operative	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo	Significance
6	2.3 (30)	1.5 (20)	1.7 (23)	2.0 (6)	p=0.65
12	1.6 (29)	0.7 (19)	1.2 (22)	3.2 (6)	p=0.08
24	1.4 (31)	2.3 (20)	2.4 (23)	4.3 (6)	p=0.02
48	2.0 (29)	1.6 (19)	2.0 (23)	3.2 (6)	p=0.48
72	1.2 (25)	1.0 (18)	1.8 (19)	2.4 (5)	p=0.30
96	0.9 (24)	0.9 (15)	1.6 (18)	2.4 (5)	p=0.16

Figure 46 shows the time trend for pain at rest for each of the four treatment groups. The laparoscopic placebo, open active and open placebo group had a peak pain score at 24 hr post-operation, whereas the laparoscopic active group peaked at the 48 hr mark. The level of pain is similar between the two laparoscopic groups; however the difference in pain is greater in the open placebo group compared with the open active group.

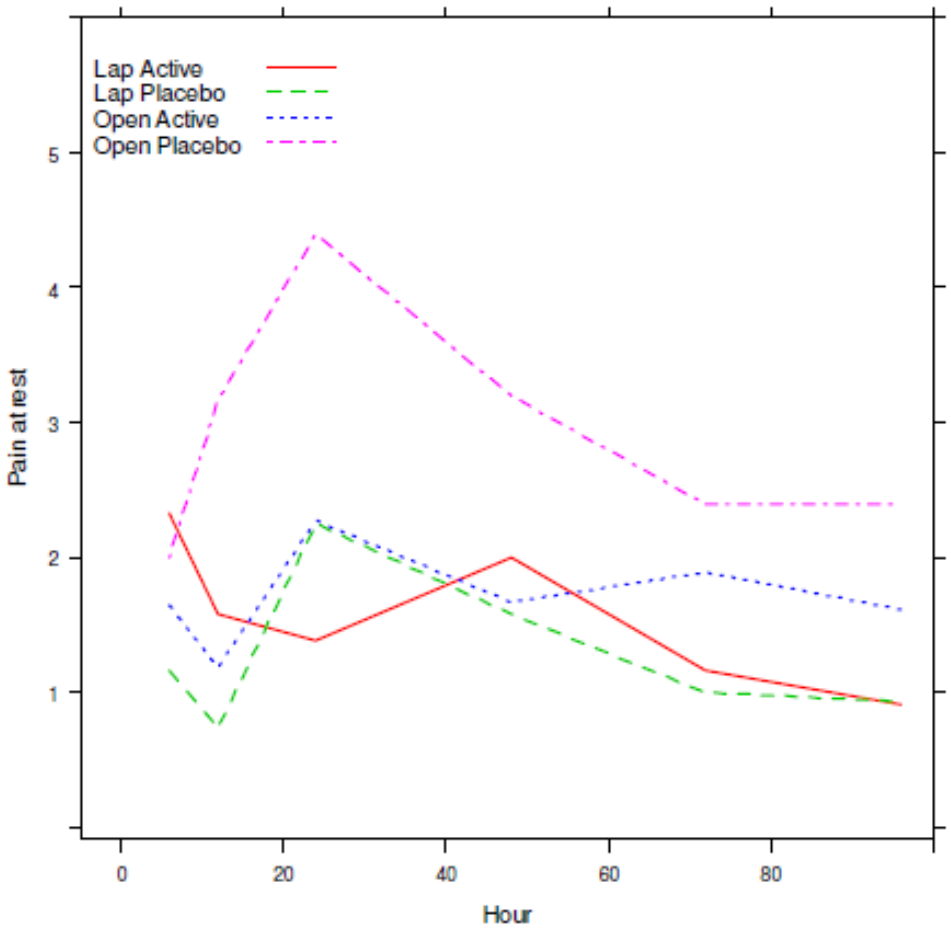

Figure 46: Pain at rest by the four treatment groups (p= 0.015 laparoscopic active and open placebo groups)

It is also interesting to note that the open active group had a similar level of pain to the two laparoscopic groups. The level of pain in the open placebo group is indicative of what patients would experience without the local anaesthetic treatment and reflects the current "status quo" of such surgery

(i.e. patients having cancer resection with open surgery). The only significant difference is at the 24 hr time-point as shown above. A repeated measures analysis of variance using a Greenhouse-Geisser adjustment shows non-significant effects for treatments (P=0.20), and the treatment type and time interaction (P=0.14).

5.2 The Effect of the Co-variates on Pain Scores at Rest

The effect of the presence or absence of a stoma, gender differences of the patients and age were further analysed to investigate their relationship with pain scores at rest.

5.2.1 Stoma

The mean pain scores at rest with either the presence or absence of a stoma are presented in Table 39 and shown graphically in Figure 47. There are significant differences between the non-stoma treatments at 24, 48, 72 and 96 hr post-operation. An analysis of all the pain at rest data at once uses a repeated measurements analysis of variance with a Greenhouse-Geisser adjustment. A significant difference was evident with the time and stoma effect (p= 0.006). This is further explained in Figure 48, where the two groups had similar levels of pain at 6 and 12 hr but then the patients with stomas experience higher levels of pain at the 24, 48, 72 and 96 hr time-points. The patients without a stoma experience their highest level of pain at 24 hr post-operation, whereas the peak level is reached at the 48 hr time-point in stoma patients.

Table 39: Pain at rest (number of patients) by hour and stoma (N= no stoma present; Y= stoma present).

Hour	Stoma	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 6)	Significance
6	N	2.2 (23)	1.5 (14)	1.8 (14)	2.0 (4)	P=0.89
	Y	2.9 (7)	1.5 (6)	1.4 (9)	2.0 (2)	P=0.69
12	N	1.5 (22)	0.6 (13)	1.2 (13)	3.5 (4)	P=0.13
	Y	1.7 (7)	1.0 (6)	1.2 (9)	2.5 (2)	P=0.79
24	N	1.4 (24)	2.1 (14)	2.2 (14)	4.8 (4)	P=0.05
	Y	1.4 (7)	2.7 (6)	2.7 (9)	3.5 (2)	P=0.56
48	N	1.3 (23)	0.9 (13)	1.4 (14)	3.8 (4)	P=0.04
	Y	4.5 (6)	3.0 (6)	3.0 (9)	2.0 (2)	P=0.52
72	N	1.1 (20)	0.2 (12)	1.6 (12)	3.0 (4)	P=0.03
	Y	1.4 (5)	2.7 (6)	2.1 (7)	0.0 (1)	P=0.44
96	N	0.9 (20)	0.3 (10)	1.8 (11)	2.5 (4)	P=0.06
	Y	1.0 (4)	2.2 (5)	1.3 (7)	2.0 (1)	P=0.49

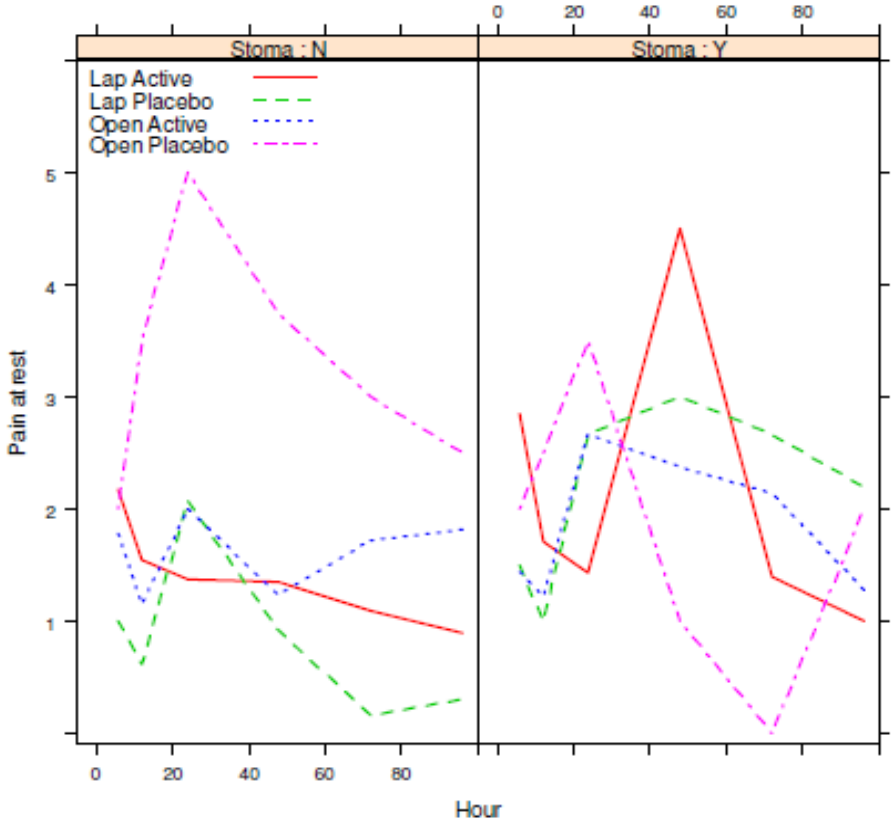

Figure 47: Pain at rest with and without the stoma among the four treatment groups.

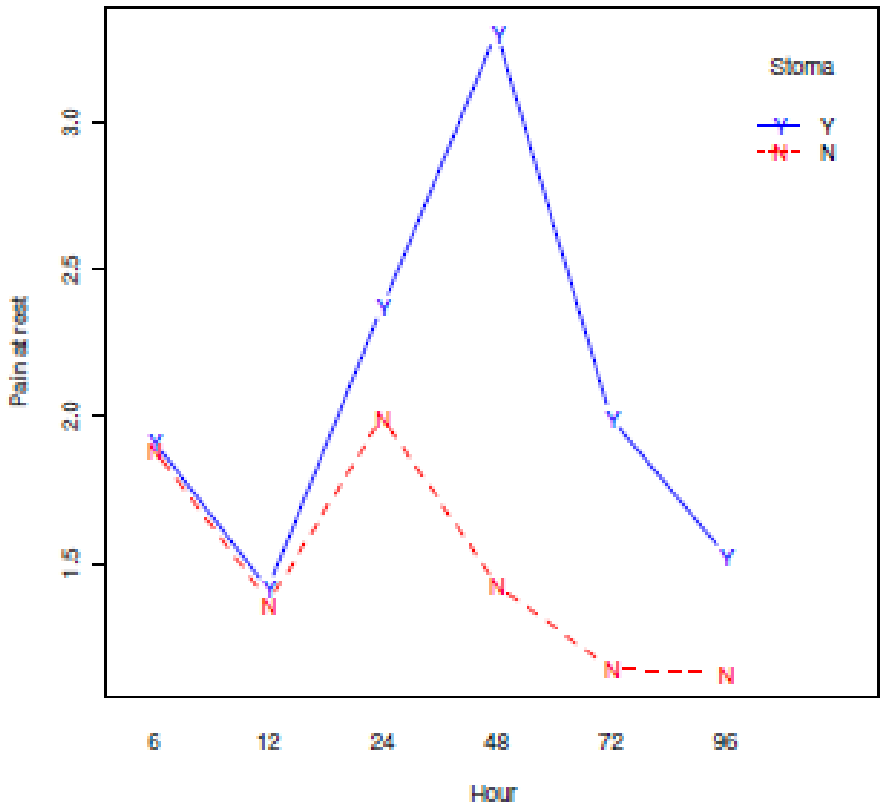

Figure 48: The pain scores at rest in patients with and without stomas (Y= stoma present; N= stoma absent; time and stoma effect- p= 0.06).

5.2.2 Gender and Pain Scores at Rest

Table 40 and Figure 49 show the pain scores at rest by gender. In the laparoscopic active group females had higher pain levels than the males at all time-points except for 6 hr and 48 hr post-operation. In the laparoscopic placebo group females' experienced greater pain than males at all time-points. This was even more obvious in the open active group. Furthermore females experienced less pain than males in the open placebo group at 6 hr and 12 hr post-operation; however, they experienced more pain from the 24 hr to 96 hr time-point. The only significant analysis for males is at the 12 hr time-point (p= 0.006) where the open placebo group reported significantly greater pain than the other three groups. A repeated measures analysis of variance showed a significant difference between genders (p= 0.0053). The gender effect reflects the fact that pain at rest was generally rated higher by females than males.

Table 40: Pain scores at rest (number of patients) by gender.

Hour	Gender	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo	Significance
6	F	2.3 (14)	2.0 (10)	2.0 (10)	0.0 (2)	P=0.67
	M	2.4 (16)	1.0 (10)	1.4 (13)	3.0 (4)	P=0.40
12	F	1.7 (12)	1.2 (9)	1.7 (10)	0.5 (2)	P=0.85
	M	1.5 (17)	0.3 (10)	0.8 (12)	4.5 (4)	P=0.006
24	F	1.8 (14)	2.6 (10)	3.6 (9)	5.0 (2)	P=0.10
	M	1.1 (17)	1.9 (10)	1.6 (14)	4.0 (4)	P=0.12
48	F	1.9 (14)	2.3 (10)	3.3 (9)	4.5 (2)	P=0.27
	M	2.1 (15)	0.8 (9)	1.1 (14)	2.5 (4)	P=0.22
72	F	1.4 (12)	1.3 (9)	2.3 (8)	2.5 (2)	P=0.73
	M	0.9 (13)	0.7 (9)	1.5 (11)	2.3 (3)	P=0.36
96	F	1.3 (12)	1.4 (8)	2.4 (8)	4.0 (2)	P=0.19
	M	0.6 (12)	0.4 (7)	1.0 (10)	1.3 (3)	P=0.50

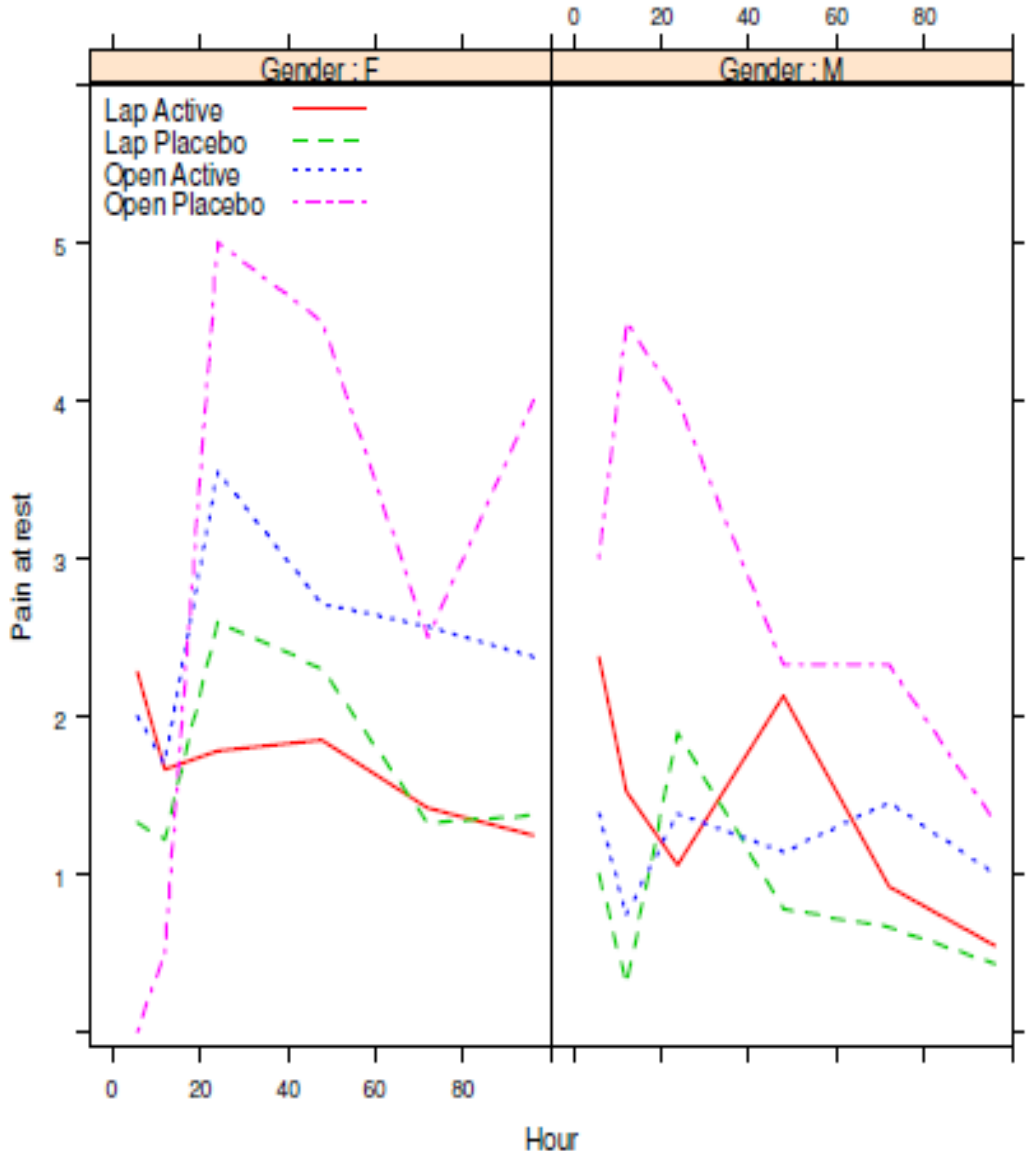

Figure 49: Pain at rest over time by gender.

5.2.3 Age

No relationship was evident between pain at rest and age. This is reinforced by Figure 50 which shows the relationship for each treatment between pain at rest and age at 24 hr post-operation, as an example.

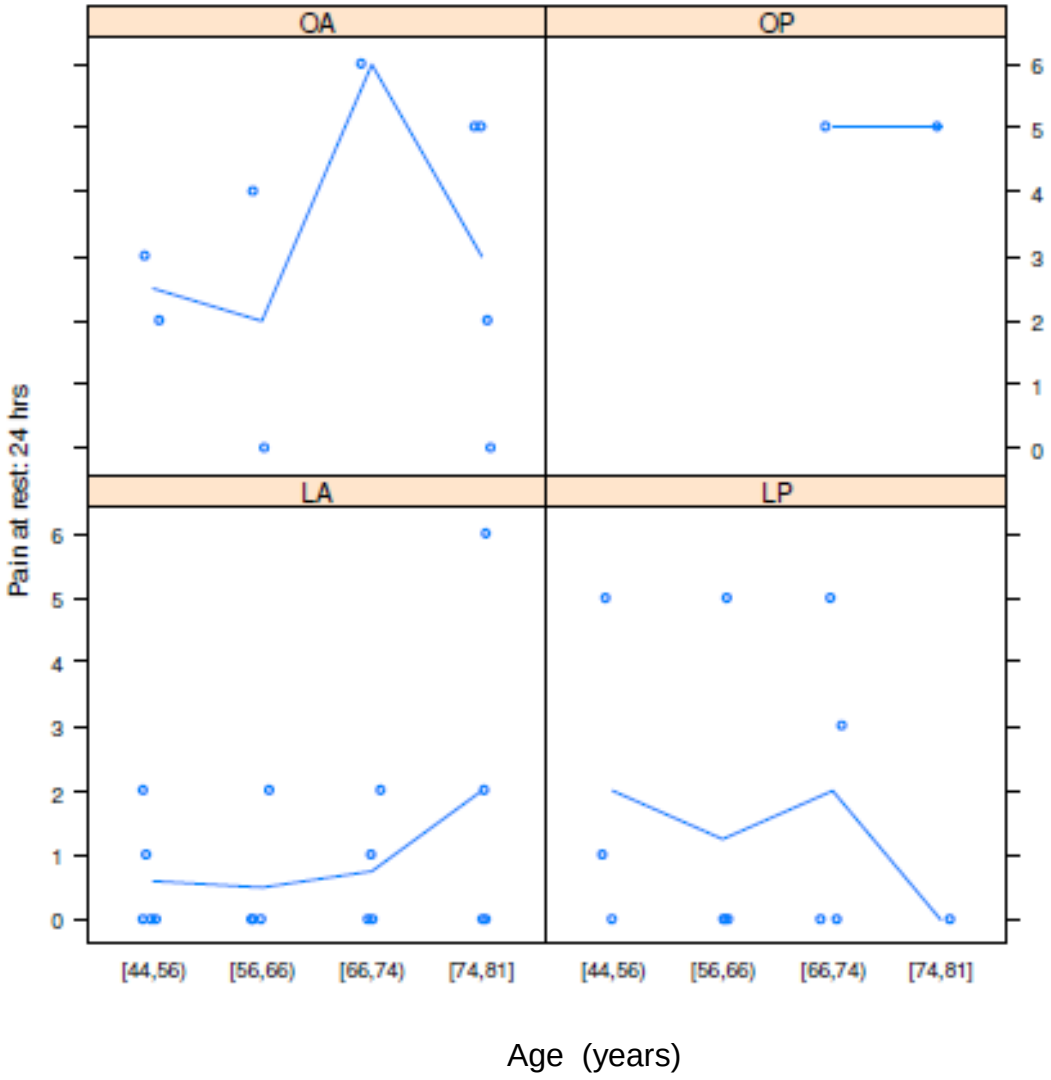

Figure 50: The relationship between pain scores at rest and age at the 24 hr time-point.

5.2.4 Summary

The above findings on the effect of the co-variates of stoma, gender and age on pain at rest are further summarised. Table 41 shows the levels of significance if pain is regressed at a particular time on treatment, age, gender and stoma. Each column is representative of one regression. The treatment is significant at 24 hr (p= 0.01) and approaches significance at 12 hr (p= 0.07) and 96 hr (p= 0.09). There is no significant difference apparent with age. Gender is significant at 24 hr (p= 0.02), 48 hr (p= 0.004) and 96 hr (p= 0.01) post-operation. There is also a significant effect of the stoma at 48 hr (p< 0.001) post-operation. Furthermore these results in Table 41 are consistent with the previous observations of pain scores and its co-variates above.

Table 41: The significance levels for regressions of pain at rest at individual times.

Effect	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr
Treatment	0.65	0.07	0.01	0.22	0.18	0.09
Age	0.81	0.18	0.38	0.84	0.17	0.65
Gender	0.74	0.40	0.02	0.004	0.12	0.01
Stoma	0.78	0.92	0.65	<0.001	0.12	0.36

5.3 Pain Scores With Movement

Table 42 displays the mean pain scores during movement. Significant differences were evident between the treatment groups at 6, 12 and 96 hr post-operation.

- At 6 hr, the level of pain for the laparoscopic active group was significantly greater than the laparoscopic placebo group (p= 0.02). Although this paradoxical result is explained above by the stoma issue.
- At 12 hr, an analysis of variance detected a difference among the treatments as a group, although Tukey's test cannot differentiate any two groups as being significantly different at p=0.05. Pain scores for both the laparoscopic active and open placebo groups are greater than the laparoscopic placebo group (p= 0.07).
- At 96 hr, the pain scores on movement for the open active group is significantly greater than the pain scores for both the laparoscopic active and laparoscopic placebo groups (p= 0.003).

As with the pain scores at rest, the open placebo group had the highest mean pain score on movement, however the small sample size indicates that it is not always significantly greater than the other groups.

Table 42: Pain scores on movement (number of patients) by treatment type.

Hour	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo .	Significance
6	4.1 (30)	1.9 (20)	2.8 (23)	5.0 (6)	P=0.02
12	3.3 (29)	1.6 (19)	2.9 (22)	4.3 (6)	P=0.04
24	3.7 (31)	3.8 (20)	4.5 (22)	5.6 (5)	P=0.41
48	3.9 (29)	3.2 (19)	3.9 (21)	4.2 (5)	P=0.68
72	2.4 (25)	2.3 (18)	3.7 (18)	4.2 (5)	P=0.10
96	1.4 (23)	1.7 (15)	3.3 (18)	3.6 (5)	P=0.003

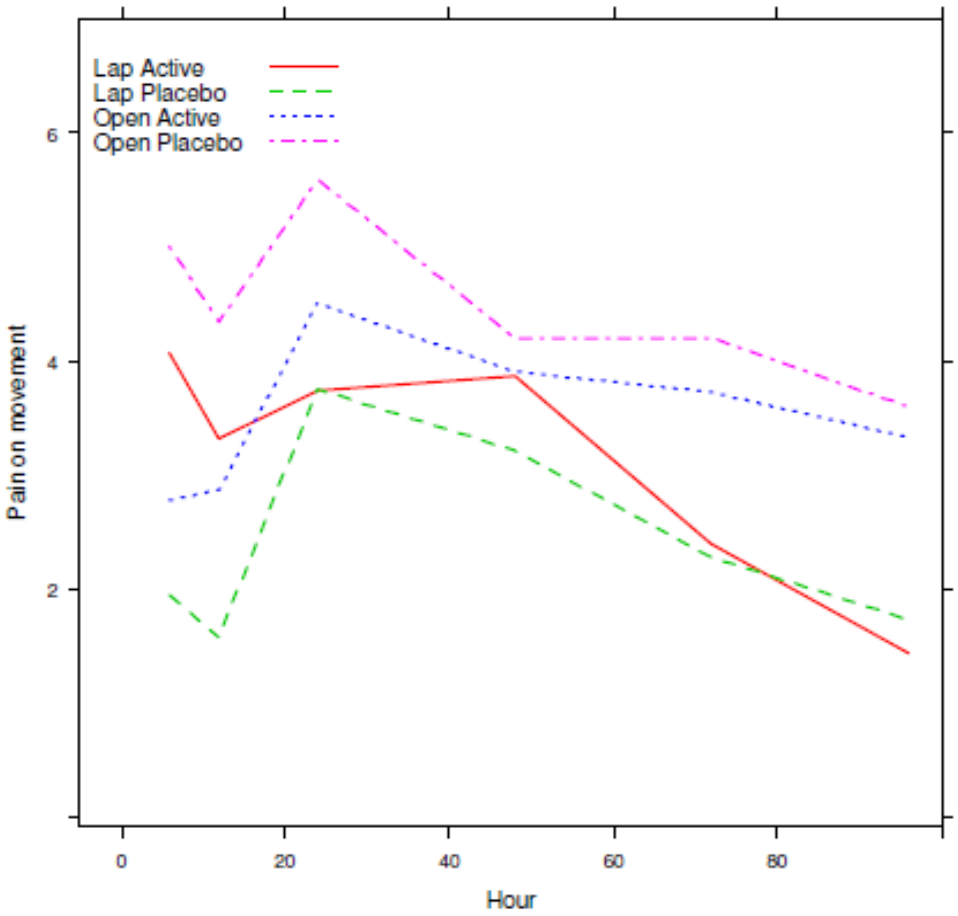

Figure 51: Pain scores on movement by treatment group.

5.4 The Effect of the Co-Variates on Pain Scores With Movement

Additional analyses were performed to detect for any potential relationships between pain scores during movement with the effect of the stoma, gender and age.

5.4.1 Stoma

The patients' pain scores during movement with the presence and absence of a stoma are presented in Table 43 and shown graphically in Figure 52. Significant differences were apparent in the pain scores with movement in patients who did not have a stoma at the 6 hr, 12 hr, 72 hr and 96 hr time-points, whereas in patients who had a stoma, the only significant difference was evident at 72 hr post-operation.

Table 43: Pain at rest (number of patients) by hour and stoma (N= no stoma present; Y= stoma present).

Hour	Stoma	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 6)	Significance
6	N	4.2 (23)	1.8 (13)	3.4 (14)	5.8 (4)	P=0.04
	Y	3.6 (7)	2.3 (6)	1.9 (9)	3.5 (2)	P=0.58
12	N	3.6 (22)	1.4 (13)	3.4 (13)	4.5 (4)	P=0.03
	Y	2.4 (7)	2.0 (6)	2.1 (9)	4.0 (2)	P=0.79
24	N	4.1 (24)	3.3 (14)	4.5 (13)	6.0 (3)	P=0.38
	Y	2.6 (7)	4.8 (6)	4.4 (9)	5.0 (2)	P=0.40
48	N	3.4 (23)	2.8 (13)	3.5 (13)	5.0 (4)	P=0.38
	Y	5.5 (6)	4.0 (6)	4.5 (8)	1.0 (1)	P=0.27
72	N	2.5 (20)	1.5 (12)	2.8 (11)	5.3 (4)	P=0.04
	Y	2.0 (5)	3.8 (6)	5.1 (7)	0.0 (1)	P=0.02
96	N	1.5 (20)	1.2 (10)	3.3 (11)	3.5 (4)	P=0.02
	Y	1.0 (3)	2.8 (5)	3.4 (7)	4.0 (1)	P=0.22

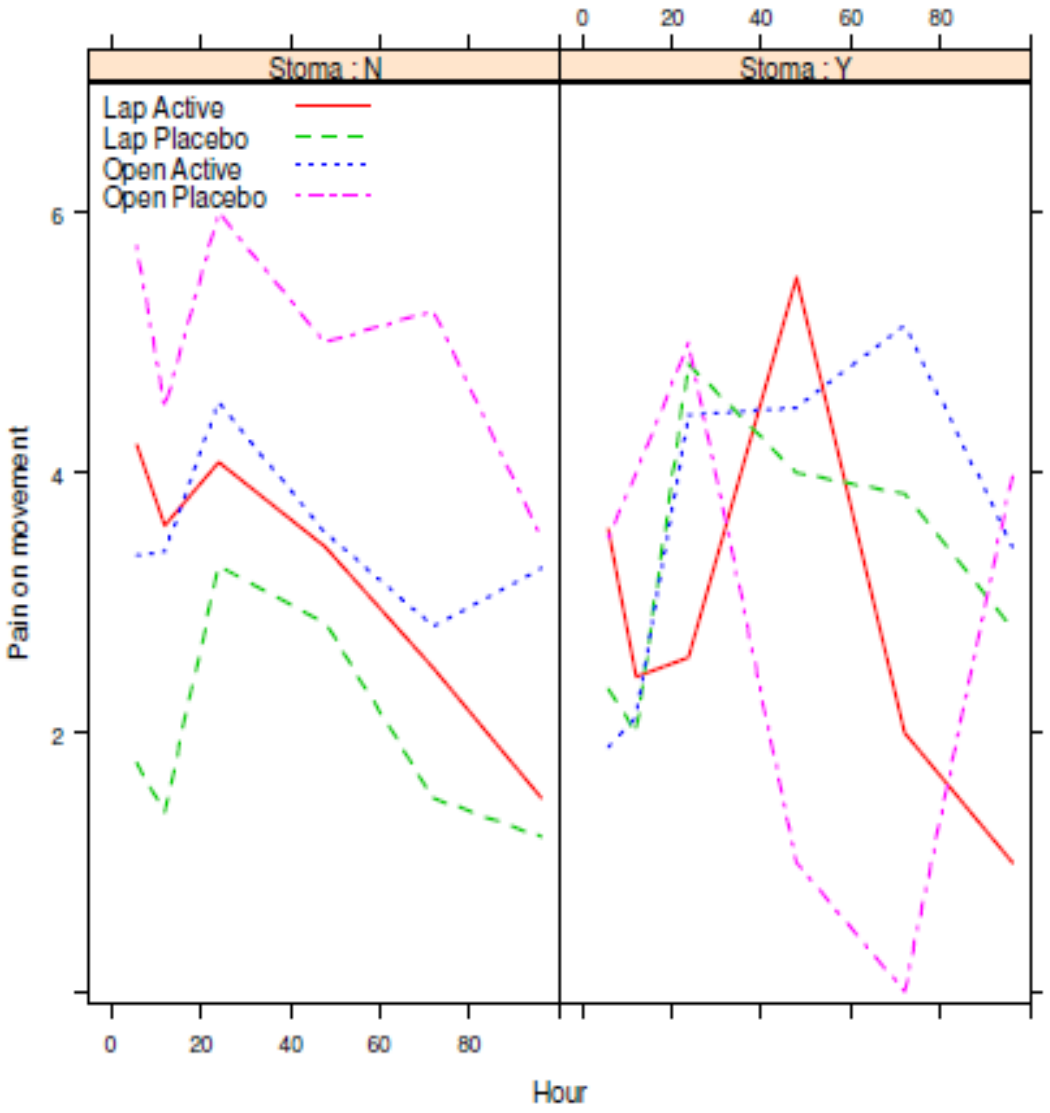

Figure 52: Pain scores with movement in patients with and without a stoma.

A repeated measures analysis showed that there was a significant interaction between the presence of stoma over time (p= 0.014) as shown on Figure 53. From the 6 hr to 24 hr mark, the patients without a stoma experienced higher levels of pain during movement, however from 24 hr post-operation the situation reversed and patients that had stomas had higher levels of pain until the 96 hr time-point.

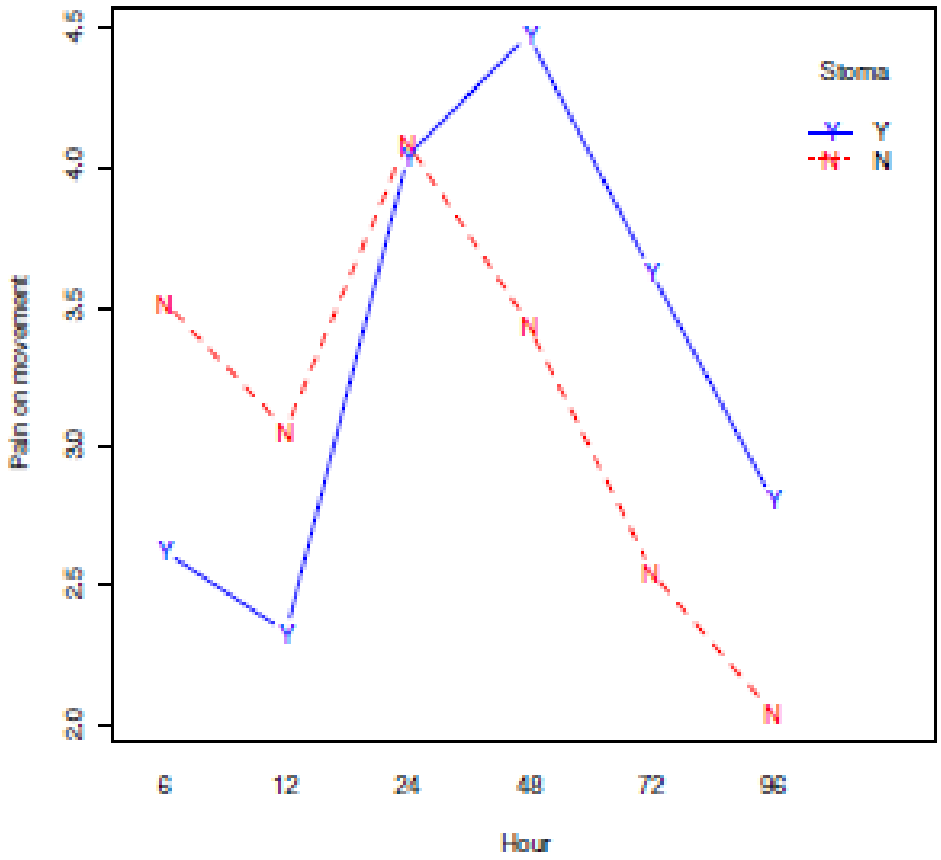

Figure 53: The interaction between time and stoma for pain scores with movement.

5.4.2 Gender

The mean pain scores during movement are displayed on Table 44 and Figure 54. Female patients had higher mean pain scores on movement at all time-points across all four treatment groups apart from 12 hr post-operation where the males reported greater pain (2.0 females versus 5.5 males; 12 hr). Significant differences were evident between male patients at 12 hr post-operation (p= 0.008) and in females at 72 hr (p= 0.04) and 96 hr (p= 0.03) post-operation. Furthermore, a repeated measures analysis of variance demonstrated that there was a significant gender effect as females rated their pain experience with movement more intensely compared to males (p= 0.007).

Table 44: Mean pain scores with movement (number of patients) by gender.

Hour	Gender	Laparoscopic Active	Laparoscopic Placebo	Open Active	Open Placebo	Significance
6	F	4.6 (14)	2.2 (9)	3.0 (10)	5.0 (2)	P=0.15
	M	3.6 (16)	1.7 (10)	2.6 (13)	5.0 (4)	P=0.21
12	F	3.6 (12)	2.3 (9)	3.1 (10)	2.0 (2)	P=0.67
	M	3.1 (17)	0.9 (10)	2.7 (12)	5.5 (4)	P=0.008
24	F	5.1 (14)	4.7 (10)	5.3 (9)	6.5 (2)	P=0.82
	M	2.6 (17)	2.8 (10)	3.9 (13)	5.0 (3)	P=0.29
48	F	4.0 (14)	4.0 (10)	5.1 (7)	5.0 (2)	P=0.66
	M	3.7 (15)	2.3 (9)	3.3 (14)	3.7 (3)	P=0.47
72	F	2.8 (12)	2.7 (9)	5.3 (7)	5.5 (2)	P=0.04
	M	2.0 (13)	1.9 (9)	2.7 (11)	3.3 (3)	P=0.68
96	F	1.8 (12)	2.4 (8)	3.9 (8)	5.0 (2)	P=0.03
	M	1.1 (7)	1.0 (7)	2.9 (10)	2.7 (3)	P=0.06

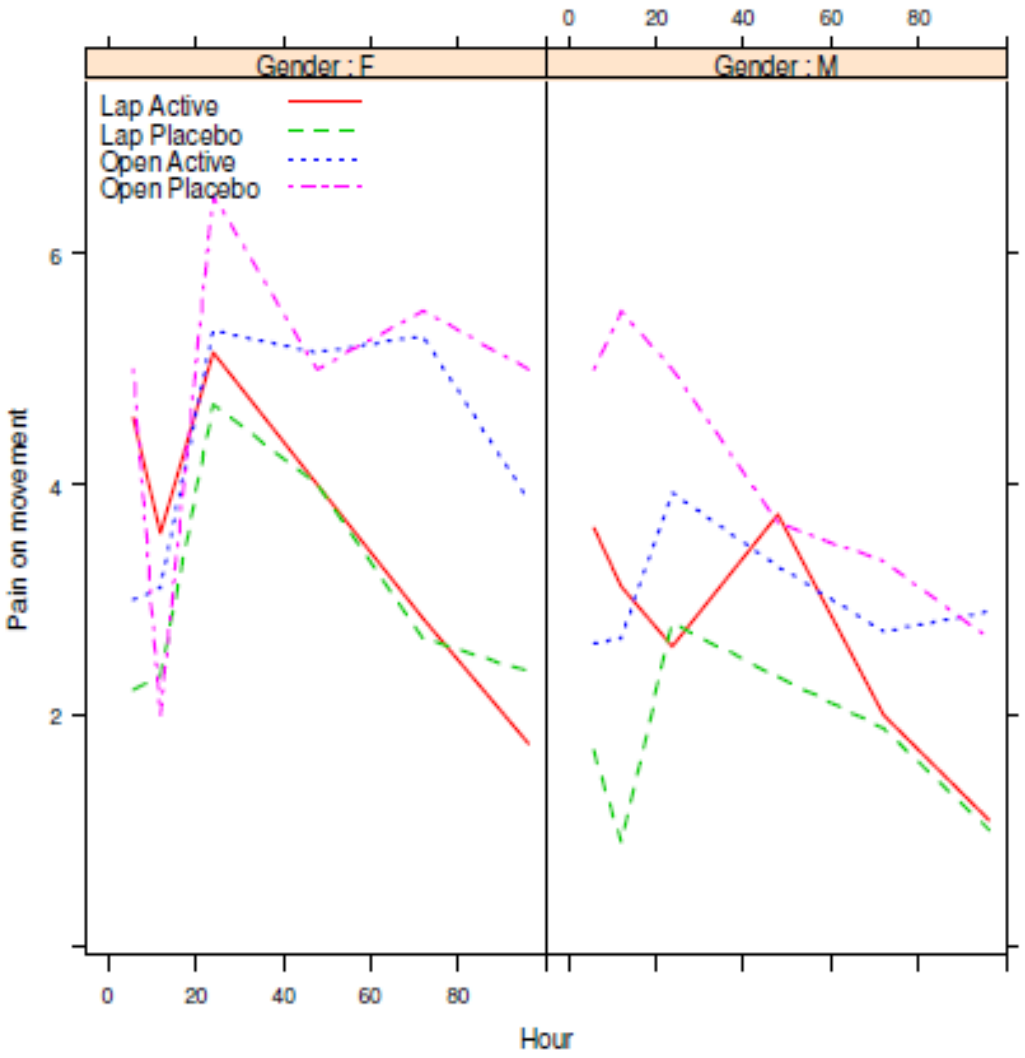

Figure 54: Pain with movement by time and gender of the four treatment groups.

5.4.3 Summary

A summary of the significance levels for regressions of pain with movement are displayed in Table 45. There was no apparent relationship between pain with movement and age. There were significant effects with treatment type at 6 hr, 12 hr, 72 hr and 96 hr post-operation. Gender effects were significant from the 24 hr to 96 hr mark and a significant stoma effect was demonstrated at 6 hr and 48 hr post-operation. In addition, these results are consistent with the previous results of the effects of the co-variates on the patients' pain scores with rest.

Table 45: Significance levels for regressions of pain with movement.

Effect	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr
Treatment	0.03	0.03	0.26	0.42	0.03	0.002
Age	0.75	0.14	0.53	0.61	0.11	0.90
Gender	0.39	0.39	0.0008	0.01	0.007	0.02
Stoma	0.08	0.16	0.99	0.03	0.14	0.40

CHAPTER 6: SECONDARY CLINICAL RESULTS, COMPLICATIONS, FAST-TRACK SURGERY & COSTING ANALYSIS

CHAPTER 6: SECONDARY CLINICAL RESULTS, COMPLICATIONS, FAST-TRACK SURGERY & COSTING ANALYSIS

6.1 Bowel Function

The time to bowel movement was similar between the four groups, although bowel function returned the earliest in the laparoscopic active group (3.5 ± 0.3 days). An unbalanced two-way analysis of variance showed no significant difference between the treatment type, operation type and their interaction.

Table 46: Time until bowel movement (days, mean ± SEM)

	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 6)
Days to Bowel Movement	3.5 ± 0.3	3.9 ± 0.3	4.0 ± 0.3	3.8 ± 0.8

6.2 Mobilisation

The mean time to mobilisation (days) for each treatment group is shown in Table 47. Patients in the laparoscopic active and laparoscopic placebo groups (1.9 and 1.5 days respectively) had an earlier time to mobilisation compared to the open active and open placebo groups (2.1 and 2.4 days respectively). There is a significant difference between treatments as shown with an analysis of variance (p= 0.03).

On average, the patients who had laparoscopic surgery were mobile in 1.8 days, whereas it took patients who had open surgery an average of 2.1 days. This was significantly different (p= 0.003). Moreover, the co-variates of age, gender and stoma did not have a significant impact on the time to mobilisation.

Table 47: Days to mobilisation

	Laparoscopic Active (n= 31)	Laparoscopic Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 6)
Days to Mobilisation	1.9	1.5	2.1	2.4

6.3 Hospitalisation and Re-Admission

Length of Hospitalisation

Table 48 displays the length of hospitalisation for each of the four treatment groups. The length of hospitalisation was identical between the two laparoscopic groups (6.5 days) and slightly longer in the open placebo group in comparison with the open active group (10.4 days versus 9.7 days). Excluding the two patients who died (1 patient from the laparoscopic active group and 1 patient from the open placebo group), an analysis of variance showed a significant difference (p= 0.03) between open and laparoscopic surgery, irrespective of the use of local anaesthetic.

Table 48: The length of hospitalisation (days) among the four patient treatment groups.

	Laparoscopic Active (n= 30)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 5)**
Hospitalisation (Days)	6.5	6.5	9.7	10.4

When age, gender and stoma were included as co-variates, a significant difference (p= 0.003) was still evident between the four treatment groups. A significant difference in length of hospitalisation was evident between laparoscopic procedures (6.5 days) and open procedures (9.8 days) (p= 0.003).

Re-Admissions

The number of patients who were re-admitted to hospital within a 30 day period is listed in Table 49. Patients were re-admitted for the following reasons: wound infections; pre-sacral collections; wound leakage; wound dehiscence; small bowel obstruction; stenosis of the rectum; urinary retention; haematuria and pneumaturia. The re-admission rate was slightly higher in the laparoscopic active group in contrast to the other three groups. Once again, the two patients who died were excluded from this analysis. There was no significant difference between the four treatment types (p= 0.97; Fisher's exact test), nor between re-admission rates for gender, age, operation type and the presence/absence of stomas and drains.

Table 49: Patient re-admission rates within 30 days.

	Laparoscopic Active (n= 30)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 5)**
Number of patients re-admitted	7 (23%)	4 (20%)	4 (17%)	1 (20%)

6.4 Complications

Complications present in this study are shown through both opioid-related side-effects, the patients' post-operative complications and the number of Painbuster catheter's falling out and leaking before the completion of the 96 hr levobupivacaine infiltration period.

6.4.1 Patient Post-Operative Complications

The post-operative opioid-related and surgical complications are shown in Table 50. Analyses using a Fisher's exact test showed that there were no significant differences between the number of complications between the four groups (p= 0.74). Furthermore, the factors of age, gender, operation type and the presence/absence of stomas and drains had no significant effect on the number of post-operative complications.

There was a trend to more patients experiencing nausea in the placebo groups (60% laparoscopic placebo and 83% open placebo) in comparison to the two active groups (52% laparoscopic active and 67% open active).

Four anastomotic leaks were evident in this study, including the laparoscopic active group (2 patients), open active group (1 patient) and open placebo group (1 patient). One patient from the laparoscopic active group who had a laparoscopic low anterior resection (not defunctioned), developed a high temperature and a contrast study confirmed that it was an anastomotic leak. This patient had further surgery, requiring a Hartmann's procedure. The other three anastomotic leaks were all verified by CT scan and were managed conservatively.

There were four wound infections recorded in the laparoscopic active group (1 patient) and open active group (3 patients). One patient from the laparoscopic active group had superficial wound dehiscence, which required suture under local anaesthetic.

Table 50: Post-operative complications by treatment group.

	Lap Active (n= 31)	Lap Placebo (n= 20)	Open Active (n= 24)	Open Placebo (n= 6)
Opioid-Related Effects				
Nausea	16 (52%)	12 (60%)	16 (67%)	5 (83%)
Vomiting	14 (45%)	6 (30%)	6 (25%)	3 (50%)
Drowsiness	8 (26%)	6 (30%)	9 (38%)	0 (0%)
Pruritis	11 (35%)	5 (25%)	10 (42%)	3 (50%)
Surgical Complications				
Wound Infections	1 (3%)	0 (0%)	3 (13%)	0 (0%)
Wound Dehiscence	1 (3%)	0 (0%)	0 (0%)	0 (0%)
High Stoma Output	1(3%)	0 (0%)	0 (0%)	0 (0%)
Ileus	3 (10%)	2 (10%)	1 (4%)	1 (17%)
Anastomotic Leak	2 (6%)	0 (0%)	1 (4%)	1 (17%)
Pre-sacral Collection	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Stenosis of rectum	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Heart Failure	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Urinary Retention	1 (3%)	1 (5%)	1 (4%)	0 (0%)
UTI	0 (0%)	0 (0%)	2 (8%)	0 (0%)
C. diff Infection	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Death	1 (3%)	0 (0%)	0 (0%)	1 (17%)

Abbreviations: Lap= laparoscopic; UTI= urinary tract infection; C. diff infection= Clostridium difficile infection.

There were two deaths during the study, which were not related to the levobupivacaine infiltration. The first death occurred in a 69 year old male patient from the laparoscopic active group who had undergone a laparoscopic high anterior resection for colovesicle fistula for diverticular disease. On post-operative day three, the patient deteriorated with cardio-pulmonary related complications. An anastomotic leak was suspected and emergency surgery was planned. Unfortunately, before this could occur, the patient suffered from cardiac arrest and died despite maximal medical support. The second

death took place in a 79 year old male from the open placebo group. This patient had a Hartmann's procedure for the surgical removal of a large sigmoid tumour. On day two post-operation, the patient suffered from aspiration pneumonia and despite full support in the intensive care unit, he passed-away on day 28 post-operation

6.4.2 Catheter Fall-Outs and Leakages

The Painbuster catheter did not last the full 96 hr period of levobupivacaine (or saline) infiltration in 16 (20%) patients (11 patients 48 to 72 hr; 5 patients 72 to 96 hr). This was due to either: excessive leakage at the catheter insertion site resulting in a prematurely empty Painbuster, or the fall out of the catheter from the incision site. There was no significant difference between the treatment groups and the catheter fall out rates (p= 0.97; Fisher's exact test). Furthermore there was no difference in rates between genders, operation type and the absence/ presence of stomas and drains in those patients who completed the infusion period to those who did not.

Table 51: The number of patients who did not complete the entire 96 hr levobupivacaine (or saline) infiltration due to catheter fall-outs and leakages.

	Laparoscopic Active (n= 31)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 6)**
Completed 96 hr infusion	24 (77%)	16 (80%)	20 (83%)	5 (83%)
Did not complete 96 hr infusion	7 (23%)	4 (20%)	4 (17%)	1 (17%)

6.5 Fast-Track Surgery Recovery Protocol Compliance

A total of 73 patients completed the fast-track surgery recovery protocol, the eight patients not included was due to the delayed implementation of the fast-track surgery protocol after the initial commencement of the trial. There were a total of 32 interventions assessed in the protocol. An average of 81% (26/32) of interventions were completed, ranging from 14 to 32 interventions completed per patient. Compliance with the protocol for each fast-track intervention is displayed in

Table 52. The degree of compliance ranged from 23 % (17 patients) of patients who had consumed 200 mL of a pre-operative carbohydrate 2 hr prior to surgery to 100% for interventions including BMI measurement, the administration of intravenous fluids post-operatively and regular paracetamol. As there were 2 deaths during the trial, only 71 of the 73 patients were included in the discharge parameter.

Table 52: The degree of protocol compliance in patients that were fast-tracked (n= 73).

Time-Point	Intervention	Number of Patients	%Degree of Compliance
Pre-Operation	BMI measurement	73	100%
	No Bowel preparation	42	58%
	No premedication	64	88%
	400 mL of pre-op carbohydrate drink (Nutricia Pre-op®)	51	70%
Day of Surgery	200 mL of pre-op carbohydrate drink 2 hr prior to surgery	17	23%
	No Nasogastric tube	71	97%
	Intravenous fluids to maintain normovolaemia	73	100%
	Levobupivacaine + Painbuster	73	100%
	Parenteral paracetamol and NSAID (parecoxib)	72	99%
	PCA as required	73	100%
On Ward	Clear fluids as tolerated (aim for 1 L)	72	99%
	IV fluid 1L Hartmann's solution/12 hr	68	93%
	Urine output ideally 30 mL/hr	67	92%
	Analgesia: Paracetamol 1g qid	72	98%
	PCA as required	73	100%
Day 1 Post-Operation	Catheter out	56	77%
	Free fluids + energy drink x2	64	88%
	3-4 hr out of bed	64	88%
	Walk: 20 m twice daily	39	53%
	Stop iv fluids	61	84%
	1 sachet movicol	55	75%
	Painbuster	73	100%
	Regular paracetamol 1g qid	73	100%
	Ibuprofen 400 mg tds	40	55%
Day 2 Post-Operation	Ward Diet	40	55%
	Walk 40m twice daily	46	63%
Day 3 Post-Operation	Ward Diet	59	81%
	Walk 40m twice daily	62	85%
Day 4 Post-Operation	Ward Diet	62	85%
	Walk 40m twice daily	60	82%
Discharge	Mobilising Safely	71	97%
	Tolerating full diet and passing flatus	71	97%

6.6 Costing

The costs of the patients period of hospitalisation from their surgery to discharge was compiled, and included individual costs derived from: imaging; pathology; pharmacy; nursing, surgical and anaesthetic costs; overheads and ICU admission (if required). The costs of fast-track surgery were not analysed due to the varying degree of compliance to the fast-track surgery protocol, as shown in Section 6.5. The costing data of the patients by the four different treatment groups are presented in Table 53. There were no significant differences in total costs between the two laparoscopic groups (p= 0.66; un-paired t-test), however a significant difference was apparent between the open active and open placebo groups (p= 0.032; un-paired t-test). The results in this section are displayed as a median cost due to the high cost ($111,315) of one patient in the open placebo group which was the result of an ICU admission lasting 20 days.

Table 53: The median total cost of the patients' hospitalisation from surgery to discharge.

	Laparoscopic Active (n= 31)	**Laparoscopic Placebo (n= 20)**	**Open Active (n= 24)**	**Open Placebo (n= 6)**
Total Cost	$11,744	$11,541	$13,085	$18,588
Range	$6,208- $30,478	$7,308- $21,287	$4,931- $47,050	$13,356- $111,315

The total costs comparing laparoscopic and open surgery (Table 54) and the active and placebo treatments (Table 55) are shown below. The cost of having open surgery was higher than that for laparoscopic surgery (p= 0.044; un-paired t-test). Although the median cost of having the active treatment ($12,581) was less compared with the cost of the placebo treatment ($13,726), regardless of operation type, it was not significantly different (p= 0.26; un-paired t-test), which may have also been affected by the one ICU patient in the open placebo group.

Table 54: The median total costs between patients who had laparoscopic surgery and patients who had open surgery, irrespective of levobupivacaine use.

	Laparoscopic (n= 51)	**Open (n= 30)**	**Significance**
Total Cost	$11,650	$13,927	p= 0.044
Range	$6,208- $30,478	$4,931- $111,315	

Table 55: The median total costs between patients who had the active treatment and patients who had the placebo treatment, irrespective of type of surgery.

	Active (n= 55)	**Placebo (n= 26)**	**Significance**
Total Cost	$12,581	$13,726	p= 0.26
Range	$4,931- $47,050	$7,308- $111,315	

CHAPTER 7: LABORATORY RESULTS

CHAPTER 7: LABORATORY RESULTS

Results from this study that were obtained through laboratory analysis consisted of the patients total plasma levobupivacaine concentrations, AAG concentrations and cortisol concentrations. The results of these parameters are presented in this section.

7.1 Plasma Levobupivacaine Concentrations

7.1.1 Validation of the HPLC Method

The retention times of levobupivacaine and ropivacaine, the internal standard, were approximately 14 min and 11 min, respectively. The HPLC method in this study was validated for its precision and accuracy prior to testing in patient samples using replicates (n=5) both within a single run and between runs on different days (Shah et al., 2000). The precision of the calibration standard replicates were expressed as a percentage coefficient of variation (CV%), and accuracy as the deviation from the expected concentration expressed as a percentage. Acceptance of each HPLC assay run was assessed by the inclusion of tri-level quality control (QC) samples in each run. The interday precision of these QC samples at concentrations of 5 mg/L, 2.5 mg/L and 1.0 mg/L were 2.6%, 5.4% and 13.5%, respectively. The interday accuracies for these samples were 101.0%, 97.6% and 97.9%. The lower limit of quantification was 0.2 mg/L.

7.1.2 Patient Plasma Levobupivacaine Concentration

Patient plasma levobupivacaine concentrations were measured to assess the margin between the concentration observed using the dosing protocols in the study (infiltrate concentration and flow-rate) and previously reported thresholds for adverse side-effects as a safety indicator. The patients' mean total plasma levobupivacaine concentrations are shown in Table 56 and depicted graphically in Figure 55. Although all the patients had their plasma sampled across the 96 hr infusion time and measured by the HPLC assay for levobupivacaine, only the results of the patients who received the active treatment are displayed due to the absence of levobupivacaine in the patients who received the placebo

treatment. Assaying all samples served as a confirmation check that the randomisation allocation was correct, i.e., patients allocated as such were indeed 'placebo'. While 55 patients received the active treatment, concentration data is only shown for 48 patients due to malfunctions of the auto-sampler in the HPLC assay, and where insufficient plasma was available to repeat these analyses. The number of samples for each time-point ranged from 48 samples (pre-dose and 6 hr post-operation) to 28 samples (72 hr post-operation). The lack of a complete collection of blood samples at all the time-points was a consequence of either a failure to collect blood at that stated time-point, inability in obtaining blood from the patient, or no need to collect blood from the patient due to the removal of the Painbuster before the 96 hr period was completed.

The concentration (mean ± SEM) of levobupivacaine at 1 hr post-operation was 0.67 ± 0.075 mg/L where it steadily increased to reach its peak concentration of 1.95 ± 0.21 mg/L at 48 hr post-operation, from there the concentration gradually declined to 1.18 ± 0.31 mg/L once the levobupivacaine infiltration had been ceased at 96 hr post-operation. From pre-dose to 96 hr post-bolus dose the mean plasma levobupivacaine concentration remained below the toxicity threshold of 2.62 mg/L reported in a study by Bardsley (1998) who investigated the onset of cardiovascular effects in 14 healthy male volunteers. It is interesting to note that these volunteers in the Bardsley (1998) study had more serious adverse-effects, whereas ours had 'more mild' effects apparent with similar maximal total levobupivacaine concentrations.

The maximum total plasma levobupivacaine concentration exceeded the toxicity threshold of 2.62 mg/L, (suggested by Bardsley (1998)) from the 6 to 96 hr time-points. This was evident in 11 of the actively treated patients (6 open cases and 5 laparoscopic cases). Observed clinical side-effects in these 11 patients included: nausea (6 patients), skin itchiness (5 patients), vomiting (4 patients) and drowsiness (3 patients). One patient did not experience any side-effects and all side-effects were not

related to the levobupivacaine infiltration. Furthermore, there was no correlation between side-effects and opioid consumption.

Table 56: Patient plasma total levobupivacaine concentrations during a 96 hr continuous infusion of 0.5% levobupivacaine post-operation.

Time-point (hr post-operation)	Concentration (mg/L) Mean ± SEM	Range (mg/L)	Number of Samples
Pre-dose	0	0-0	48
1	0.68 ± 0.075	<0.2- 2.47	40
6	0.84 ± 0.087	<0.2- 2.74	48
12	0.95 ± 0.088	<0.2- 3.33	47
24	1.25 ± 0.11	<0.2- 3.00	43
48	1.95 ± 0.21	<0.2- >5.0	41
72	1.26 ± 0.16	0.20- 3.67	28
96	1.18 ± 0.31	<0.2- >5.0	33

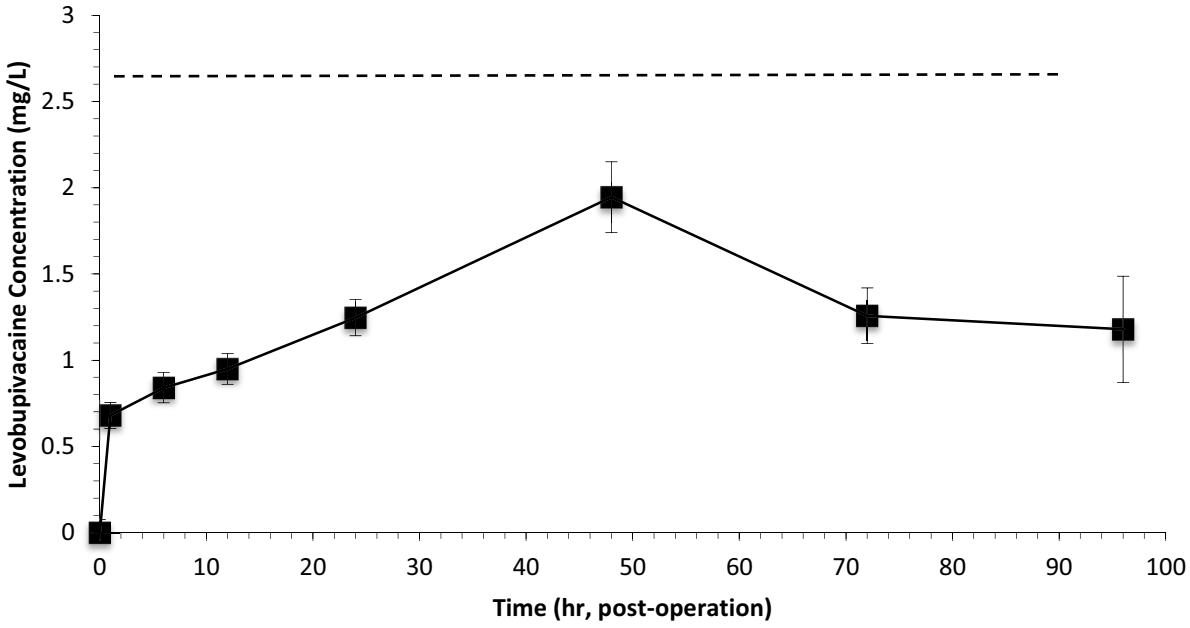

Figure 55: The average plasma levobupivacaine concentrations (mg/L, mean ± SEM) in active patients (n=48) during a continuous 96 hr infiltration of 0.5% levobupivacaine. ("- - - - -" indicates toxicity threshold based on previous literature by Bardsley (1998) where a concentration of 2.62 mg/L was achieved during the onset of cardiovascular effects).

7.2 AAG Concentration

Patient AAG concentrations were measured as an indicator of protein binding following surgical stress. Hence it is an important parameter when relating to the implications for unbound (pharmacologically active) concentration and unbound fraction of levobupivacaine. The patients' AAG concentrations are shown in Table 57 and the percentage change in AAG concentrations from pre-dose to 48 hr post-operatively are shown graphically in Figure 56, with the mean (±SEM) values shown in Figure 57. The data represents the results obtained from only 21 out of the 55 patients that had received the active treatment as only patients that had samples collected from the pre-dose, 12 hr and 48 hr time-points, and where sufficient plasma was still available, were included.

As shown in Figure 57, the mean (±SEM) patient AAG concentration increased significantly from 0.84 (± 0.06) pre-surgery to 1.23 (± 0.08) g/L at 48 hr post-surgery ($p = 0.0004$, $n=21$). There was no significant difference from the pre-dose AAG concentrations to 12 hr post-surgery (2.3 %; $p > 0.05$; Mann-Whitney test),

Table 57: AAG concentrations (g/L) and changes (%) in AAG concentrations before surgery and 12 hr and 48 hr after surgery.

Time-point	AAG Concentration (g/L) Mean ± SEM	Range	% Change	P value
Pre-dose	0.83 ± 0.060	0.50- 1.63	-	-
12 hr post surgery	0.81 ± 0.052	0.33- 1.37	2.31	0.98
48 hr post surgery	1.23 ± 0.080	0.50- 2.20	55.22***	0.0004

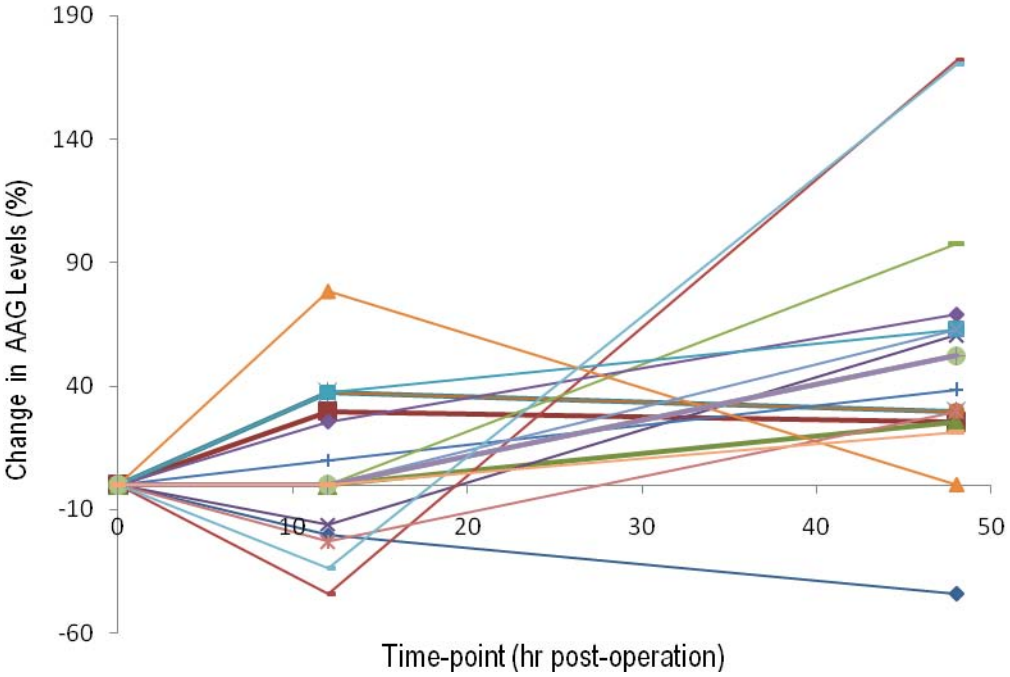

Figure 56: Percentage changes in AAG concentrations before surgery to 12 hr and 48 hr post-operation (n=21).

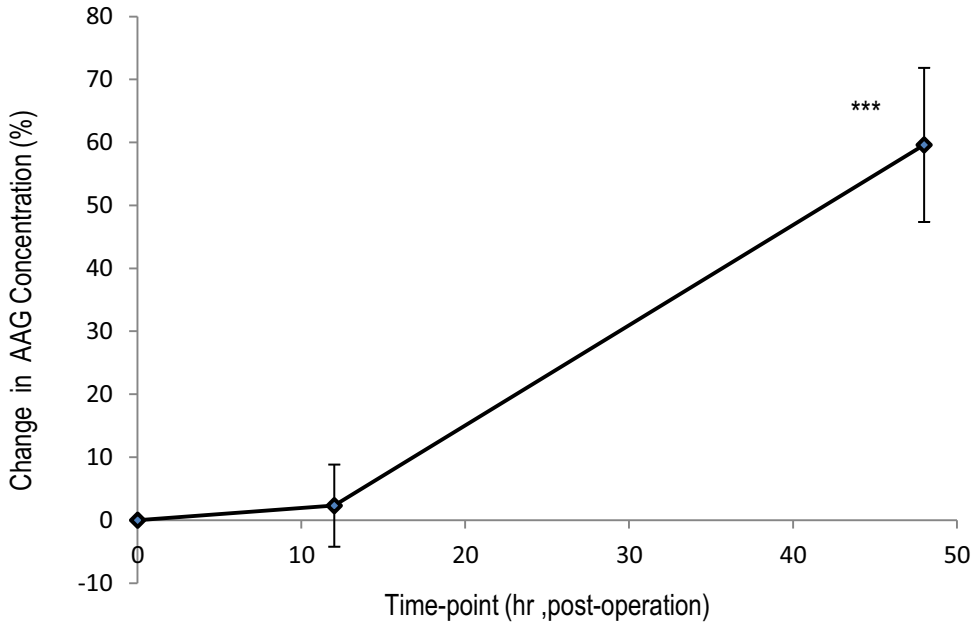

Figure 57: The mean (±SEM) percentage changes in AAG concentrations before surgery to 12 hr and 48 hr post-operation (n=21). (***p <0.001, pre-dose to 48 hr, Mann-Whitney test).

7.3 Cortisol Concentration

Patient cortisol concentrations were measured as a further indicator of surgical stress. This was measured in all patients regardless of their treatment type; however, only data for 79 patients are presented due to the unavailability of results for 2 patients. Missing samples at the stated time-points (Table 58) can be attributed to an insufficient volume of plasma required to perform the cortisol assay or blood not being collected at that time-point. The mean (± SEM) baseline cortisol level was 287.3 ± 15.42 nmol/L, which sharply rose to a peak of 838.0 ± 40.9 nmol/L immediately following surgery at the 1 hr post-bolus dose of levobupivacaine (i.e. usually 2 to 4 hr after the start of surgery). From then onwards the cortisol concentrations returned to near baseline levels from 24 to 96 hr post-operation. Hence the cortisol response to surgical stress time course appears different to AAG.

Table 58: Patient cortisol concentrations before surgery and during a 96 hr period after surgery.

Time-point (hr post-operation)	Cortisol Concentration (nmol/L) Mean ± SEM	Range	Number of Samples
Pre-dose	287.3 ± 15.42	102- 673	57
1	838.0 ± 40.9	129- 1584	65
6	702.5 ± 43.32	48- 1684	74
12	463.1 ± 37.19	33- 1393	71
24	366.8 ± 35.75	23- 1116	65
48	393.2 ± 26.19	19- 985	58
72	446.7 ± 25.59	86- 812	44
96	443.7 ± 59.54	96- 2888	47

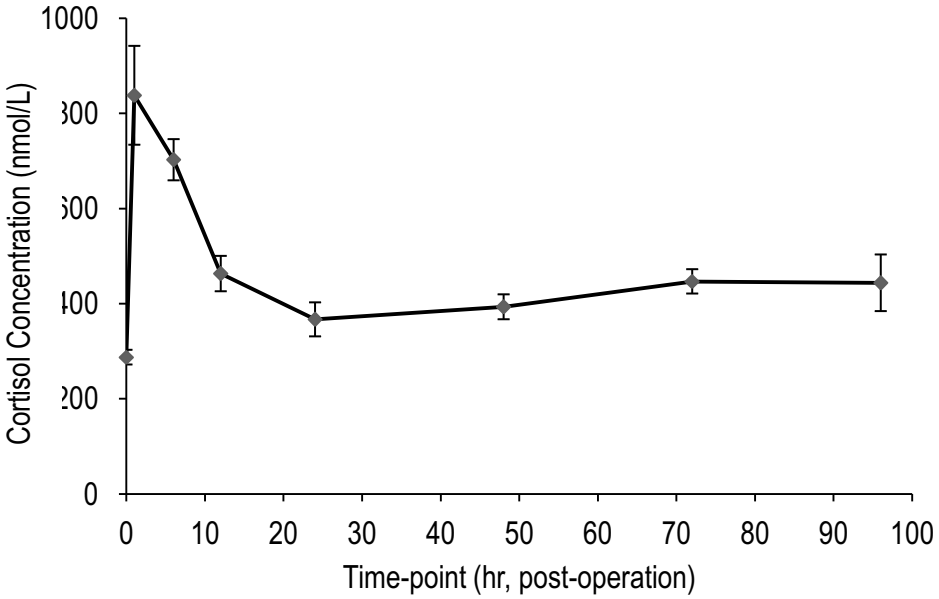

Figure 58: Patient mean (± SEM) cortisol concentration up to 96 hr post-operation (n=79).

There were no significant differences (p= 0.91; one-way analysis of variance) in cortisol concentrations between the four different treatment groups, as shown in Figure 59.

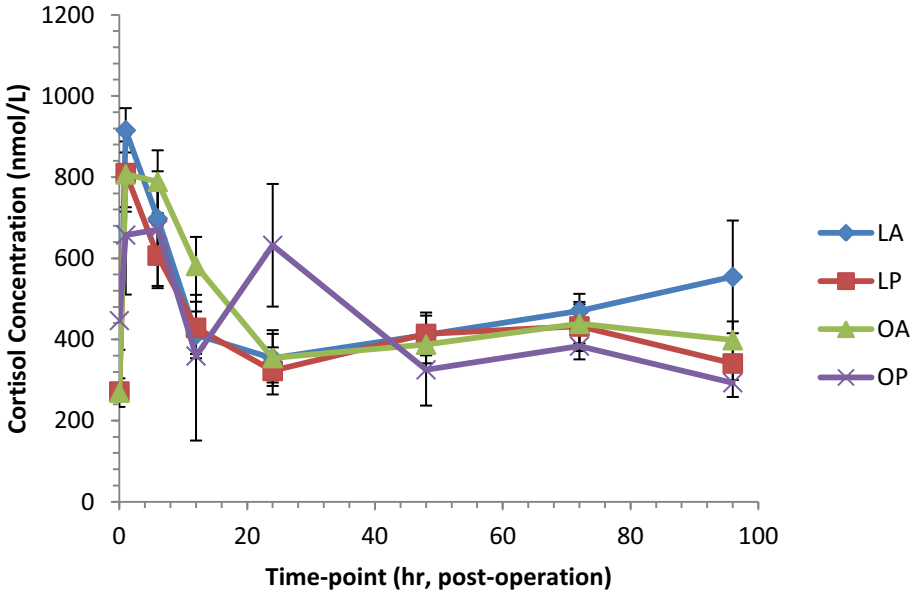

Figure 59: Patient mean (± SEM) cortisol concentrations between the four treatment groups.

Furthermore, no significant differences (p= 0.92; un-paired t-test) were evident in cortisol concentrations between laparoscopic and open procedures, regardless of the presence of levobupivacaine. This is shown graphically in Figure 60.

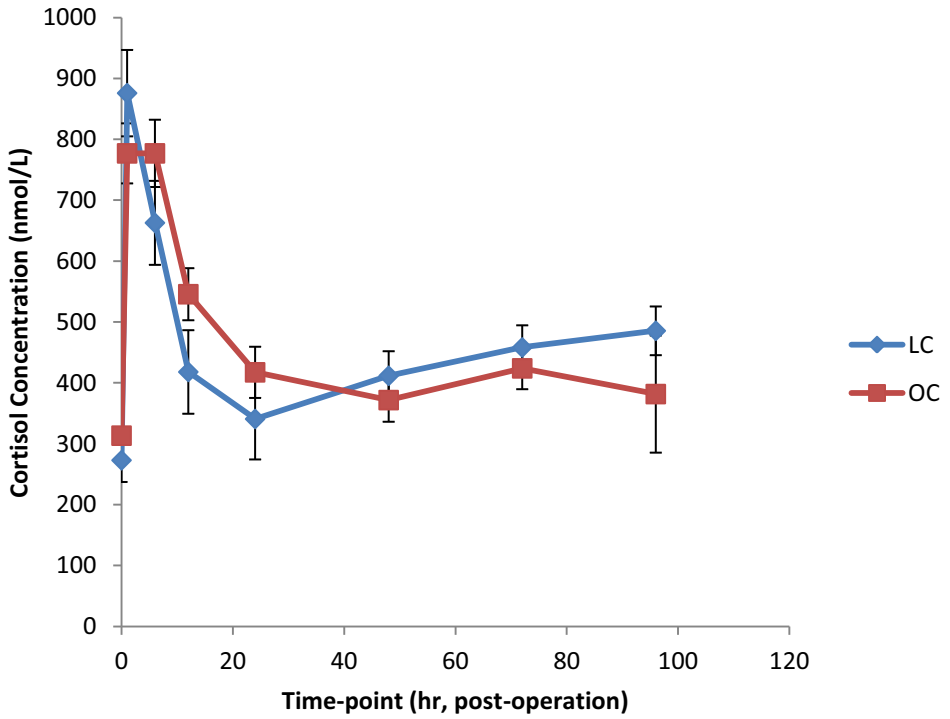

Figure 60: Patient mean (± SEM) cortisol concentration by laparoscopic and open surgery (LC= laparoscopic combined surgical cases; OC= open combined surgical cases).

CHAPTER 8: DISCUSSION

CHAPTER 8: DISCUSSION

8.1 General Perspective

The use of local anaesthetics for post-operative pain management has the potential to decrease the magnitude of pain following surgery and hence lead to better patient outcomes.

Surgery leads to the generation of pain signals and produces a secondary inflammatory response which can significantly amplify post-operative pain. Therefore the administration of local anaesthetics at the site of injury, the incision site, can block the transmission of pain signals at a local level. It is a considerably safe approach and additionally limits the unwanted side-effects related to opioid use. Furthermore, the continuous infiltration of levobupivacaine immediately during the post-operative period can provide a form of pre-emptive analgesia in which a steady level of post-operative pain is maintained without enhancing the pain experienced by patients.

A systematic review and meta-analysis by Karthikesalingam (2008) analysed five trials involving 542 patients undergoing laparotomies. Significant differences on the patients pain with movement and a reduction in opioid consumption was apparent although no significant effects were noted in terms of pain at rest, the recovery of bowel function and hospitalisation. Karthikesalingam concluded that although it is a promising technique there is no conclusive evidence of its benefits and further research is needed.

Hence the primary aim of this study was to investigate the efficacy of 0.5% levobupivacaine infiltrated at the incision site in order to provide adequate pain management to patients who had either laparoscopic or open abdominal surgery. The differences in this study from common practice include the extension of the duration of infusion from either 48 or 72 hr post-operation (in previous studies) to 96 hr post-operation, the placement of the Painbuster catheter in the deeper muscle layers, where the nerves are located, to avoid a need for the drug to diffuse to the site of action, and using a relatively high dose

(concentration x flow rate of drug). The intent therefore was to provide a more targeted analgesic effect and enhance the opportunity for a therapeutic response. Furthermore no studies to date have investigated the benefit and clinical outcomes of continuous wound infiltrations with local anaesthetics after laparoscopic colorectal surgery.

The results presented in Chapter 3, 4, 5, 6 and 7 are further interpreted and evaluated in this section in order to determine if the continuous infiltration of levobupivacaine into the incision site is a valuable adjunct in the management of post-operative pain following open or laparoscopic open abdominal surgery.

8.2 Evaluation of the Clinical Component

This section will firstly evaluate the primary clinical outcome indices of the patients' opioid consumption and pain scores and factors that can have an impact on these indices. Subsequently, the patient's return of bowel function, time to mobilisation and hospitalisation, complications and an assessment of the fast-track surgery protocol will be elucidated concluding with the limitations in this study.

8.2.1 Opioid Consumption, Demand and Pain Scores

Opioid Consumption and Demand

The findings in this study demonstrated a significant difference in total opioid consumption between the four treatment groups. In patients who had open surgery the active treatment was associated with a reduced opioid consumption compared to patients in the open placebo group. However, patients in the laparoscopic active group paradoxically had a higher total opioid consumption than patients in the laparoscopic placebo group. This trend between the groups was also reflected by the patients demand for opioids. Possible explanations for these observations are further discussed in Section 8.2.2. To date, no other group has investigated the outcome of local anaesthetic wound infiltration in patients who have

had colorectal laparoscopic surgery, however, in relation to open surgery the results obtained in this study are similar to the general trend evident in the literature.

Baig (2006) and colleagues compared 35 patients who received a 0.5% bupivacaine infiltration in a double-catheter Painbuster to 35 patients who received a saline infiltration in a double catheter Painbuster for 72 hr post-operation after midline laparotomy. All patients received morphine-PCA post-operatively. The active treatment was associated with a reduction in total and daily opioid consumption compared to the placebo group (115.5 ± 51.3 mg versus 207.6 ± 240 mg respectively; $p< 0.04$). However, opioid consumption in the Baig study was the lowest on day 1 post-operation compared to our study where the highest consumption recorded was on day 1 post-operation. Although the time of the operations in the Baig study is not known, it could have been in the late afternoon/ evening where patients sleep soon after their surgery, hence the PCA does not function if the patient does not press the button. Similar to our research, total opioid demands in the Baig study was 299 ± 317 pushes of the PCA button in the placebo group compared to 149 ± 117 pushes of the PCA button in the active group, hence patients without the local anaesthetic demanded twice as much opioids as those with the local anaesthetic suggesting the effectiveness of the local anaesthetic in providing pain relief. Furthermore, a difference was apparent (Table 31) between demands, the number of times the patient pushed the PCA button/ requested opioids to the effective demand, the number of times the dose was actually received in our study. This further supports the notion that pain is under-treated, as the patients need pain relief but are not receiving it. However, it could be that the dosage lock-outs are too conservative or that there is a need for additional treatment.

These findings were also supported by Cheong (2001) and Wang (2010). Cheong and team compared 35 patients who received an intermittent intravenous morphine infusion on demand, to patients who received 0.5% bupivacaine in a single catheter Painbuster for 60 hr post-operation after laparotomy for major colorectal surgery. Opioid consumption was greater in the morphine group than the bupivacaine

group (38 mg versus 0 mg; p< 0.001). However, the patients were not blinded to treatment in this study as the morphine group did not receive a Painbuster, hence the placebo effect could be apparent in the bupivacaine group. Furthermore, in the unblinded setting, there could be an array of possibilities that could have influenced the results presented; for example, they could have felt hesitant about requesting opioid analgesia knowing they were receiving the innovative treatment, local anaesthetic, for their pain relief in view of the expectations of the investigators. Wang (2010) compared 28 patients who received 0.25% ropivacaine in a double catheter Painbuster to 27 patients who received a saline infiltration in a double catheter Painbuster for 48 hr post-operation after laparotomy. All patients received morphine for breakthrough pain. Similar to our study, opioid consumption was significantly greater in the placebo group (110.6 mg to 78.7 mg; p= 0.01). This study was well controlled as a single surgeon operated on all patients (unlike our study) and furthermore, the catheter was placed in the pre-peritoneal layer as in our study and unlike most of the other studies.

Contradictory to our results and other literature, Polglase (2007) found no difference in opioid consumption between 143 patients who received a 0.54% ropivacaine infiltration to 167 patients who received a saline infiltration in a double catheter Painbuster for 72 hr after laparotomy (day 1 34.1 mg versus 37.4 mg; day 2 21.3 mg versus 24.3 mg; day 3 15.4 mg versus 16.4 mg). In contrast to the other studies but similar to ours, Polglase used best practice multimodal analgesia including tramadol, parecoxib and paracetamol, which could also explain the similarities in opioid consumption between the two groups, however our patients were also placed under a similar protocol and differences in opioid consumption between open active and placebo groups were apparent. However, in the Polglase (2007) study, the catheter was placed in the subcutaneous layer, hence the diffusion of the local anaesthetic may not have targeted the pain nerves most affected, which could explain for the discrepancy in results between the Polglase (2007) study and our study.

Pain Scores

Interestingly, the open active group had similar levels of pain at rest and movement to the two laparoscopic groups, suggesting the effectiveness of the levobupicaine infusion at the incision site. The open placebo group, although small in number, had a higher level of pain at rest and movement. This group is effectively the "status quo" for such procedures in most hospitals, hence indicative of what would normally occur in a clinical setting without the addition of local anaesthesia. This further supports the notion, alluded to in the introduction that post-operative pain continues to be under-managed and under-treated. In patients who had laparoscopic surgery, the active treatment was paradoxically associated with an increase in pain scores. Possible reasonings behind this are elucidated in Section 8.2.2.

Resembling this study, the general consensus in the literature is indicative of no significant treatment effect on pain scores with local anaesthesia at rest. However, various significant effects were evident with pain during movement. Baig (2006) found no difference in overall post-operative pain between the local anaesthetic and placebo treated groups. Both Baig and our study noted a significant difference in treatment type on day 2 post-operation (Baig p= 0.006, ours p= 0.02), although VAS pain scores in the Baig study were higher on day 1 (6.75 local anaesthetic group, 7.53 placebo group) compared to our study on post-operative day 1 (2.3 laparoscopic active; 1.5 laparoscopic placebo; 1.7 open active; 2.0 open placebo). In the Baig (2006) study, the catheters were placed in the subcutaneous layer; hence the local anaesthetic may not have reached the nerve fibres most affected by the incision, which could account for the high levels of pain observed. The high levels also correlate to the low opioid consumption in their patients on day 1. Unfortunately, Baig did not measure pain scores with movement. In the Wang (2010) study no differences were apparent between pain scores at rest and movement between the local anaesthetic and placebo groups, suggesting that a reduced opioid consumption did not result in higher pain scores. This was supported by Polglase (2007) who concluded that there was

no significant difference on pain at rest although differences were noted at pain on movement on day 1 post-operation.

Interestingly, the paradoxical pain scores observed in our study between the two laparoscopic groups was reflected in the Cheong study in patients undergoing open surgery. Their patients who received the PCA had a pain score of 0 from day 1 to 3 post-operation, whereas patients who received the bupivacaine infiltration, had a pain score of 2 on day 1 post-operation ($p= 0.03$) before recording 0 on day 2 and 3 post-operation. No significant differences were evident on pain scores at movement, although the initial reading was 5 with PCA compared to 3 with bupivacaine before being identical until the conclusion of treatment.

8.2.2 Factors Influencing Opioid Consumption and Pain Scores

There was a paradoxical result in opioid consumption and pain scores, as described in Section 8.2.1, between the laparoscopic active and laparoscopic placebo group where the group mean data suggested greater opioid usage and pain in the group receiving the active treatment. Potential factors influencing these indices include: the presence of stomas or drains, the gender of the patient, patient characteristics, surgical factors and the placebo effect. In making these further observations and explanations, it is acknowledged from a philosophical perspective, that had one obtained a significant result consistent with one's pre-conceived 'expected or desired outcome' (for example, active treatment better than placebo) then one would be unlikely to go looking for further explanations (as in the following discussion) that might potentially render such a 'desired result' non-significant and explained by factors other than the active treatment.

8.2.2 (a) Stoma and Drains

The presence of stomas and drains could be a potential reason as to why patients in the laparoscopic active group experienced more pain and hence had a higher opioid consumption than patients in the laparoscopic placebo group. Twenty-six percent (8/31) of patients in the laparoscopic active group had stomas compared to (1/20) 5% in the laparoscopic placebo group. Additionally, more patients in the laparoscopic active group had drains inserted in comparison to the laparoscopic group (19% (6/31) versus 10% (2/20) respectively). As the Painbuster soaker catheter does not necessarily cover the stoma and drain sites as these may not be in the same dermatome, the beneficial effects of levobupivacaine on the surgical site in the laparoscopic active group may have been under-estimated due to pain from other sites more distant from the incision site. Hence this result may have been biased by the chance disparity in the number of stomas or drains in the two groups. Similarly although it is not known how many patients in the placebo group in the Cheong (2001) study had stomas and drains, 13 patients in the local anaesthetic treated group had stomas, and 15 had drains inserted thus providing an explanation for the lack of difference in pain scores between the two treatment types. Furthermore, as previously mentioned, the Polglase (2007) study found no difference in pain scores at rest and opioid consumption between the treatment and placebo groups, however, the percentage of patients who had stomas and drains were similar between the two groups, therefore eliminating it as an influencing factor on pain perception and opioid consumption.

Another possibility could be due to the psychological issues of patients with stomas. Wade (1990) reported that 25% of patients with stoma suffered from psychological conditions such as depression and anxiety, which impact on the level of pain and hence opioid consumption. Fifty-six per cent of their patients reported pain up to ten weeks after surgery suggesting the somatopsychic experience of the stoma. This is consistent with other literature by White and Hunt (1997) and Thomas (1987).

A Cochrane Review by Gurusamy (2007) retrospectively analysed five trials involving 281 patients who had drains to 310 patients without drains after laparoscopic cholecystectomy. There was a statistically significant difference in the first 12 hr after surgery in pain perception (standard mean difference 0.55, CI 0.13 to 0.97) between the two groups, although there was no indication if the pain was at the abdomen or elsewhere in the body. Furthermore, Merad (1999) retrospectively compared 248 patients who had drains to 246 patients without drains after rectal surgery. Although the levels of pain were not assessed, complications were 8.6% in the drain group compared to 2.1% in patients without drains. Consequently, the increased risk of complications could contribute to higher levels of pain and hence opioid consumption.

8.2.2 (b) Gender Differences

Although gender was well balanced between the four different treatment groups in our study, gender differences could explain some of the variability observed between differing pain levels and opioid consumption. In essence, females in our study reported greater pain at rest and movement, while requiring and demanding less opioid in comparison to males. Gender differences between pain perception and opioid consumption are well described throughout the literature.

Research conducted by Joels (2003) retrospectively analysed intravenous morphine consumption in 481 patients (235 males and 246 females) who had colectomies. Females consumed significantly less opioids (131.8 mg versus 190.0 mg; p= 0.02) than males. However, pain scores were not measured in this study making outcome comparisons difficult. This was supported by De Kock and Scholtes (1991) who also found that females consumed less morphine than males following abdominal surgery.

Gender differences observed in our study and the literature can be attributed to physiological reasons and differences between drug metabolism between males and females. Gonadal steroid hormones impact on opioid analgesia by interacting with opioid pharmacokinetics and pharmacodynamics by

influencing opioid distribution, absorption and metabolism (Gibson, 2006). Despite requiring less opioids than males, females are more sensitive to pain and less sensitive to pain inhibition. For example, females may be more sensitive to κ-opioid analgesia or the female neural circuit modulating κ-opioid analgesia may have a higher output in contrast to males (Craft et al., 2004).

Females receive more analgesia from equal doses of opioids suggesting the presence of gender variability in drug-receptor interactions. It is thought that drugs are more rapidly metabolised in females due to the enhanced activity of cytochrome P450. In addition, different pain modulator circuits may be apparent between the genders (Craft et al., 2004). Females may have more variable responses to drug distribution due to higher body fat content and changes in the water and electrolyte balance during the menstrual cycle that can have an effect on plasma drug concentration.

8.2.2 (c) Patient Characteristics

There was no significant relationship between age and the level of pain in our study. However, opioid consumption and demand decreased with increasing age. This was also observed by Joels (2003) who found a negative correlation between age and opioid consumption ($r= -0.37$, $p= 0.0001$) as morphine consumption decreased from 251.7 mg in patients under 40 years to 169.5 mg in patients in the 40 to 70 year age group to 89.3 mg in patients over 70 years. This could be due to nociceptive changes coupled with the physiological changes in opioid pharmacodynamics, leading to changes in the clinical response to opioid analgesia in the elderly. Aging is related to changes in the nervous, endocrine, musculoskeletal and immune systems in addition to psychological changes. The elderly have also been reported to have a lower intensity of post-operative pain (Loan and Morrison, 1967). This is supported by experimental testing which has shown an age-related decrease in pain sensitivity in response to noxious stimuli (Gibson, 2006). Another reason that patients over the age of 50 years have a reduced analgesic requirement could be due to the reluctance of medical staff to administer opioids in the elderly due to the fear of adverse reactions, particularly respiratory depression and constipation (Rowlingson,

2001). However, although these findings could contribute to some of the variability between pain scores and opioid consumption, age was generally well- controlled between the four treatment groups in this study.

Furthermore, the pre-existing medical condition of the patient, particularly involving experiences with opioids, can impact pain levels and opioid consumption. As suggested by Joels (2003) patients that have inflammatory bowel conditions such as Crohn's disease and ulcerative colitis tend to have a higher opioid consumption than patients with cancer. However, in our study neither of the laparoscopic treatment groups included patients with these diseases, although it was present in open patients. However, 13% of the laparoscopic active group and 10% of the laparoscopic placebo group had diverticular disease. Moreover 6% (2/31) patients in the laparoscopic active group suffered from anxiety and depression while none of the patients in the laparoscopic placebo group had this co-morbidity. These psychological conditions are linked to higher levels of pain. In the open active group 8% of patients also suffered from this co-morbidity (none in the open placebo group). In addition, as suggested by Creekmore et al., (2004), patients who are current or former smokers, who were suspended from cigarettes during hospital admission, had significantly higher opioid consumption than non-smokers. This could be another possibility of variance in pain scores and opioid levels, as in our study smokers and reformed smokers were specifically not excluded from our study due to the likelihood of a high incidence of smokers in the trial recruitment population.

8.2.2 (d) Surgical Factors

Surgical factors which can influence pain perception and opioid consumption can possibly provide an explanation for the paradoxical effects between the two laparoscopic groups. As expected there was a significant difference between incision length in terms of laparoscopic and open procedures. Patients in the laparoscopic group had smaller fascial incisions therefore did not experience significant discomfort, hence required minimal opioids compared to patients who had open surgery. Twenty-nine per cent

(9/31) of patients in the laparoscopic active group had midline incisions compared to the laparoscopic placebo group in which only 15% (3/20) of incisions were midline, which could have contributed to the increased pain and opioid requirement in the laparoscopic active group. Furthermore 16% (5/31) of patients in the laparoscopic active group had transverse incisions, which was less than the laparoscopic placebo group where 40% (8/20) had transverse incisions. The abdominal wall is innervated by the first lumbar nerve and the lower six thoracic nerves. They are located between the transverse and internal oblique muscles. The ninth intercostal nerves pass transversely across the abdomen between the umbilicus and xiphoid process. Nerves located above this line diverge upwards, whereas the nerves located below this line diverge downwards. Hence an incision made transversely, lateral to the midline is the least likely to result in nerve damage and pain (Grantcharov and Rosenberg, 2001).

In addition, 35% (11/31) of the laparoscopic active patients had right hemicolectomy procedures compared to 50% (10/20) in the laparoscopic placebo group. Joels (2003) established that patients who had right hemicolectomies compared to subtotal colectomies, total colectomies, Hartmann's procedures and low anterior resections required less opioid ($p= 0.007$) due to the less extensive dissection. Furthermore, Joels established a trend towards a longer duration of surgery and opioid consumption. In our study, a significant relationship was observed between duration of surgery and opioid consumption, but this was only evident in the laparoscopic active group.

8.2.2 (e) Placebo Effect

As this study was placebo-controlled, the placebo effect could explain the discrepancies between the two treatment types in the laparoscopic patients. As established by Turner (1994) the patients expectations of their treatment has a distinct influence on their response. Also a patient with a highly positive attitude toward their treatment has been shown to lead to improvements in their outcome. In relation to the placebo patients in this study, it is important to understand that the placebo response is not imagined pain by the patients and it does not have the same response as not doing anything; it is a

physiological response that includes effects mediated by the endogenous opioid system (Rowbotham, 2001). However, the open active group had less pain than the open placebo group thereby decreasing the strength of the placebo response as a possible rationalisation to the paradoxical pain results in laparoscopic active patients. It is a possibility that the magnitude of the incision in the open patients and its associated pain was too great to be accounted for by the placebo response, hence the additional local anaesthetic effect was a real added therapeutic effect. Whereas the laparoscopic patients had a smaller incision and associated pain, hence it was more difficult to demonstrate a benefit of therapy over and above the placebo response.

Another consideration arises from a theory from previous literature. Dickenson (1995) suggested that normal saline infusion, as given to the placebo group can dilute or remove certain humoral agents such as histamine or vaso-active peptides which are important in the genesis of pain. However, when looking at the open groups, the placebo group (albeit in a small number of patients) had higher pain scores at rest and movement and required more opioids than the active group. Hence, it is a possibility that a genuine placebo effect was apparent in this study.

8.2.3 Bowel Function. Mobilisation and Hospitalisation

The impact of continuous wound infiltration with levobupivacaine on the clinical outcomes of the patients' return of bowel function, time to mobilisation and length of hospitalisation are evaluated in this section.

Bowel Function

The continuous infiltration of levobupivacaine did not have a discernible effect on the return of bowel function in this study. Our results demonstrated that in regards to laparoscopic surgery the active and placebo group had a similar return of bowel function (3.5 days versus 3.9 days, respectively) which was also the case in relation to patients who had open surgery where bowel function returned in 4.0 days for the active group and 3.8 days for the placebo group, thereby suggesting that the use of local anaesthetic was of no advantage in providing an earlier return of bowel function in this study. It should also be noted that patients in our study were under a fast-track surgery recovery protocol, which was not evident in other studies assessing bowel function after continuous local anaesthetic wound infiltrations.

This finding appears to be the general consensus in the literature. In the Baig (2006) study, the time to first bowel movement was 3.66 days in the local anaesthetic group and 4.24 days in the placebo group. This difference was not significant and can be correlated to opioid consumption as the inhibition of bowel movements is a side-effect of opioid use. This was comparable to the Cheong (2001) study, where average return of bowel function was 3 days in both the local anaesthetic (0- 4 days) and morphine (1-4 days) groups, although in the Cheong study, the local anaesthetic group had no opioid requirements.

However, the study by Thorson and Faria (2001) did show significant differences in the return of bowel function (3.7 days versus 4.9 days; p= 0.001) between 64 patient who received 0.5% bupivacaine for 48 hr post-operation via the Painbuster to 65 patients who received ketorolac via PCA. Although ketorolac,

a NSAID, may have had an effect on delaying gastro-intestinal recovery, as it has a range of known gastro-intestinal side-effects including constipation. The local anaesthetic group had a comparable return of bowel function time to our study.

Mobilisation

The time to mobilisation was comparable between the two laparoscopic groups and two open groups, i.e. irrespective of the local anaesthetic or placebo treatment. Laparoscopic cases took an average of 1.8 days and open cases an average of 2.1 days. This could be due to the smaller size of the surgical incision in laparoscopic cases compared to open cases in commencing mobilisation. This suggests that operation type rather than treatment type may be more important in promoting earlier mobilisation. These findings were comparable to the Baig (2006) study in which the first day to mobilisation was 2.03 days in the local anaesthetic group and 2.34 days in the placebo group.

Hospitalisation

There was no evidence that the treatment group with levobupivacaine reduced the length of hospitalisation in our study. The length of hospitalisation was 6.5 days for both the laparoscopic groups and 9.7 days and 10.4 days for the open active and open placebo groups respectively. However, a significant difference was apparent between laparoscopic and open cases (6.5 days versus 9.8 days; p= 0.003). The trend seen in the length of hospitalisation was also apparent in the Hewett (2008) study. Hewett and colleagues compared the short-term outcomes of patient undergoing laparoscopic surgery (n =294; 9.8 days) to open surgery (n= 298; 10.1 days) for colorectal cancer. In the Baig (2006) study the length of hospitalisation was 10.1 days in the placebo groups and 9.8 days in the local anaesthetic group, hence that was no significant advantage of reduced hospitalisation with the treatment. This finding was supported by Thorson and Faria (2001) where the length of hospitalisation was 7.8 days in the local anaesthetic group compared to 8.6 days in the placebo group. The difference was not significant. Both of these studies only involved open cases and not laparoscopic cases. The length of

hospitalisation is not only determined by earlier mobilisation and an earlier return of bowel function. Other factors that impact on the length of hospitalisation include: other concurrent morbidities and the attitude of the patient, availability of medical care in a non-acute setting (for example traditional care), family and social support after discharge for the patient, the expectations of the treating surgeon and the discharge planning measures of the hospital.

8.2.4 Complications

Nausea and vomiting were the most common side-effects observed in our study. More patients in the laparoscopic active group experienced nausea and vomiting compared to the laparoscopic placebo group, whereas patients in the open active group experienced less nausea and vomiting compared to the open placebo group. This approximates to the opioid consumption evident amongst the four treatment groups, hence it could be a result of its side-effects. Similar to our study, Wang (2010) had slightly more patients in their treatment group who experienced nausea (39% (11/28) versus 26% (7/27), respectively), and vomiting (7% (2/28) versus 3% (1/27), respectively). However, the opioid consumption in the active treatment group was significantly less than the placebo group suggesting it could also be a result of the local anaesthetic, the effects of general anaesthesia, other surgical complications, or combinations of these. Despite this, the percentage of patients with nausea and vomiting was considerably less in the Wang (2010) study than in our study. In the Baig (2006) study more patients in the placebo group experienced vomiting, which was the most common side-effect observed, and was correlated to the significantly higher opioid intake in the placebo group than the local anaesthetic group.

Six per cent of patients (2/31) had wound infections in the laparoscopic active group and 8% (2/24) of patients had wound infections in the open active group. The wound infection rate is below the guidelines of surgical site infection, as patients undergoing colorectal surgery have up to a 30% chance of developing wound infection (Serra-Aracil et al., 2011, Krieger et al., 2011). Interestingly, wound

complications were only present in the patients that had the active treatment. This is contradictory to literature which suggests that the use of local anaesthesia may improve tissue oxygen tension, as low oxygen tension is a predictor of the development of wound infection (Greif et al., 2000). As all patients (both active and placebo treatment groups) had soaker catheters inserted that were silver-impregnated (SilvaGard®) to enhance anti-microbial protection, wound complications should have been independent of the four treatment groups. Hence, the reason for this observation is not clear, but may simply reflect "chance" given the low numbers of patients with infections in each of the four treatment groups (0-3 patients). The percentage of patients with wound complications observed in our study was comparable to the literature. In the Baig (2006) study, the local anaesthetic group and placebo group had one wound infection each, whereas wound infection in the Wang (2010) study was 7% (2/28) in the local anaesthetic group and 11% (3/27) in the placebo group.

Furthermore, both of the laparoscopic groups in our study had a 10% rate of post-operative ileus, whereas ileus was less prevalent in the open active group compared to the open placebo group (4% versus 17%, respectively). This is comparable to other findings. The Wang (2010) study had more cases of post-operative ileus in the placebo group compared to the local anaesthetic group (33% (9/27) versus 7% (2/28), respectively), whereas the Baig (2006) study had one more case of ileus present in the local anaesthetic treated group (8/35 versus 7/35). The low rate of ileus in the open active group could be due to the effectiveness of the fast-track surgery recovery protocol, in which one of the objectives was to reduce post-operative ileus, however this was not observed across all the treatment groups in our study. In addition, the measurement of post-operative ileus is intrinsically flawed as there is no set standard for diagnosis, and patients do not necessarily report their symptoms, and bowel sounds do not necessarily mirror bowel activity.

8.2.5 Assessment of Fast-Track Surgery Recovery Protocol

Key objectives of a fast-track surgery recovery protocol, such as the return of bowel function, time to mobilisation and complication rate as discussed above in Section 8.2.3 and 8.2.4, and were comparable to the current literature. However, common issues which can impact on the efficiency and efficacy of the fast-track surgery recovery protocol such as high-re-admission rates after discharge and poor compliance to the protocol are further evaluated.

The re-admission rate for the 73 patients that were fast-tracked in our study was 12% (9/73). This figure was mid-range in comparison to other studies. Scatizzi (2010) retrospectively studied 101 patients that had been fast-tracked after laparoscopic colorectal surgery and reported a re-admission rate of 21.9%. This was higher than our study, although patients in Scatizzi's study had a shorter length of hospitalisation (4.7 days versus 6.5 days for our laparoscopic patients). Scatizzi's study only involved patients that had laparoscopic surgery whereas our study included both laparoscopic and open cases. This suggests that the re-admission rate after colorectal surgery is hard to predict, but that an intention to discharge one day later could potentially reduce re-admissions to acceptable levels. These findings by Scatizzi (2010) were supported by Basse (2004) who concluded a re-admission rate of 20% in 130 patients who were retrospectively analysed after colorectal surgery. Despite the high re-admission rate, patients in the Basse study were hospitalised for only 2 days. However, a controversial aspect to that study was that they selectively excluded patients from their analysis who had their surgery while the primary research team were absent. In contrast, our study included all patients who satisfied the inclusion/exclusion criteria who consented to participate, and also included all normally rostered theatre staff.

However, despite the re-admission rates in our study and Scatizzi's (2010) study and Basse's (2004) study, in a smaller study, Anderson (2003) demonstrated that it was possible to achieve a re-admission rate of 0%. Anderson compared 14 patients who had been fast-tracked to 11 patients who were treated

under traditional care post-operatively after either right or left hemicolectomies. The absence of any patients being re-admitted to hospital is suggestive of the well-controlled nature of the study as one surgeon operated on all the patients. Furthermore, only one patient had an ASA score of 3, compared to 24 in our study. Also the sample size of the patients fast-tracked was small (14 compared to 73 in ours and 101 and 130 in Scatizzi's (2010) and Basse's study, respectively).

Despite indication that poor compliance to the fast-track surgery recovery protocol is an issue, there is only a limited number of studies currently available. In terms of the avoidance of bowel preparation, it was the hospital's colorectal unit's surgical protocol that patients undergoing an ultra-low anterior resection requiring an ileostomy were obliged to have a bowel preparation, so this was applied to the 16% of patients in this study that had that surgery. Furthermore, as there was a range of surgeons involved in the present study, some of these surgeons required that some of their patients had bowel preparations despite not undergoing an ultra-low anterior resection, hence supporting the notion that established surgical practices and tradition can be difficult to change.

The intervention with the lowest degree of compliance in our study was the administration of 200 mL of the carbohydrate drink 2 hr prior to surgery, which had a compliance of just 23%. However, a study by Polle (2007) who compared 55 patients that had been fast-tracked to patients under traditional care, had a degree of compliance of 67% of patients who had consumed the carbohydrate drink 2 hr pre-operatively. A reason for the low compliance with this intervention in our study could be attributed to the pre-operative protocols administered by our hospital's Anaesthetic Department. As stated in the Methods Section 2.1.5 (c), patients with conditions such as diabetes and gastro-oesophageal reflux disease, were prevented from taking liquids 2 hr pre-operatively, hence many of the patients in our study had these conditions thereby falling into this category. So there is a need for those protagonists of fast-track surgery strategies to communicate with the anaesthetists with a view to revisiting the established protocol if this is to become the new direction. Furthermore, it had been noted that members

of the hospital staff had advised eligible patients not to consume the drink before surgery, which could be due to a lack of training of hospital personnel in adapting to new strategies of the pre-operative fasting protocol, which has largely been bound by tradition. This low compliance in our study highlights the difficulty of introducing change in surgical protocols.

In contrast to the pre-operative drink issue above, there was a high degree of protocol compliance in our study in relation to measures such as the avoidance of the nasogastric tube, and the administration of clear fluids, monitoring urine output and encouraging the patient to be out of bed on day 1 post-operation. This was also evident in the Polle (2007) study. High compliance to these measures is suggestive of the reasoning that the above mentioned interventions are becoming accepted in daily practice as positive factors supporting post-operative care following laparoscopic surgery. However, the Polle (2007) study had a 100% compliance to the omission of bowel preparation pre-operatively, whereas our study had a compliance of 58%.

An average of 81% (26/32) of all fast-track interventions were completed, ranging from 14 to 32 interventions completed per patient. This is higher than the Polle (2007) study where 57% of interventions were completed, ranging from 7 interventions completed per patient to 13. The measures in the Polle (2007) study were similar to ours although the Polle protocol included the use of epidural analgesia and was less analgesic focused than our study and only included ASA 1 and ASA 2 patients. Despite the low overall protocol compliance observed in the Polle study, hospital stay was reduced without impacting on morbidity (4.0 days fast-tracked patients versus 6.0 days traditional care patients; morbidity 14.6 % fast-tracked patients versus 15.4% traditional care patients). These findings were similar to our study, thus suggesting that post-operative recovery under a protocol rather than a combined effect of each intervention can potentially be beneficial in enhancing recovery following surgery. Furthermore, it highlights the need and importance of a dedicated, collaborative and supportive multi-disciplinary team.

In addition to the clinical benefits to the patient, the potential economic benefits of fast-track surgery are an important issue, with limited supporting research. However, the cost balance equation for a fast-track surgical approach is complex. Whilst it was in our intention to undertake a costing analysis however due to the complexity of interventions and variability between patients, procedures and treatment groups this was unachievable.

8.2.6 Limitations

There were several limiting factors present in the clinical component of this study that should be addressed.

Firstly, randomisation in the study was for either the active treatment (levobupivacaine) or placebo (saline) treatment. This was regardless of whether the patient was having laparoscopic or open surgery. This decision was at the surgeons' clinical judgement. The intention of the randomisation was to stratify successive patients satisfying the inclusion/exclusion criteria and consenting in a 2:1 ratio of the active treatment to the placebo treatment, irrespective of the intended surgery type. Unfortunately, at the end of the study, there were only 6 patients in the open placebo group. The reasons for this included:

(1) Chance alone, based upon the clinical presentation leading to the surgical type clinical decision mentioned above. In addition, there was always the likelihood of some patients being switched during the surgery from laparoscopic to open for clinical reasons, rendering the initial allocation "flawed".

(2) Our colorectal surgical group have a strong 'research' emphasis, as exemplified by the very existence of this study, and are particularly interested in state-of-the-art technologies and innovative surgical methods, including laparoscopic methods. So it is not surprising, therefore, that they would be inclined to apply such methods for the benefit of their patients wherever possible and open surgery would be the fall-back position when laparoscopic methods were not applicable in the particular patient.

(3) In retrospect, it was arguably a mistake to do a 2:1 allocation to active or placebo treatment that results in less patients being allocated to the placebo arms. Had this been 1:1 then there would have been more patients in the open placebo group.

When the pain scores and opioid consumption results were examined, there was no significant difference between both the active and placebo groups in open surgery. One possible explanation may be due to a case of type 2 error as a result of the small sample size in the open placebo group.

Another limitation in the study was the use of two different opioids. The opioid treatments used in the trial were intravenous fentanyl, intravenous oxycodone and oral oxycodone. Intravenous fentanyl was used in the initial patient recruitment into the trial but was subsequently changed to oxycodone as it can be administered either intravenously or orally (hence less restrictive than maintaining an intravenous line linked to PCA equipment on a stand at the bedside) so advantaging early mobilisation under the fast-track recovery philosophy. A conversion factor was applied so as to combine dosing data, which was rather simplistic as, the conversion between opioids (from fentanyl to oxycodone) is not always straightforward as there is variability with opioids metabolism among different individuals.

The conversion rate of laparoscopic to open procedures was another limiting factor. Three patients in the laparoscopic active group had their procedures converted to open cases, whilst two patients in the laparoscopic placebo group had their procedures converted. Hence, these patients who would have initially received a double catheter Painbuster only received a single catheter, therefore not receiving the same amount of local anaesthetic as patients in the open group, which could contribute to higher opioid consumption and pain scores. The Painbuster was prepared by Pharmacy the day before the surgery and due to a lack of staff, the blinding nature of the protocol and scheduling requirements could not be prepared on short notice during the surgery. However, our study was based on an 'intention to treat' analysis, which included unplanned clinical situations such as this.

The measurement of pain is an obvious weakness in this and many other similar studies for the following reasons:

(1) The VNRS does not address pain coming from specific sites, such as stoma and drain sites, as being separate from the surgical incision site.

(2) As detailed in the introduction, pain measurement is difficult due to the inter-individual variability, subjectivity and complexity, including the range of parameters that influence the accuracy of the patient's voluntary reporting of their pain experience.

(3) The lack of correlation between the neurophysiologic and subjective aspects of pain is another issue as accurate pain reporting should consider cognitive and social effects of pain. However, in many scales, such as the VNRS patients sum up the multi-dimensional aspects of their total pain as just one number.

Furthermore, the inability of the Painbuster to last the 96 hr was a limiting factor, as 20% (16/81) of patients failed to the reach the end of the duration of infusion at 96 hr. The manufacturer claims that the accuracy of the flow-rate selector is ± 20%, so the earliest that a Painbuster reservoir should be empty should be 80% of 96 hr, i.e., 77 hr. So the reason for the number being empty at earlier time points is concerning. There was an incidence of catheters falling out in the days following surgery. Obviously, once fallen out, the treatment solution (levobupivacaine or saline) was no longer delivered as intended. This was remedied during the study by having the catheter secured with a suture, which did reduce the occurrence of such fall-outs.

In a study of this dimension, it is likely that there will be missing data for a wide variety of reasons. For example, blood samples not collected when scheduled, measurement not recorded, etc. Whilst this was kept to a minimum, it was perhaps inevitable and impossible to avoid in clinical practice and missing data where relevant was accounted for.

The co-ordination of the fast-track surgery recovery protocol was an additional limiting factor. At various stages a lack of multi-disciplinary collaboration was evident as surgical staff, the anaesthetists and nursing staff had conflicting views in regards to clinical practice thereby decreasing the likelihood of high protocol compliance. Furthermore due to the high turnover of staff and changes from morning to night shifts, many staff where not trained in the interventions required to enhance care post-operatively with the fast-track surgery recovery protocol.

As alluded to above for some of the other published studies, it would probably be possible to obtain more erudite data if the patients were all operated on by a single surgeon, a single anaesthetist, and cared for by a single small nursing team. However, that would have been at the expense of being less than a 'real world' situation in a busy surgical unit and would have taken far longer to recruit the planned number of patients based on typical throughput at this hospital, certainly beyond the length of this candidature. However, in hindsight, it would have been an advantage to have spent more time in training the range of surgical staff involved so that they were more familiar with the requirements of the study before patients that were included were under their care. Whilst formal presentations about the study were made to nursing staff in the Recovery Unit and Surgical Ward in the planning phase, this was always at the expense of those who were not able to attend due to various shift arrangements, or new staff joining the surgical unit over the ensuing two years during recruitment. Although the fast-track surgery recovery protocol, including detailed instructions was placed in each of the patient's case notes, this did not seem to be as effective as verbal presentations.

The inclusion of smokers or reformed smokers has been alluded to above. Whilst it would have been highly desirable not to do so, again this would have been at the expense of a significantly compromised recruitment rate given the high incidence of smokers in the colorectal cancer population. The same could also be said of some other therapeutic drugs that were co-administered, but not excluded, in this population.

8.3 Evaluation of the Laboratory Component

8.3.1 Plasma Levobupivacaine Concentration

The mean total plasma levobupivacaine concentration absorbed from the incision site into the systemic circulation was 0.73 mg/L where it progressively increased to its peak concentration of 1.94 mg/L at 48 hr post-operation and steadily decreased to 1.19 mg/L at the cessation of infusion at 96 hr post-operation. To date, no other study has investigated the plasma concentrations of 0.5% levobupivacaine following continuous wound infiltration after major abdominal surgery. A study by Pintaric (2008) investigated the concentration of 0.5% levobupivacaine in 12 patients undergoing a parathyroidectomy. Venous blood samples were collected up to 60 min after the epidural administration of levobupivacaine. The mean levobupivacaine concentration level was 0.52 to 0.58 mg/L, although one patient reached a maximum concentration of 1.5 mg/L at 20 min post levobupivacaine dose. The levobupivacaine concentration in Pintaric's (2008) study was lower than our study. It was most likely due to the different routes of administration and relative absorption from the two sites, or less likely the method of analysis as our samples were analysed by HPLC, whereas the samples in Pintaric's (2008) study was analysed by gas chromatography. The vascularity of the site of infusion could contribute to the lower plasma levobupivacaine concentration as infiltration in the Pintaric (2008) study was in the cervical plane, an area of relatively high blood flow, hence rapid absorption, whereas ours was in the abdomen, a site of lower flow. In a study conducted by Allegri (2010), 29 patients received 0.125% levobupivacaine epidurally following major abdominal or urological surgery. Arterial blood samples were taken until 60 hr post-operation. There was a marked increase in plasma levobupivacaine concentrations throughout the 48 hr infusion period; the highest concentration of 1.5 mg/L was reached when the pump was turned off. Increasing plasma levobupivacaine concentrations in Allegri's (2010) study reflected changes of the plasma protein binding related increase in AAG concentrations. Blood collected in our study and the Pintaric's (2008) study was reflective of venous levobupivacaine concentrations whereas Allegri's (2010) study consisted of arterial concentrations. Tucker (1986) showed that arterial concentrations of local anaesthetics had an earlier Tmax than venous concentrations.

Currently, there is no reliable plasma concentration established as a toxicity threshold for levobupivacaine (Lauprecht et al., 2011). However, cardiac effects such as a decrease in stroke volume index can be detected at plasma concentrations below 2 mg/L, and subjective symptoms of intoxication take place with plasma levobupivacaine concentrations higher than 2 mg/L, (Foster and Markham, 2000), importantly this was present in an acute experimental setting. There is a case report suggesting that the first signs of neurological symptoms such as disorientation, restlessness and slurred speech were associated with a concentration of 2.7 mg/L (Kopacz and Allen, 1999) following accidental intravascular injection. However, it is not clear what the peak plasma levobupivacaine concentration was, as the blood sample was obtained 14 min after the initial onset of symptoms. Peak concentrations would have likely been higher if the blood sample was obtained 10 to 15 min earlier. In animal studies life threatening cardiovascular symptoms and cardiovascular collapse were apparent at concentrations of 9.4 mg/L. The threshold for potential reported cardio/neurotoxicity after iv infusion of levobupivacaine in 14 healthy volunteers in the literature is 2.62 mg/L and hence used as the toxicity threshold in our study (Bardsley et al., 1998). From the 6 hr to 96 hr time-point in our study, the toxicity threshold of 2.62 mg/L was reached in 11 patients, however, no signs of levobupivacaine toxicity were observed. This could be explained by the changes in the levobupivacaine plasma protein binding and the changes to AAG concentration during the post-operative period of surgical stress. For these reasons, one should separate results seen in acute setting, potentially in volunteers, from those seen in clinical trials conducted over days following surgery, as side-effects are typically rare after surgery (Thomas and Schug, 1999).

8.3.2 AAG and Protein Binding

As discussed, no classic local anaesthetic toxicity was observed in our study despite relatively high levobupivacaine concentrations observed in some patients approaching or exceeding a suggested toxicity threshold proposed in the literature and adopted for this study. This can be explained by increases in the concentration of the specific binding protein AAG, in response to surgical stress. The

net result of this change is that in this post-operative period, the pharmacologically active unbound fraction represents a smaller proportion of the total drug concentration (as usually measured and referred to in Section 8.3.1 above) when establishing such thresholds. The result of this change in AAG binding following surgical stress is that the threshold plasma levobupivacaine concentration for toxicity will be significantly higher. So thresholds established in an acute exposure and not following such surgical stress (i.e. where AAG concentration is "normal") will not predict the likely toxicity threshold for post-surgical situations. It would be reasonable to suggest that a post-operative threshold should be established in the future as a more meaningful index of drug safety. This also means that:

(1) Current dosing protocols based upon treatment in non-surgical patients are flawed as these are based upon normal protein binding.

(2) Higher levobupivacaine doses (concentration x infusion rate) could be used with safety in such post-operative patients to further enhance the therapeutic benefit to such patients and enhance their pain management.

The mean change (%) in AAG concentrations in our study slightly decreased by 2% from the pre-surgery baseline time-point to the 12 hr post-operation time-point from where there was a steady increase to a rise of 55% above baseline at 48 hr post-operation. However, noticeable in a few (4/21) of the patients, the AAG concentrations peaked at 12 hr but then appeared to decrease by the 48 hr time-point. These findings were consistent with those of Veering (2002), who analysed six patients receiving a bupivacaine epidural after hip surgery. They showed AAG concentrations initially decreased after surgery then increased significantly ($p < 0.0001$) after the 12 hr time-point to the 48 hr time-point. AAG concentrations in the Corso (2007) pilot study to the present study reported a 63% increase from baseline to 48 hr after surgery in 5 patients who received a 0.2% ropivacaine infusion after abdominal surgery. Our study used levobupivacaine which was even more highly bound to AAG than the drugs used in the other studies (levobupivacaine 97%; bupivacaine 95%; ropivacaine 94%). Although the sample size in the Veering (n= 6) and Corso (n= 5) study were smaller than our study (n= 21, being the

number of patient samples where the AAG was determined). The changes observed were comparable in magnitude, supporting the result that the AAG concentration increase after surgery is a clinically significant phenomenon that does need to be accounted for when designing local anaesthetic protocols for post-operative pain management, such as local anaesthetic infiltration. As stated above, it is reasonable to consider giving larger doses than would be given to acute patients where these protein binding changes are not present. In so doing, it is conceivable that better pain management could result without increasing the toxicity risk.

8.3.3 Cortisol Concentration

The surgical stress response is a result of metabolic and endocrine changes that lead to a widespread modification in organ function. These changes are a factor in increased pain, post-operative ileus, hypoxaemia, fatigue, infections, cardiopulmonary and thrombo-embolitic complications (Donohoe et al., 2011). Cortisol is a stress hormone that has been shown to increase in the systemic circulation following surgery (Clarke et al., 1970).

An initial increase in cortisol concentration was evident in our study. Cortisol concentrations in our patients increased to a peak level at 1 hr post-operation; from there it returned to a concentration just above baseline by 24 hr and remained there until the end of the (levobupivacaine or saline) infiltration. Increases in cortisol concentrations after colorectal surgery was also determined by Hong (2006), where peak concentrations were reached 6 hr post-operation. Furthermore, Kato (1997) measured cortisol concentrations during and after upper abdominal surgery in 10 patients. Kato (1997) found that cortisol concentrations increased after skin incision and that the cortisol concentration reached maximal values 2 hr after start of surgery, where it then decreased and gradually returned to almost normal values within 3 day post-operation. Similar to our study, a study by Ozarda Ilçöl (2002) determined increased circulating cortisol concentrations in 16 patients undergoing abdominal surgery. Maximal concentrations were reached at 1 hr post-operation. Like the Kato (1997) study, cortisol concentrations returned to near

baseline levels by day 3 post-operation. Therefore, our findings are consistent with others that stress following surgery can be reflected in such biochemical changes as increases in cortisol and acute phase proteins such as AAG. What is particularly interesting is that cortisol rise is only maintained for approximately 24 hr after surgery, whereas AAG appears to remain elevated for a longer period. Whilst we only recorded AAG concentrations to 48 hr post-surgery, there are other studies showing that this increase is maintained for several weeks (Rutten et al., 1992). The rise in serum cortisol is related to the protein binding of the local anaesthetic as discussed in Section 8.3.2. Furthermore, our study also showed that the presence of the local anaesthetic infiltration did not have a significant effect on cortisol concentrations between the four treatment groups, nor was there any difference in cortisol concentrations by either laparoscopic or open surgery.

8.3.4 Limitations

There were limitations present with the laboratory methodology in this study.

Blood samples not collected when scheduled or not collected at all was a limitation in this study. Blood samples were taken by the intern doctors before being sent to the laboratory for analysis. The colorectal surgical ward was often quite busy and hence the intern doctors on occasion had medical duties to deal with that were prioritised over blood sampling for the trial patient(s). Adding to this issue, under the established protocols of the surgical ward the nursing staff were not allowed to take blood. In the future this could be avoided by training the research team in blood taking protocols. Furthermore, on occasion the patient would refuse to have their blood taken due to either feeling unwell or general refusal. However, a factor like this was hard to avoid in clinical practice and the data, where missing, was accounted for.

Other limitations were present in the HPLC assay and AAG assay techniques. Firstly, the resultant peaks which were used to determine the levobupivacaine to ropivacaine (internal standard) peak height

ratio and hence concentration were recorded manually from a chart recorder, so had to be measured with a ruler with limitations for the measurement of smaller peaks. The sensitivity of measurement was also evident in the AAG assay adopted. The diameter of the AAG precipitin rings were measured using a ruler with sub-millimetre graduations and then correlated to a calibration table provided in the kit comparing the readings to the corresponding AAG concentration. Once again this was highly sensitive as even a difference of one millimetre could result in a substantial difference in the corresponding AAG concentration. As a result we would not advocate the present kit AAG method adopted in the study as being ideal for such future studies.

CHAPTER 9: CONCLUSIONS

CHAPTER 9: CONCLUSIONS

9.1 General Conclusions

Post-operative pain continues to remain under-treated and under-managed despite the development of new analgesics and advancements in the field of pain research. Untreated post-operative pain may adversely affect organ function or lead to chronic pain, hence delaying patient recovery and therefore prolonging hospitalisation. For that reason, this thesis intended to investigate possible techniques that may lead to a reduction in post-operative pain and consequently enhance patient recovery following surgery. In order to achieve this, the following goals were completed:

(1) A randomised double-blinded placebo controlled trial investigating if 0.5% levobupivacaine using the Painbuster, a commercial infiltration device could lead to minimisation or elimination of opioid analgesia following laparoscopic or open abdominal surgery. Novel aspects of this study included: the placement of the soaker catheter in the deeper muscle years of the abdomen adjacent to the sensory nerve fibres most affected so avoiding the reliance on diffusion of drug from superficial sites through the various tissues before reaching the pain nerves leading to a less predictable response; the higher concentration of the local anaesthetic infused at the surgical incison site; and the longer duration of post-operative local anaesthetic infusion to 96 hr from the recommended practice of 48 hr. Furthermore, this was the first study that examined the use of continuous local anaesthetic infiltration in colorectal laparoscopic surgery.

(2) The determination of the plasma levobupivacaine concentration in order to establish if it was safe and below the suggested toxicity threshold. AAG concentrations and cortisol concentrations were further measured in order to determine the impact of protein binding changes and the surgical stress response following surgery. In addition, to date no other study has investigated the plasma levobupivacaine concentrations with the use of a continuous wound infiltration device following laparoscopic and open abdominal surgery.

(3) In order to enhance patient recovery, by decreasing hospitalisation and post-operative complications and improving patient pain management, a fast-track surgery protocol was implemented. Issues which could impact on the effectiveness of the protocol were also evaluated.

The key findings found from this research are outlined below:

(1) Although there was no difference in opioid consumption between the laparoscopic active and laparoscopic placebo groups, there was a trend towards reduced opioid consumption in the open active group suggesting the effectiveness of the levobupivacaine infiltration at the incision site. Furthermore, while the opioid consumption was reduced in the two laparoscopic groups and comparable to the open active group, the opioid consumption in the open placebo group remained high, hence maintaining what would typically occur clinically in open surgery without the addition of local anaesthetics. This also supports the notion that post-operative pain remains under-treated despite the availability of pain medications and advancements in pain medicine. The strength of this conclusion was diluted by the limited number of patients recruited into the open placebo arm for reasons detailed in earlier sections, and requires further studies in larger sample to verify this conclusion.

(2) In patients undergoing open surgery, the active treatment was associated with a trend towards a reduction in pain scores at rest and movement. Again, this conclusion was compromised by the number of patients in the open placebo arm. There was no overall difference in pain scores at rest and movement between the two laparoscopic groups, although paradoxically, the pain scores at rest and movement in the laparoscopic active group were higher than the laparoscopic placebo group at certain time-points.

(3) Variables which could influence opioid consumption and pain scores were analysed. Patients who had a stoma present had a higher perception of pain and required more opioid therapy; this was also reflected in patients who had a drain inserted. Female patients had higher levels of pain compared to

male patients, although they used less opioid. Opioid consumption decreased with increasing age, however no relationship was evident between age and pain perception.

(4) The continuous wound infiltration of levobupivacaine, not surprisingly, appeared to be independent of recovery of bowel function or time to first mobilisation. Furthermore, it did not have a significant effect on the length of hospitalisation and re-admission rate.

(5) Nausea and vomiting were the most common side-effects present amongst the four treatment groups and was independent of the presence of local anaesthetic. Surgical complications were comparable with current literature. No classic local anaesthetic adverse effects were observed, suggesting that the higher dosage adopted was safe.

(6) An average of 81% of all fast-track interventions were completed with a degree of compliance ranging from 17% to 100%. This suggested that there was need of even greater education and communication to advance this philosophy further as part of a collaborative and dedicated multi-disciplinary team approach. Furthermore, it is important to understand that the aim of fast-track surgery is to aspire to improving patient recovery by reducing morbidity and promoting earlier discharge without precipitating unacceptable readmission rates, rather than just focusing on early discharge alone.

(7) The mean total levobupivacaine concentrations were below the toxicity threshold proposed in the acute patient setting, suggestive the safety of the drug. The recognised increase of the plasma protein AAG following surgical stress was observed. This increase is a clinically significant phenomenon that has implications for the design of local anaesthetic protocols for post-operative pain management, such as local anaesthetic infusion. As stated in the Discussion above, it is reasonable to consider giving larger doses than would be given to acute patients where these protein binding changes are not present. In so doing, it is conceivable that better pain management could result without increasing the

toxicity risk. Furthermore, cortisol concentrations rose after surgery reinforcing the biochemical changes following surgical stress as also reflect in the AAG response; however, the cortisol concentration returned to near pre-operative levels by 24 hr and remained so to 96 hr. In contrast, the AAG concentration remained elevated to 48 hr, consistent with published data indicating that this remains elevated for several weeks.

In essence, these findings suggest that a 96 hr continuous local anaesthetic infiltration post abdominal surgery may be a favourable method of pain control in patients undergoing open surgery. This could be due to the well located catheter, the increased local anaesthetic concentration and a longer post-operative infiltration period.

9.2 Future Research

In order to build upon the resultant findings in this study and to further contribute towards research into the field of pain management, there are several potential ideas of prospective studies which could potentially be explored. Future research may involve:

(1) Studies which increase the dose of the local anaesthetic beyond the higher dose selected in this study. In this study it was shown that 0.5% levobupivacaine was safe and efficacious without resulting in any local anaesthetic induced toxicity. Hence increasing the dose to 0.75%, or more, could further enhance pain relief and reduce the need of opioid analgesia.

(2) Studies involving measurement of un-bound levobupivacaine concentrations, rather than total plasma levobupivacaine concentrations, would provide a direct estimate of the pharmacologically active moiety and so avert the complexities of the post-surgical increases in AAG concentrations rendering the total levobupivacaine concentration a flawed index of possible toxicity. This may require more sensitive assay technology than HPLC-UV (used in the present study), such as HPLC-mass spectrometry, given the very low concentration (1-2% of total concentration) present. This would also address the situation seen in the present study where not all patients appeared to demonstrate the change in protein binding associated with increased AAG concentrations, and the establishment of a reliable toxicity threshold for unbound levobupivacaine, so independent of the protein binding status and pre- or post-surgical clinical scenario

(3) The inclusion of studies involving anxiety and/or psychological tests. The subjective nature of pain and the psychological condition of the pain impact on anxiety and the psychological nature of the patient. Hence further research may eliminate these variables and provide researchers with a clearer understanding leading to individualised pain management that incorporates such parameters.

(4) Enhanced strategies for the use of Painbuster technologies in laparoscopic surgery. This could include catheter location(s) or new catheter technique(s) where the catheter also covers the stoma and drain site in addition to the primary surgical incision, hence incorporating all operative pain sources.

Hence, the above mentioned future studies may contribute to research in improving patient pain management. Post-operative pain, although an expected outcome following surgery, has the potential to be eliminated thereby reducing patient distress and the burden on the health care system. Therefore this thesis has been an important contributing factor aimed at achieving this.

"Pain is inevitable, suffering is optional" - Dante A Lavey

REFERENCES

ABBOTT (2006) Product information. Chirocaine *Abbott Australasia Pty Ltd,* Version 02.

ABRAHAM, N. & ALBAYATI, S. (2011) Enhanced recovery after surgery programs hasten recovery after colorectal resections *World Journal of Gastrointestinal Surgery* 3(1)**,** 1-6.

ABRAHAM, N. S. (2011) Is laparoscopic resection for colorectal cancer the way to the future? . *Medical Journal of Australia,* 194(9)**,** 441-2.

ALBRIGHT, G. A. (1979) Cardiac arrest following regional anesthesia with etidocaine and bupivacaine. *Anesthesiology,* 51**,** 285-7

ALESSANDRI, F., MISTRANGELO, E., LIJOI, D., FERRERO, S. & RAGNI, N. (2006) A prospective, randomized trial comparing immediate versus delayed catheter removal following hysterectomy *Acta Obstetricia et Gynecologica Scandinavica* 85(6)**,** 716-20.

ALLEGRI, M., NIEBEL, T., BALDI, C., BETTINELLI, S., CUSATO, M., BRASCHI, A. & REGAZZI, M. (2010) Plasma concentrations of levobupivacaine increase under continuous infusion after a major surgery *Acta Anaesthesiologica Scandinavica,* 4(5)**,** 654-5.

ALMY, T. P. & HOWELL, D. A. (1980) Diverticular disease of the colon. *The New England Journal of Medicine* 302(6)**,** 324-31.

ANDERSEN, J., HJORT-JAKOBSEN, D., CHRISTIANSEN, P. S. & KEHLET, H. (2007) Readmission rates after a planned hospital stay of 2 versus 3 days in fast-track colonic surgery *British Journal of Surgery,* 94(7)**,** 890-3.

ANDERSON, A. D., MCNAUGHT, C. E., MACFIE, J., TRING, I., BARKER, P. & MITCHELL, C. J. (2003) Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *British Journal of Surgery,* 90(12)**,** 1497-504.

ANONYMOUS (2011) Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the american society of anesthesiologists committee on standards and practice parameters. An updated report by the American Society of Anesthesiologists *Anesthesiology,* 114(3)**,** 495-511.

ARDIZZONE, S. & BIANCHI PORRO, G. (2002) Inflammatory bowel disease: new insights into pathogenesis and treatment. *Journal of Internal Medicine* 252**,** 475-96.

ARIAS, M. G. (2002) Levobupivacaine: a long acting local anaesthetic, with less cardiac and neurotoxicty. *Update in Anaesthesia,* 14**,** 1-6.

ASLAKSEN, P. M., MYRBAKK, I. N., HOIFODT, R. S. & FLATEN, M. A. (2007) The effect of experimenter gender on autonomic and subjective responses to pain stimuli *Pain,* 129**,** 260-8.

AUSTRALIAN AND NEW ZEALAND COLLEGE OF ANAESTHETISTS, AUSTRALIAN PAIN SOCIETY, CHRONIC PAIN AUSTRALIA, MBF FOUNDATION & UNIVERSITY OF SYDNEY, PAIN MANAGEMENT RESEARCH INSTITUTE, (2010) National pain strategy. pain management for all Australians. *National Pain Summit.* Canberra, Australia.

BAIG, M. K., ZMORA, O., DERDEMZI, J., WEISS, E. G., NOGUERAS, J. J. & WEXNER, S. D. (2006) Use of the ON-Q pain management system is associated with decreased postoperative analgesic requirement: double blind randomized placebo pilot study. *Journal of the American College of Surgeons* 202**,** 297-305.

BARDSLEY, H., GRISTWOOD, R., BAKER, H., WATSON, N. & NIMMO, W. (1998) A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *British Journal of Clinical Pharmacology* 46**,** 245-9.

BASSE, L., THORBØL, J. E., LØSSL, K. & KEHLET, H. (2004) Colonic surgery with accelerated rehabilitation or conventional care *Diseases of the Colon and Rectum,* 47(3)**,** 271-7.

BEAUSSIER, M., EL'AYOUBI, H., SCHIFFER, E., ROLLIN, M., PARC, Y., MAZOIT, J. X., AZIZI, L., GERVAZ, P., ROHR, S., BIERMANN, C., LIENHART, A. & EIEDJAM, J. J. (2007) Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. *Anesthesiology,* 107 (3)**,** 461-8.

BENEDETTI, F. (2007) Placebo analgesia, nocebo hyperalgesia. *Pain Clinical Updates IASP,* XV (1)**,** 1-4.

BENHAMOU, D. (1998) Evaluation of postoperative pain. *Annales francaises d'anesthesie et de reanimation* 17**,** 555-72.

BERGUER, R., SMITH, W. D. & CHUNG, Y. H. (2001) Performing laparoscopic surgery is significantly more stressful for the surgeon than open surgery. *Surgical Endoscopy,* 15 (10)**,** 1204-7.

BERRISFORD, R. G., SABANATHAN, S., MEARNS, A. J., CLARKE, B. J. & HAMDI, A. (1993) Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block. *British Journal of Anaesthesia,* 70(2)**,** 201-4.

BESSON, J. M. (1997) The complexity of physiopharmacologic aspects of pain *Drugs* 53 (2)**,** 1-9

BIRKETT, D. J. (1998) *Pharmacokinetics made easy- Australian presciber: an independent review,* The McGraw Hill Companies Inc.

BLACKFORD, D., HEWETT, P., PANDE, G., NGUYEN, H., CHILVERS, C. & ROBERTSON, I. (2008) Future of analgesia for abdominal laparotomy. *ANZ Journal of Surgery,* 78**,** 527-9.

BLAKE, D. W., BJORKSTEN, A., DAWSON, P. & HISCOCK, R. (1994) Pharmacokinetics of bupivacaine enantiomers during interpleural infusion. *Anaesthesia and Intensive Care* 22(5)**,** 522-8.

BOND, M. & BREIVIK, H. (2004) Why pain control matters in a world full of killer diseases. *Pain Clinical Updates IASP,* XII (4)**,** 4.

BOTTI, M., BUCKNALL, T. & MANIAS, E. (2004) The problem of post-operative pain: Issues for future research. *International Journal of Nursing Practice,* 10**,** 257-263.

BOWER, S. & HULL, C. (1982) Comparative pharmacokinetics of fentanyl and alfentanil. *British Journal of Anaesthesia,* 54(8)**,** 871-77.

BRADY, M., KINN, S. & STUART, P. (2003) Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database of Systemic Reviews,* 4**,** 1-153.

BRAGA, M., VIGNALI, A., GIANOTTI, L., ZULIANI, W., RADAELLI, G., GRUARIN, P., DELLABONA, P. & DI CARLO, V. (2002) Laparoscopic versus open colorectal surgery. *Annals of Surgery,* 236(6)**,** 759-67.

BRANDSTRUP, B., TØNNESEN, H., BEIER-HOLGERSEN, R., HJORTSØ, E., ØRDING, H., LINDORFF-LARSEN, K., RASMUSSEN, M. S., LANNG, C., WALLIN, L., IVERSEN, L. H., GRAMKOW, C. S., OKHOLM, M., BLEMMER, T., SVENDSEN, P. E., ROTTENSTEN, H. H., THAGE, B., RIIS, J., JEPPESEN, I. S., TEILUM, D., CHRISTENSEN, A. M., GRAUNGAARD, B. & POTT, F. (2003) Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Annals of Surgery,* 238(5)**,** 641-8.

BRANNON, L. & FEIST, J. (2000) *Health psychology: An introduction to behaviour and health* USA, Cole.

BRENNAN, F. & COUSINS, M. J. (2004) Pain relief as a human right. *Pain Clinical Updates IASP,* XII (5)**,** 4.

BRENNAN, T. J., ZAHN, P. K. & POGATZKI-ZAHN, E., M, (2005) Mechanisms of incisional pain. *Anesthesiology Clinics of North America,* 23**,** 1-20.

BREUER, J. P., VON DOSSOW, V., VON HEYMANN, C., GRIESBACH, M., VON SCHICKFUS, M., MACKH, E., HACKER C, ELGETI, U., KONERTZ, W., WERNECKE, K. D. & SPIES, C. D. (2006) Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery *Anesthesia & Analgesia,* 103(5)**,** 1099-108.

BRODY, H. (1985) Placebo effect: an examination of Grunbaum's definition. IN WHITE, L., TURSKY, B. & SCHWARTZ, G. E. (Eds.) *Placebo: Theory, Research and Mechanisms.* New York, N.Y., Guilford Press

BURGER, J. W., VAN 'T RIET, M. & JEEKEL, J. (2002) Abdominal incisions: techniques and postoperative complications. *Scandinavian Journal of Surgery* 91**,** 315-21

BURLACU, C. L. & BUGGY, D. J. (2008) Update on local anesthetics: focus on levobupivacaine. . *Therapeutics and Clinical Risk Management* 4(2)**,** 381-92.

BURSTAL, R., WEGENER, F., HAYES, C. & LANTRY, G. (1998) Epidural analgesia: prospective audit of 1062 patients. *Anaesthesia and Intensive Care,* 26**,** 165-72.

CANCER COUNCIL SA (2007) Bowel (colorectal) cancer http://www.cancersa.org.au/aspx/home.aspx accessed: December 2007.

CARLI, F., CHARLEBOIS, P., BALDINI, G., CACHERO, O. & STEIN, B. (2009) An integrated multidisciplinary approach to implementation of a fast-track program for laparoscopic colorectal surgery *Canadian Journal of Anesthesia,* 56**,** 837-42.

CARR, D. (1993) Pain control: The new "whys" and "hows". *Pain Clinical Updates IASP,* 1**,** 8.

CARR, D. (1996) Preemptive analgesia implies prevention. *Anesthesiology* 85**,** 1498.

CASATI, A. & PUTZU, M. (2005) Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? . *Best Practice & Research Clinical Anaesthesiology* 19(2)**,** 247-68.

CHAHL, L. A. (1996) Opioids- mechanism of action *Australian Prescriber,* 19**,** 63-5.

CHANG, D. H., LADD, L. A., WILSON, K. A., GELGOR, L. & MATHER, L. E. (2000) Tolerability of large-dose intravenous levobupivacaine in sheep. *Anesthesia & Analgesia,* 91**,** 671-9.

CHAPMAN, C. R. (2005) Pain perception and assessment. *Minerva Anestesiologica,* 71**,** 413-7.

CHARLTON, S., CYNA, A., MIDDLETON, P. & GRIFFITHS, J. (2010) Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery *Cochrane Database of Systemic Reviews,* 12(CD007705).

CHENG, C. R., SU, T. H., HUNG, Y. C. & WENG, P. T. (2002) A comparative study of the safety and efficacy of 0.5% levobupivacaine and 0.5% bupivacaine for epidural anesthesia in subjects undergoing elective caesarean section. *Acta Anaesthesiologica Sinica,* 40(1)**,** 13-20.

CHEONG, W. K., SEOW-CHOEN, F., EU, K. W., TANG, C. L. & HEAH, S. M. (2001) Randomized clinical trial of local bupivacaine perfusion versus parenteral morphine infusion for pain relief after laparotomy *British Journal of Surgery,* 88**,** 357-9.

CHUNG, F. (1998) Unanticipated admission after ambulatory surgery- a prospective study. *Canadian Journal of Anesthesia,* 45**,** 612-9.

CLANCY, J. & MCVICAR, A. (1992) Subjectivity of pain. *British Journal of Nursing,* 1**,** 8-12.

CLARKE, R. S. J., JOHNSTON, H. & SHERIDAN, B. (1970) The influence of anaesthesia and surgery on plasma cortisol, insulin and free fatty acids. *British Journal of Anaesthesia,* 42**,** 295-9.

COLL, A. M., AMEEN, J. R. M. & MEAD, D. (2004) Postoperative pain assessment tools in day surgery: literature review. *Journal of Advanced Nursing,* 46**,** 124-33.

CORDELL, W. H., KEENE, K. K., GILES, B. K., JONES, J. B. & BRIZENDINE, E. J. (2002) The high prevalence of pain in emergency medical care. *American Journal of Emergency Medicine,* 20**,** 165-9.

CORSO, O. H., MORRIS, R. G., HEWETT, P. & KARATASSAS, A. (2007a) Safety of 96-hour incision-site continuous infusion of ropivacaine for postoperative analgesia after bowel cancer resection. *Ther Drug Monit,* 29**,** 57-63.

CORSO, O. H., MORRIS, R. G., HEWETT, P. J. & KARATASSAS, A. (2007b) Safety of 96-hour incision-site continuous infusion of ropivacaine for postoperative analgesia after bowel cancer resection. *Therapeutic Drug Monitoring* 29(1)**,** 57-63.

COUNIHAN, T. C. & FAVUZZA, J. (2009) Fast Track Colorectal Surgery. *Clinics in Colon and Rectal Surgery,* 22**,** 60-72.

COUSINS, M. J. & MATHER, L. E. (1980) Local Anaesthetics. *Anaesthesia and Intensive Care,* VIII(3)**,** 259-77.

COX, C. R., FACCENDA, K. A., GILHOOLY, C., BANNISTER, J., SCOTT, N. B. & MORRISON, L. M. (1998) Extradural S(-)-bupivacaine comparison with racemic RS-bupivacaine. *British Journal of Anaesthesia,* 80(3)**,** 289-93.

CRAFT, R. M., MOGIL, J. S. & ALOISI, A. M. (2004) Sex differences in pain and analgesia: the role of gonadal hormones *European Journal of Pain,* 8**,** 397-411.

CREEKMORE, F. M., LUGO, R. A. & WEILAND, K. J. (2004) Postoperative opiate analgesia requirements of smokers and nonsmokers *The Annals of Pharmacotherapy* 38**,** 949-53.

CUMMING, G., FIDLER, F. & VAUX, D. (2007) Error bars in experimental biology *The Journal of Cell Biology* 177(1)**,** 7-11

DAHL, J. B., HANSEN, B. L., HJORTSO, N. C., ERICHSEN, C. J., MOINICHE, S. & KEHLET, H. (1992) Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia,* 69**,** 4-12.

DAHL, J. B. & KEHLET, H. (1991) Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *British Journal of Anaesthesia,* 66**,** 703-12.

DAHL, J. L. (2011) The three faces of fentanyl *WCPI Focus on Pain Series http://aspi.wisc.edu/ accessed 04-2011*.

DE KOCK, M. & SCHOLTES, J. L. (1991) Postoperative P.C.A. in abdominal surgery. Analysis of 200 consecutive patients. *Acta Anaesthesiologica Belgica,* 42(2)**,** 85-91.

DELANEY, C. P., FAZIO, V. W., SENAGORE, A. J., ROBINSON, B., HALVERSON, A. L. & REMZI, F. H. (2001) 'Fast track" postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvis colorectal surgery *British Journal of Surgery,* 88(11)**,** 1533-8.

DELEO, J. A. (2006) Basic science of pain. *The Journal of Bone and Joint Surgery* 88**,** 58-62.

DERNEDDE, M., STADLER, M., BARDIAU, F. & BOOGAERTS, J. G. (2003) Comparison of different concentrations of levobupivacaine for post-operative epidural analgesia. *Acta Anaesthesiologica Scandinavica,* 47**,** 884-90.

DESBOROUGH, J. P. (2000) The stress response to trauma and surgery. *British Journal of Anaesthesia,* 85(1)**,** 109-17.

DICKENSON, A. H. (1995) Spinal cord pharmacology of pain. *British Journal of Anaesthesia,* 75**,** 193-200.

DINICOLA, N. (2003) Post-operative pain. *The Virtual Anaesthesia Textbook* 1-8.

DIRKS, J., MOINICHE, S., HILSTED, K. L. & DAHL, J. B. (2002) Mechanisms of postoperative pain: clinical indications for a contribution of central neuronal sensitization *Anesthesiology,* 97.

DONATI, D., BROWN, S. R., EU, K. W., HO, Y. H. & SEOW-CHOEN, F. (2002) Comparison between midline incision and limited right skin crease incision for right-sided colonic cancers *Techniques in Coloproctology* 6(1)**,** 1-4.

DONOHOE, C. L., NGUYEN, M., COOK, J., MURRAY, S. G., CHEN, N., ZAKI, F., MEHIGAN, B. J., MCCORMICK, P. H. & REYNOLDS, J. V. (2011) Fast-track protocols in colorectal surgery. *The Surgeon* 9(2)**,** 95-103.

DOWD, N. P., TAYLOR, A., MORIARTY, D. C. & BLUNNIE, W. P. (1997) Single dose omeprazole on plasma bupivacaine concentrations following epidural administration *Canadian Journal of Anesthesia,* 44**,** 1029.

EDGCOMBE, H. & HOCKING, G. (2005) Local anaesthetic pharmacology *Update in Anaesthesia***,** 125-7.

ELLIS, H. (1939) *My life,* Boston Houghton Mifflin Company

ENQUIST, A., BRANDT, M. R., FERNANDES, A. & KEHLET, H. (1977) The blocking effect of epidural analgesia on the adrenocortical and hyperglycaemic responses to surgery. *Acta Anaesthesiologica Scandinavica,* 21**,** 330-5.

FARISS, B. L., FORESMAN, P. A., RODEHEAVER, G. T., CHANG, D. E., SMITH, J. F., MORGAN, R. F. & EDLICH, R. F. (1987) Anesthetic properties and toxicity of bupivacaine and lidocaine for infiltration anesthesia. *The Journal of Emergency Medicine,* 5(4)**,** 275-82.

FEARON, K. C., LJUNGQVIST, O., VON MEYENFELDT, M., REVHAUG, A., DEJONG, C. H., LASSEN, K., NYGREN, J., HAUSEL, J., SOOP, M., ANDERSEN, J. & KEHLET, H. (2005) Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clinical Nutrition,* 24(3)**,** 466-77.

FERLAY, J., SHIN, H. R., BRAY, F., FORMAN, D., MATHERS, C. & PARKIN, D. M. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer,* 127(12)**,** 2893-917.

FILLINGIM, R. B. & GEAR, R. W. (2004) Sex differences in opioid analgesia: clinical and experimental findings. *European Journal of Pain,* 8**,** 413-25.

FILLINGIM, R. B., KING, C. D., RIBEIRO-DASILVA, M. C., RAHIM-WILLIAMS, B. & RILEY, J. L. (2009) Sex, gender, and pain: a review of recent clinical and experimental findings. *The Journal of Pain* 10 (5)**,** 447-85.

FINK, R. (2000) Pain assessment: the cornerstone to optimal pain management. *Baylor University Medical Center Proceedings,* 13**,** 236-9.

FOSTER, R. H. & MARKHAM, A. (2000) Levobupivacaine. A review of its pharmacology and use as a local anaesthetic. *Drugs,* 59(3)**,** 551-79.

GAN, T. J., MEYER, T. & APFEL, C. C. (2003) Consensus guidelines for managing postoperative nausea and vomiting. *Anesthesia & Analgesia,* 97**,** 62-71.

GATT, M., ANDERSON, A. D., REDDY, B. S., HAYWARD-SAMPSON, P., TRING, I. C. & MACFIE, J. (2005) Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *British Journal of Surgery,* 92(11)**,** 1354-62.

GEAR, J. S. S., WARE, A., FURSDON, P., MANN, J. I., NOLAN, D. J., BRODRIBB, A. J. M. & VESSEY, M. P. (1979) Symptomless diverticular disease and intake of dietary fibre. *The Lancet,* 8115**,** 511-14.

GIBSON, S. J. (2006) Older people's pain. *Pain Clinical Updates IASP,* XIV (3)**,** 1-4.

GOTTSCHALK, A., WU, C. L. & OCHROCH, E. A. (2002) Current treatment options for acute pain *Expert Opinion on Pharmacotherapy* 3 (11)**,** 1599-1611.

GOUVAS, N., TAN, E., WINDSOR, A., XYNOS, E. & TEKKIS, P. P. (2009) Fast-track vs standard care in colorectal surgery: a meta-analysis update. *International Journal of Colorectal Disease* 24**,** 1119-31.

GRANTCHAROV, T. P. & ROSENBERG, J. (2001) Vertical compared with transverse incisions in abdominal surgery. *European Journal of Surgery,* 167**,** 260-7.

GREIF, R., AKÇA, O., HORN, E. P., KURZ, A. & SESSLER, D. I. (2000) Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *New England Journal of Medicine,* 342(3)**,** 161-7.

GRIFFITHS, R. & FERNANDEZ, R. (2007) Strategies for the removal of short-term indwelling urethral catheters in adults *Cochrane Database of Systemic Reviews,* 18(2)**,** 1-83.

GRISTWOOD, R. W. (2002) Cardiac and CNS toxicity of levobupivacaine: strengths of evidence for advantage over bupivacaine. *Drug Safety,* 25 (3)**,** 153-63.

GRISTWOOD, R. W. & GREAVES, J. L. (1999) Levobupivacaine: a new safer long acting local anaesthetic agent. *Expert Opinion on Investigational Drugs,* 8 (6)**,** 861-76.

GURUSAMY, K. S., SAMRAJ, K., MULLERAT, P. & DAVIDSON, B. R. (2007) Routine abdominal drainage for uncomplicated laparoscopic cholecystectomy. *Cochrane Database of Systemic Reviews,* 18(3).

HALL, G. M., YOUNG, C., HOLDCROFT, A. & ALAGHBAND-ZADEH, J. (1978) Substrate mobilisation during surgery. A comparison with halothane anaesthesia. *Anaesthesia,* 33**,** 924-30.

HAUSEL, J., NYGREN, J., LAGERKRANSER, M., HELLSTRÖM, P. M., HAMMARQVIST, F., ALMSTRÖM, C., LINDH, A., THORELL, A. & LJUNGQVIST, O. (2001) A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesthesia & Analgesia,* 93(5)**,** 1344-50.

HEWETT, P. J., ALLARDYCE, R. A., BAGSHAW, P. F., FRAMPTON, C. M., FRIZELLE, F. A., RIEGER, N. A., SMITH, J. S., SOLOMON, M. J., STEPHENS, J. A. & STEVENSON, A. R. L. (2008) Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer *Annals of Surgery* 248(5)**,** 728-38.

HOLTE, K., FOSS, N. B. & ANDERSEN, J. (2007) Liberal or restrictive fluid administration in fast track colonic surgery: a randomized, double-blind study. *British Journal of Anaesthesia,* 99(4)**,** 500-8.

HONG, X., YE, T. H., ZHANG, X. H., REN, H. Z., HUANG, Y. G. & BU, Y. F. (2006) Changes of interleukin-6 and related factors as well as gastric intramucosal pH during colorectal and orthopaedic surgical procedures. *Chinese Medical Sceinces Journal* 21(1)**,** 57-61.

HORTON, R. (2004) Vioxx, the implosion of Merck, and aftershocks at the FDA. *Lancet,* 364(9450)**,** 1995-6.

ILCOL, Y. O., OZYURT, G., KILICTURGAY, S., UNCU, G. & ULUS, I. H. (2002) The decline in serum choline concentration in humans during and after surgery is associated with the elevation of cortisol, adrenocorticotropic hormone, prolactin and βετα-endorphin concentrations. *Neuroscience Letters,* 324**,** 41-4.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (1986) Pain terms *Pain* 26.

JEMAL, A., SIEGEL, R., WARD, E., MURRAY, T., XU, J. & THUN, M. J. (2007) Cancer statistics, 2007. *A Cancer Journal for Clinicians,* 57(1)**,** 43-66.

JIN, F. & CHUNG, F. (2001) Multimodal analgesia for postoperative pain control *Journal of Clinical Anesthesia,* 13**,** 524-539.

JOELS, C. S., MOSTAFA, G., MATTHEWS, B. D., KERCHER, K. W., SING, R. F., NORTON, H. J. & HENIFORD, B. T. (2003) Factors affecting intravenous analgesic requirements after colectomy. *Journal of the American College of Surgeons,* 197(5)**,** 780-5.

KALLAI, I., BARKE, A. & VOSS, U. (2004) The effects of experimenter characteristics on pain reports in women and men. *Pain,* 112**,** 142-7

KALSO, E. (2007) How different is oxycodone from morphine? . *Pain,* 132(3)**,** 227-8.

KARATASSAS, A. (1992) The effect of regional blood flow on the pharmacokinetics of infiltrated doses of lignocaine. *MS Thesis* Surgery The University of Adelaide.

KARATASSAS, A., MORRIS, R. G. & SLAVOTINEK, A. H. (1993) The relationship between regional blood flow and absorption of lignocaine. *The Australian and New Zealand Journal of Surgery* 63**,** 766-71.

KARTHIKESALINGAM, A., WALSH, S. R., MARKAR, S. R., SADAT, U., TANG, T. Y. & MALATA, C. M. (2008) Continuous wound infusion of local anaesthetic agents following colorectal surgery: systematic review and meta-analysis. *World Journal of Gastroenterology* 14 (34)**,** 5301-5.

KATO, M., SUZUKI, H., MURAKAMI, M., AKAMA, M., MATSUKAWA, S. & HASHIMOTO, Y. (1997) Elevated plasma levels of interleukin-6, interleukin-8, and granulocyte colony-stimulating factor during and after major abdominal surgery. *Journal of Clinical Anesthesia,* 9(4)**,** 293-8.

KAWAMATA, M., TAKAHASHI, T., KOZUKA, Y., NAWA, Y., NISHIKAWA, K., NARIMATSU, E., WATANABE, H. & NAMIKI, A. (2002) Experimental incision-induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia *Pain* 100**,** 77-89.

KEATS, A. S. (1978) The ASA classification of physical status- a recapitulation. *Anesthesiology,* 49**,** 233-6.

KEHLET, H. (1994) Postoperative pain relief- what is the issue? *British Journal of Anaesthesia,* 72 (4)**,** 375-8

KEHLET, H. (2006) Future perspectives and research initiatives in fast-track surgery. *Langenbecks Archives of Surgery,* 391**,** 495-8.

KEHLET, H. (2008) Fast-track colorectal surgery. *The Lancet,* 371**,** 791-3.

KEHLET, H., RUNG, G. W. & CALLESEN, T. (1996) Postoperative opioid analgesia: time for a reconsideration? *Journal of Clinical Anesthesia,* 8**,** 441-5.

KELLY, D. J., AHMAD, M. & BRULL, S. J. (2001) Preemptive analgesia I: physioloigcal pathways and pharmacological modalities. *Canadian Journal of Anesthesia,* 48 (10)**,** 1000-10.

KIRSNER, J. B. (1991) Inflammatory bowel disease. Part II: clinical and therapeutic aspects. *Disease-A-Month* 37(11)**,** 669-746.

KISSIN, I. (2005) Preemptive analgesia at the crossroad. *Pain Medicine,* 100**,** 754-6.

KISSIN, I. (2010) Preemptive analgesia: problems with assessment of clinical significance *Methods in molecular biology* 617**,** 475-82.

KLINGSTEDT, C., GIESECKE, K., HAMBERGER, B. & JANBERG, P. O. (1987) High- and low-dose fentanyl anaesthesia, circulatory and catecholamine responses during cholecystectomy. *British Journal of Anaesthesia,* 59**,** 184-8.

KLOPFENSTEIN, C. E., HERRMANN, F. R., MAMIE, C., VAN GESSEL, E. & FORSTER, A. (2000) A comparison between patients' reported assessments and nurses' and physicians' observations. *Acta Anaesthesiologica Scandinavica,* 44**,** 58-62.

KNUDSEN, K., SUURKULA, M. B., BLOMBERG, S., SJOVALL, S. & EDVARDSON, N. (1997) Central nervous and cardiovascular effects of i.v. infusion of ropivacaine, bupivacaine and placebo in volunteers. *British Journal of Anaesthesia,* 78**,** 507-14.

KOBAYASHI, M., MOHRI, Y., INOUE, Y., OKITA, Y., MIKI, C. & KUSUNOKI, M. (2008) Continuous follow-up of surgical site infections for 30 days after colorectal surgery *World Journal of Surgery* 32(6)**,** 1142-6.

KOPACZ, D. J. & ALLEN, H. W. (1999) Accidental intravenous levobupivacaine. *Anesthesia & Analgesia,* 89(4)**,** 1027-9.

KOPACZ, D. J., ALLEN, H. W. & THOMPSON, G. E. (2000) A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. *Anesthesia & Analgesia,* 90 (3)**,** 642-8.

KRAFT, M., ERSTAD, B. L. & MATUSZEWSKI, K. (2005) Improving postoperative ileus. *US Pharmacist* Johnson Publication

KRIEGER, B. R., DAVIS, D. M., SANCHEZ, J. E., MATEKA, J. J., NFONSAM, V. N., FRATTINI, J. C. & MARCET, J. E. (2011) The use of silver nylon in preventing surgical site infections following colon and rectal surgery. *Diseases of the Colon and Rectum,* 54(8).

KUCHARZIK, T., MAASER, C., LUGERING, A., KAGNOFF, M., MAYER, L., TARGAN, S. & DOMSCHKE, W. (2006) Recent understanding of IBD pathogenesis: implications for future therapies. *Inflammatory Bowel Diseases,* 12(11)**,** 1068-1083.

KUGATHASAN, S. & FIOCCHI, C. (2007) Progress in basic inflammatory bowel disease research *Seminars in Pedriatic Surgery* 16(3)**,** 146-53.

KUHN, S., COOKE, K., COLLINS, M., JONES, J. M. & MUCKLOW, J. C. (1990) Perceptions of pain relief after surgery. *British Medical Journal,* 300(6741).

KUNE, G. A. (2010) The Melbourne colorectal cancer study: refelections on a 30-year experience. *Medical Journal of Australia,* 193(11/12)**,** 648-52.

LACOUMENTA, S., YEO, T. H., BURRIN, J. M., BLOOM, S. R., PATERSON, J. L. & HALL, G. M. (1987) Fentanyl and the beta-endorphin, ACTH and glycoregulatory hormonal responses to surgery. *British Journal of Anaesthesia,* 59**,** 713-20.

LALOVIC, B., KHARASCH, E., HOFFER, C., RISLER, L., LIU-CHEN, L. Y. & SHEN, D. D. (2006) Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clinical Pharmacology and Therapeutics,* 79(5)**,** 461-79.

LASAGNA, L., LATIES, V. G. & J.L., D. (1958) Further studies on the "pharmacology" of placebo administration. *The Journal of Clinical Investigation* 37**,** 533-7.

LAUPRECHT, A., WENGER, F. A., EL FADIL, O., M.K., W. & GROEBEN, H. (2011) Levobupivacaine plasma concentrations following major liver resection. *Journal of Anesthesia,* 25**,** 369-75.

LEBLANC, K. A., BELLANGER, D., RHYNES, V. K. & HAUSMANN, M. (2004) Evaluation of continuous infusion of 0.5% bupivacaine by elastomeric pump for postoperative pain management after open inguinal hernia repair. *Journal of the American College of Surgeons,* 200 (2)**,** 198-202.

LEONE, S., DI GIANNI, S., CASATI, A. & FANELLI, G. (2008) Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine *Acta Bio Medica,* 79**,** 92-105.

LEVINE, J. D., FIELDS, H. L. & BASBAUN, A. I. (1993) Peptides and the primary afferent nociceptor. *The journal of neuroscience* 13 (6)**,** 2273-86.

LIERZ, P. & PUNSMANN, S. (2001) Opioids in pain therapy *The Internet Journal of Pharmacology* 1**,** 1-27.

LIU, S. S., RICHMAN, J. M., THIRLBY, R. C. & WU, C. L. (2006) Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *Journal of the American College of Surgeons,* 203 (6)**,** 914-32.

LOAN, W. B. & MORRISON, J. D. (1967) The incidence and severity of postoperative pain *British Journal of Anaesthesia,* 39**,** 695-8.

MACINTYRE, P. E., SCOTT, D. A., SCHUG, S. A., VISSER, E. J. & WALKER, S. M. (Eds.) (2010) *Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence 3rd Edition.* .

MAIN, C. J. & WATSON, P. J. (1999) Psychological aspects of pain *Manual Therapy* 4(4)**,** 203-15.

MARKS, D. F., MURRAY, M., EVANS, B., WILLIG, C., WOODALL, C. & SYKES, C. M. (2005) Health psychology: Theory, research & practice. *Chapter 16- Pain* 2ed., London Sage.

MARTIN-DUCE, A. (2002) A developmental history of local anaesthesia *Ambulatory Surgery,* 9(4)**,** 187-9.

MATHER, L. E. & COUSINS, M. J. (1992) The pharmacological relief of pain- contemporary issues. *The Medical Journal of Australia* 156**,** 796-801

MAYES, S. & FERRONE, M. (2006) Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. *The Annals of Pharmacotherapy,* 40(12)**,** 178-86.

MBF (2009) World-first national pain strategy launched. *National Pain Summit.* Canberra.

MCHUGH, G. A. & THOMS, M. M. (2002) The management of pain following day-case surgery. *Anaesthesia,* 57**,** 266-283.

MCQUAY, H. J. (1995) Pre-emptive analgesia: a systemic review of clinical studies *Annals of Medicine* 27**,** 249-256.

MELIS, G. C., VA LEEUWEN, P. A., VON BLOOMBERG-VAN DER FLIER, B. M., GOEDHRT-HIDDINGA, A. C., UITDEHAAG, B. M., STRACK VAN SCHIJNDEL, R. J., WUISMAN, P. I. & VAN BOKHORST-DE VAN DER SCHUEREN, M. A. (2006) A carbohydrate-rich beverage prior to surgery prevents surgery-induced immunodepression: a randomized controlled clinical trial *Journal of Parenteral and Enteral Nutrition* 30(1)**,** 21-6.

MELZACK, R. (1993) Pain: Past, present and future. *Canadian Journal of Experimental Psychology,* 47**,** 615-29.

MELZACK, R. (1999) Pain- an overview. *Acta Anaesthesiologica Scandinavica,* 43**,** 880-84.

MERAD, F., HAY, J. M., FINGERHUT, A., YAHCHOUCHI, E., LABORDE, Y., PÉLISSIER, E., MSIKA, S. & FLAMANT, Y. (1999) Is prophylactic pelvic drainage useful after elective rectal or anal anastomosis? A multicenter controlled randomized trial. French Association for Surgical Research. *Surgery,* 125(5):529-35.

MERSKEY, H. (1968) Psychological aspects of pain. *Postgraduate Medical Journal* 44**,** 297-306.

MILLER, D. (1994) Intravenous infusion anaesthesia and delivery devices. *Canadian Journal of Anesthesia,* 41(7)**,** 639-52.

MIMS (2008) Chirocaine. MIMS prescribing information. *MIMS Australia* 16(a) Anaesthetics- local and general- surgical preparations.

MIYAZAKI, R. & YAMAMOTO, T. (2009) Sex and/or gender differences in pain *The Japenese Journal of Anesthesiology* 58**,** 34-9.

MOINICHE, S., KEHLET, H. & DAHL, J. B. (2002) A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. *Anesthesiology,* 96**,** 725-41.

MOINICHE, S., MIKKELSEN, S., WETTERSLEV, J. & DAHL, J. B. (1998) A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations *British Journal of Anaesthesia,* 81**,** 377-83.

MORRIS, R. G., KARATASSAS, A. & ORFANOS, A. (1993) Regional blood flow as a determinant of drug absorption. Description of an animal model. *Journal of Pharmacological and Toxicological Methods* 30**,** 39-45.

NAEF, M., KASEMODEL, G. K., MOUTON, W. G. & WAGNER, H. E. (2010) Outcome of colorectal cancer surgery in the early fast-track era with special regard to elderly patients *International Surgery* 95(2)**,** 153-9.

NICHOLSON, G., HALL, G. M. & BURRIN, J. M. (1998) Peri-operative steroid supplementation. *Anaesthesia,* 53**,** 1091-4.

NISANEVICH, V., FELSENSTEIN, I., ALMOGY, G., WEISSMAN, C., EINAV, S. & MATOT, I. (2005) Effect of intraoperative fluid management on outcome after intra-abdominal surgery *Anesthesiology,* 103(1)**,** 25-32.

NYGREN, J., SOOP, M., THORELL, A., EFENDIC, S., NAIR, K. S. & LJUNGQVIST, O. (1998) Preoperative oral carbohydrate administration reduces postoperative insulin resistance *Clinical Nutrition* 17(2)**,** 65-71.

OATES, J. D. L., SNOWDON, S. L. & JAYSON, D. W. H. (1994) Attitudes of ward staff and patients to postoperative analgesia. *Anaesthesia,* 49**,** 755-8.

OCHROCH, A., MARDINI, I. A. & GOTTSCHALK, A. (2003) What is the role of NSAIDs in pre-emptive analgesia. *Drugs,* 63**,** 2709-23.

ONG, K. S., LIRK, P. & SEYMOUR, R. A. (2005) The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesthesia and Analgesia* 100**,** 757-73.

OZARDA ILÇÖL, Y., OZYURTM G, KILICTURGAY, S., UNCU, G. & ULUS, I. H. (2002) The decline in serum choline concentration in humans during and after surgery is associated with the elevation of cortisol, adrenocorticotropic hormone, prolactin and beta-endorphin concentrations. *Neuroscience Letters,* 324(1)**,** 41-4.

PASERO, C. (2003a) Epidural analgesia for postoperative pain, part 2: multimodal recovery programs improve patient outcomes. *American Journal of Nursing,* 103 (11)**,** 43-5

PASERO, C. (2003b) Epidural analgesia for postoperative pain: excellent analgesia and improved patient outcomes after major surgery. *American Journal of Nursing,* 103 (10)**,** 62-4.

PAUL, J. E., BERTRAM, B., ANTONI, K., KAMPF, M., KIYOWSKI, T., CHENG, J. & THABANE, L. (2010) Impact of a comprehensive safety initiative on patient-controlled analgesia errors. *Anesthesiology,* 113**,** 1427-32.

PENA-SORIA, M. J., MAYOL, J. M., ANULA-FERNANDEZ, R., ARBEO-ESCOLAR, A. & FERNANDEZ-REPRESA, J. A. (2007) Mechanical bowel preparation for elective colorectal surgery with primary intraperitoneal anastomosis by a single surgeon: interim analysis of a prospective single-blinded randomized trial *Journal of Gastrointestinal Surgery* 11(5)**,** 562-7.

PHILIP, B. K., REESE, P. R. & BURCH, S. P. (2002) The economic impact of opioids on postoperative pain management *Journal of Clinical Anesthesia* 14**,** 354-64.

PINTARIC, T. S., KOZELJ, G., STANOVNIK, L., CASATI, A., HOCEVAR, M. & JANKOVIC, V. N. (2008) Pharmacokinetics of levobupivacaine 0.5% after superficial or combined (deep and superficial) cervical plexus block in patients undergoing minimally invasive parathyroidectomy. *Journal of Clinical Anesthesia,* 20**,** 333-7.

PLUMPTON, F. S., BESSER, G. M. & COLE, P. V. (1969) Corticosteroid treatment and surgery. 1: An investigation of the indications for steroid cover. *Anaesthesia,* 24(1)**,** 3-11.

POLGLASE, A. L., MCMURRICK, P. J., SIMPSON, P. J. B., WALE, R. J., CARNE, P. W. G., JOHNSON, W., CHEE, J., OOI, C. W., CHONG, J. W. D., KINGSLAND, S. R. & BUCHBINDER, R. (2007) Continuous wound infusion of local anaesthetic for the control of pain after elective abdominal colorectal surgery *Diseases of the Colon and Rectum,* 50**,** 2158-67.

POLLE, S. W., WIND, J., FUHRING, J. W., HOFLAND, J., GOUMA, D. J. & BEMELMAN, W. A. (2007) Implementation of a fast-track perioperative care program: what are the difficulties? . *Digestive Surgery,* 24**,** 441-9.

PORTER, J. M., KELLERHER, N., FYLNN, R. & SHORTEN, G. D. (2001) Epidural ropivacaine hydrochloride during labour: protein binding, placental transfer and neonatal outcome. *Anaesthesia,* 56**,** 418-23.

PU, L. L. (2006) The use of a pain pump for optimal postoperative pain management. *Journal of the American Society of Plastic Surgeons* 117 (6)**,** 2066-9.

RANNEY, D. (1996) Anatomy of pain *Ontario Inter-Urban Pain Conference.* Waterloo.

REGNARD, C. & PELHAM, A. (2003) Severe respiratory depression and sedation with transdermal fentanyl: four case studies. *Palliative Medicine,* 17(8)**,** 714-6.

REIDEL, M. A., KNAEBEL, H. P., SEILER, C. M., KNAUER, C., MOTSCH, J., VICTOR, N. & BÜCHLER, M. W. (2003) Postsurgical pain outcome of vertical and transverse abdominal incision: design of a randomized controlled equivalence trial [ISRCTN60734227] *BMC Surgery,* 13**,** 3-9.

REVILL, S. I., ROBINSON, J. O., ROSEN, M. & HOGG, M. I. J. (1976) The reliability of a linear analogue for evaluating pain *Anaesthesia,* 31**,** 1191-8.

ROIG, J. V., GARCIA-FADRIQUE, A., REDONDO, C., VILLALBA, F. L., SALVADOR, A. & GARCIA-ARMENGOL, J. (2009) Perioperative care in colorectal surgery: current practice patterns and opinions *Colorectal Disease,* 11**,** 976-83.

ROUTLEDGE, P. A. (1986) The plasma protein binding of basic drugs. *British Journal of Clinical Pharmacology,* 22(5)**,** 499-506.

ROWBOTHAM, D. J. (2001) Endogenous opioids, placebo response, and pain *The Lancet* 357**,** 1901-2

ROWLINGSON, J. C. (2001) How can local anesthetic in the wound not help? *Anesthesia & Analgesia,* 92**,** 3-4.

RUETSCH, Y. A., BONI, T. & BORGEAT, A. (2001) From cocaine to ropivacaine: the history of local anesthetic drugs. *Current Topics in Medicinal Chemistry* 1(3)**,** 1715-82.

RUSBY, J. E., WELCH, C. M. M. & LAMPARELLI, M. J. (2005) Fast-track surgery. *British Journal of Surgery,* 92**,** 783-4.

RUTTEN, A., MATHER, L. E., PLUMMER, J. L. & HENNING, E. C. (1992) Postoperative course of plasma protein binding of lignocaine, ropivacaine and bupivacaine in sheep. *Journal of Pharmacy and Pharmacology,* 44(4)**,** 355-8.

RYGNESTAD, H., ZAHLSEN, K., BERGSLIEN, O. & DALE, O. (1999) Focus on mobilization after lower abdominal surgery. A double-blind randomized comparison of epidural bupivacaine with morphine vs. lidocaine with morphine for postoperative analgesia. *Acta Anaesthesiologica Scandinavica,* 43**,** 380-7.

SANDS, D. R. & WEXNER, S. D. (1999) Nasogastric tubes and dietary advancement after laparoscopic and open colorectal surgery *Nutrition* 15(5)**,** 347-50.

SCATIZZI, M., KRONING, K. C., BODDI, V., DE PRIZIO, M. & FEROCI, F. (2010) Fast-track surgery after laparoscopic colorectal surgery: is it feasible in a general surgical unit? . *Surgery* 147(2)**,** 219-26.

SCHUBERT, A. (1995) Side effects of mild hypothermia *Journal of Neurological Anesthesiology* 7(2)**,** 139-47.

SCOTT, D. B., LEE, A., FAGAN, D., BOWLER, G. M., BLOOMFIELD, P. & LUNDH, R. (1989) Acute toxicity of ropivacaine compared with that of ropivacaine. *Anesthesia & Analgesia,* 69**,** 563-9

SEILER, C. M., DECKERT, A., DIENER, M. K., KNAEBEL, H. P., WEIGAND, M. A., VICTOR, N. & BUCHLER, M. W. (2009) Midline versus transverse incision in major abdominal surgery. *Annals of Surgery,* 249(6)**,** 913-20.

SERRA-ARACIL, X., GARCı´A-DOMINGO, M., PARE´S, D., ESPIN-BASANY, E., BIONDO, S., GUIRAO, X., ORREGO, C. & SITGES-SERRA, A. (2011) Surgical Site Infection in Elective Operations for Colorectal Cancer After the Application of Preventive Measures. *Archives of Surgery,* 146(5)**,** 606-12.

SESSEL, D. I. (1997) Mild perioperative hypothermia *The New England Journal of Medicine,* 11**,** 976-83.

SHAH, V. P., MIDHA, K. K., FINDLAY, J. W. A., HILL, H. M., HULSE, J. D., MCGILVERAY, I. J., MCKAY, G., MILLER, K. J., PATNAIK, R. N., POWELL, M. L., TONELLI, A., VISWANATHAN, C. T. & YACOBI, A. (2000) Bioanalytical method validation- A revisit with a decade of progress. *Pharmaceutical Research,* 17**,** 1551-7.

SHEPHERTD, T. (2008) QEH bed crisis 'could cost lives' *The Advertiser.* Adelaide.

SIDDIQUI, M., SAJID, M., UNCLES, D., CHEEK, L. & BAIG, M. K. (2011) A meta-analysis on the clinical effectiveness of transversus abdominis plane block *Journal of Clinical Anesthesia,* 23**,** 7-14.

SILVIS, R. S. (1955) Abdominal incisions for operations on the colon and rectum. *California Medicine,* 82(4)**,** 326-9.

SIMON, M. J. G., VEERING, B. T., STIENSTRA, R., VAN KLEEF, J. W. & BURM, A. G. L. (2004) Effect of age on the clinical profile and systemic absorption and disposition of levobupivacaine after epidural administration. *British Journal of Anaesthesia,* 93(4)**,** 512-20.

SINATRA, R. S. (1991) Current methods of controlling post-operative pain *The Yale Journal of Biology and Medicine,* 64**,** 351-74.

SINGH, J., HUM, M., COHEN, S., LIBERMAN, H., THORSON, A. & DINE, A. (2007) Multicenter infection surveillance study comparing two types of postoperative pain management, surgical site using ON-Q SilverSoaker and local anaesthetics vs. systemic narcotics following colorectal procedures. *47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)* Chicago, IL.

SINNOTT, C. J. & STRICHARTS, G. R. (2003) Levobupivacaine versus ropivacaine for sciatic nerve block in the rat. *Regional Anesthesia and Pain Medicine,* 28**,** 294-303.

SMITH, T. (2007) Systemic toxic effects of local anaesthetics. *Anaesthesia and Intensive Care Medicine,* 8(6)**,** 155-8.

SPANJERSBERG, W. R., REURINGS, J., KEUS, F. & VAN LAARHOVEN, C. J. (2011) Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database of Systemic Reviews,* 16(2)**,** 1-36.

STEWART, J. & KELLETT, N. (2003) The central nervous system and cardiovascular effects of levobupivacaine and ropivacaine in healthy volunteers. *Anesthesia & Analgesia,* 97**,** 412-6.

STOLLMAN, N. H. & RASKIN, J. B. (1999) Diagnosis and management of diverticular disease of the colon in adults. *The American Journal of Gastroenterology,* 94(11)**,** 3110-21.

STOTTMEIER, S., HARLING, H., WILLE-JORGENSEN, P., BALLEBY, L. & KEHLET, H. (2010) Pathogenesis of morbidity after fast-track laparoscopic colonic cancer surgery. *Colorectal Disease.*

SUMMITT, R. L., STOVALL, T. G. & BRAN, D. F. (1994) Prospective comparison of indwelling bladder catheter drainage versus no catheter after vaginal hysterectomy *American Journal of Obstetrics and Gynecology* 170(6)**,** 1815-21.

SWERDLOW, M. & JONES, R. (1970) The duration of action of bupivacaine, prilocaine, and lignocaine. *British Journal of Anaesthesia,* 42**,** 335-9.

SYMRENG, I. & FISHMAN, S. M. (2004) Anxiety and Pain *Pain Clinical Updates IASP,* XII (7)**,** 1-6.

TAENZER, P., MELZACK, R. & JEANS, M. (1986) Influence of psychological factors on postoperative pain, mood and analgesic requirements *Pain,* 24**,** 331-42.

TAHERI, S. T., COGSWELL, L. P., GENT, A. & STRICHARTZ, G. R. (2003) Hydrophobic and ionic factors in the binding of local anaesthetics to the major variant of human alpha1-acid glycoprotein. *Pharmacology and Experimental Therapeutics,* 304(1)**,** 71=89.

TEKKIS, P. P., SENAGORE, A. J., DELANEY, C. P. & FAZIO, V. W. (2005) Evaluation of the learning curve in laparoscopic colorectal surgery *Annals of Surgery,* 242(1)**,** 83-91.

THOMAS, C., MADDEN, F. & JEHU, D. (1987) Psychological effects of stomas--I. Psychosocial morbidity one year after surgery. *Journal of Psychosomatic Research* 31(3)**,** 311-6.

THOMAS, J. M. & SCHUG, S. A. (1999) Recent advances in the pharmacokinetics of local anaesthetics. Long-acting amide enantiomers and continuous infusions. *Clinical Pharmacokinetics,* 36(1)**,** 67-83.

THORSON, A. & FARIA, J. (2001) The ON-Q pain management system in the control of post-operative pain in colon and rectal surgery *United European Gastroenterology week* 1-7.

TODD, E. M. & KUCHARSKI, A. (2004) *Principles and practice of pain medicine,* Warfield, CA, McGraw Hill

TRAYNOR, C. & HALL, G. M. (1981) Endocrine and metabolic changes during surgery: anaesthetic implications. *British Journal of Anaesthesia,* 53**,** 153-60.

TSIKITIS, V. L., HOLUBAR, S. D., DOZOIS, E. J., CIMA, R. R., PEMBERTON, J. H. & LARSON, D. W. (2010) Advantages of fast-track recovery after laparoscopic right hemicolectomy for colon cancer. *Surgical Endoscopy* 24(8)**,** 1191-6.

TUCKER, G. T. (1986) Pharmacokinetics of Local Anaesthetics. *British Journal of Anaesthesia,* 58**,** 717-31.

TUCKLEY, J. M. (1994) Pharmacology of local anaesthetic agents. *Update in Anaesthesia* 4**,** 19-24.

TURK, D. C. (1993) Assess the person, not just the pain. *Pain Clinical Updates IASP,* 1 (3)**,** 8.

TURNER, J. A., DEYO, R. A., LOESER, J. D., VON KORFF, M. & FORDYCE, W. E. (1994) The importance of placebo effects in pain treatment and research. *Journal of the American Medical Association* 271 (20)**,** 1609-14.

VEERING, B. T., BURM, A. G. L., FEYEN, H. M., OLIEMAN, W., SOUVERIJN, J. H. M. & VAN KLEEF, J. W. (2002) Pharmacokinetics of bupivacaine during postoperative epidural infusion. . *Anesthesiology,* 96(5)**,** 1062-9.

WADE, B. E. (1990) Colostomy patients: psychological adjustment at 10 weeks and 1 year after surgery in districts which employed stoma-care nurses and districts which did not. *Journal of Advanced Nursing,* 15(11)**,** 1297-304.

WALL, P. D. (1978) The gate control theory of pain mechanisms. *Brain,* 101**,** 1-18.

WALTERS, A. (1963) The psychological aspects of bodily pain *Applied therapeutics,* 5**,** 853-6.

WANG, G., JIANG, Z. W., XU, J., GONG, J. F., BAO, Y., XIE, L. F. & LI, J. S. (2011) Fast-track rehabilitation program vs conventional care after colorectal resection: a randomised clinical trial *World Journal of Gastroenterology,* 17(5)**,** 671-6.

WANG, L. W., WONG, S. W., CROWE, P. J., KHOR, K. E., JASTRZAB, G., PARASYN, A. D. & WALSH, W. R. (2010) Wound infusion with local anaesthesia after laparotomy: a randomized controlled trial. *ANZ Journal of Surgery* 80(11)**,** 794-801.

WANG, Y., YUE, Y., SHI, L., WU, A. S., FENG, C. S. & NI, C. (2007) Spinal release of the amino acids with a time course in a rat model of postoperative pain. *Chinese Medical Journal,* 120**,** 1969-74.

WATSON, A., EL-DEREDY, W., IANNETTI, G. D., LLOYD, D., TRACEY, I., VOGT, B. A., NADEAU, V. & JONES, A. K. P. (2009) Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. *Pain,* 145**,** 24-30.

WHITE, C. A. & HUNT, J. C. (1997) Psychological factors in postoperative adjustment to stoma surgery. *Annals of the Royal College of Surgeons of England* 79(1)**,** 3-7.

WHITESIDE, J. B. & WILDSMITH, J. A. W. (2000) Local Anaesthetics. *The Royal College of Anaesthetists Bulletin* 2**,** 64-7.

WILLE-JORGENSEN, P., GUENAGA, K. F., MATOS, D. & CASTRO, A. (2005) Preoperative mechanical bowel cleansing or not? . *Colorectal Disease,* 7**,** 304-10.

WILLIAMSON, A. & HOGGART, B. (2005) Pain: a review of three commonly used pain rating scales. . *Journal of Clinical Nursing,* 14**,** 798-804.

WILMORE, D. W. & KEHLET, H. (2001) Recent advances: management of patients in fast track surgery. *British Medical Journal* 332**,** 473-6.

WOODSIDE, J. R. (2000) Female smokers have increased postoperative narcotic requirements. *Journal of Addictive Diseases,* 19 (4)**,** 1-10.

YARDENI, I. Z., SHAVIT, Y., BESSLER, H., MAYBURD, E., GRINEVICH, G. & BEILIN, B. (2007) Comparison of postoperative pain management techniques on endocrine response to surgery: a randomised controlled trial. *International Journal of Surgery,* 5**,** 239-43.

YUE, Y. (2007) Mechanisms of postoperative pain. *Chinese Medical Journal* 120**,** 1949-50.

YUN, Y. (2007) Mechanisms of postoperative pain. *Chinese Medical Journal* 120**,** 1949-50.

ZIMBERG, S. E. (2003) Reducing pain and costs with innovative postoperative pain management. . *Managed Care Quarterly,* 11(1)**,** 34-36

APPENDICES

Appendix 1

Government of South Australia
SA Health

Ethics of Human Research Committee

29 April 2008

The Queen Elizabeth Hospital
28 Woodville Road
WOODVILLE SOUTH SA 5011
Lyell McEwin Hospital
Haydown Road
ELIZABETH VALE SA 5112

Mr P Hewett
Department of Surgery
The Queen Elizabeth Hospital

Dear Mr Hewett Application Number 2008006

The Ethics of Human Research Committee Chairman has considered additional information to your protocol entitled:

"Efficacy of 96hr duration local anaesthesia (levobupivacaine) infused at the incision site compared with saline controls for post operative pain management following open or laparoscopic abdominal surgery. An application to fast track surgery."

The following documents have been reviewed and approved:

- CNAHS Ethics of Human Research Committee Application Form, Version dated 23 April 2008
- Patient Information Sheet and Consent Form, Version dated 24 April 2008
- Response to Queries (Author: A/Prof R Morris), dated 18 April 2008

Approval Status: **FINAL**

Period of Approval**: 29 April 2008 – 29 April 2009**

***Please note the terms under which Ethical approval is granted:**

1. Researchers are required to immediately report to the Ethics of Human Research Committee anything which might warrant review of ethical approval of the protocol, including:

a) serious or unexpected adverse effects on participants;
b) proposed changes in the protocol; and
c) unforseen events that might affect continued ethical acceptability of the project

2. Protocols are approved for up to twelve months only and a report is required at the end of the study or 12 month period. Extensions will not be granted without a report to the Committee.
3. Confidentiality of the research subjects shall be maintained at all times as required by law
4. All research subjects shall be provided with a Patient Information Sheet and Consent Form, unless otherwise approved by the Committee
5. The Patient Information Sheet and Consent Form shall be printed on the relevant site letterhead stating the contact details for the researchers
6. The Patient Information Sheet must state that the Executive Officer can be contacted for information regarding conduct of the study, policies and procedures, or if the participant wishes to make a confidential complaint
7. A report and a copy of any published material should be forwarded to the Committee at the completion of the project.

Yours sincerely

A/Prof Timothy Mathew
Chairman
Ethics of Human Research Committee (TQEH & LMH)

Ethics of Human Research Committee (TQEH & LMH)
Ph: +61 08 8222 6841
Fax: +61 08 8222 6007

Government of South Australia
SA Health
Ethics of Human Research Committee

29 April 2008

The Queen Elizabeth Hospital
28 Woodville Road
WOODVILLE SOUTH SA 5011
Lyell McEwin Hospital
Haydown Road
ELIZABETH VALE SA 5112

Mr P Hewett
Department of Surgery
The Queen Elizabeth Hospital

Dear Mr Hewett Application Number 2008006

The Ethics of Human Research Committee Chairman has considered additional information to your protocol entitled:

"Efficacy of 96hr duration local anaesthesia (levobupivacaine) infused at the incision site compared with saline controls for post operative pain management following open or laparoscopic abdominal surgery. An application to fast track surgery."

The following documents have been reviewed and approved:

- CNAHS Ethics of Human Research Committee Application Form, Version dated 23 April 2008
- Patient Information Sheet and Consent Form, Version dated 24 April 2008
- Response to Queries (Author: A/Prof R Morris), dated 18 April 2008

Approval Status: **FINAL**

Period of Approval**: 29 April 2008 – 29 April 2009**

***Please note the terms under which Ethical approval is granted:**

1. Researchers are required to immediately report to the Ethics of Human Research Committee anything which might warrant review of ethical approval of the protocol, including:

a) serious or unexpected adverse effects on participants;
b) proposed changes in the protocol; and
c) unforseen events that might affect continued ethical acceptability of the project

2. Protocols are approved for up to twelve months only and a report is required at the end of the study or 12 month period. Extensions will not be granted without a report to the Committee.
3. Confidentiality of the research subjects shall be maintained at all times as required by law
4. All research subjects shall be provided with a Patient Information Sheet and Consent Form, unless otherwise approved by the Committee
5. The Patient Information Sheet and Consent Form shall be printed on the relevant site letterhead stating the contact details for the researchers
6. The Patient Information Sheet must state that the Executive Officer can be contacted for information regarding conduct of the study, policies and procedures, or if the participant wishes to make a confidential complaint
7. A report and a copy of any published material should be forwarded to the Committee at the completion of the project.

Yours sincerely

A/Prof Timothy Mathew
Chairman
Ethics of Human Research Committee (TQEH & LMH)

Ethics of Human Research Committee (TQEH & LMH)
Ph: +61 08 8222 6841
Fax: +61 08 8222 6007

Appendix 2

The Queen Elizabeth Hospital
Clinical Pharmacology Department
28 Woodville Rd
Woodville South. SA. 5011
ABN 21 464 837 384
www.nwahs.sa.gov.au
Tel: (61 8) 8222 6753
Fax: (61 8) 8222 6033

Prof TH Mathew
Chairman
Ethics of Human Research Committee, TQEH

12 August 2008

Dear Prof Mathew,

Re: **Protocol Number: 2006127**

Further to our previous correspondence and approval of this study, and following further discussions with the Surgical team, we would like to, amend our research protocol.

Our exclusion criteria drug list (section 5(b) page 24) shows omeprazole due to a possible interaction with our study drug levobupivacaine, as both are metabolised by the cytochrome P450 enzyme system. However, many patients undergoing abdominal colorectal surgery use the proton pump inhibitors, hence this has compromising our recruitment. The initial listing of omeprazole was based on its inclusion in the manufacturer's product information sheet. Attempts to communicate with this manufacturer to get the basis of this assertion (eg., theoretical concern, case report, actual clinical studies, etc) were fruitless.

However, we have found a study conducted by Dowd et al (Can J Anaesth 1997 Sep 44(9): 1029, copy attached) who compared 20 patients receiving epidural bupivacaine with or without 40 mg of omeprazole 2 hours before bupivacaine administration. There was no significant difference in plasma bupivacaine concentrations between the two groups, suggesting minimal/no clinically significant interaction. Based on this evidence we would like to remove omeprazole from our exclusion criteria list.

Thank you for your consideration of this additional information, please let me know if I can assist further.

Yours sincerely,

Raymond G Morris, PhD
Chief Medical Scientist
Clinical Pharmacology Laboratory.
Affiliate Associate Professor,
Dept of Clinical & Experimental Pharmacology
University of Adelaide

Cc Mr Peter Hewett, Mr Alex Karatassas, Ms Julie Tonkin

Government of South Australia
Central Northern Adelaide Health Services

Appendix 3

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth, Royal Adelaide & Lyell McEwin Hospitals

PATIENT INFORMATION SHEET

Title: **Efficacy of 96hr duration local anaesthesia (levobupivacaine) infused at the incision site compared with saline controls for post-operative pain management following open or laparoscopic abdominal surgery. An application to "Fast-Track" surgery.**

Protocol Number: 200612

PURPOSE OF THE RESEACH

We are undertaking an extension to our earlier research investigating the use of local purpose. To understand objectively whether the local anaesthetic approach is as effective, or more effective, than established pain-killers, we need to do this research in a series of patients like yourself and assess just how successful it may be.anaesthesia for pain management after surgery as an alternative to traditional pain-killer drugs used for this purpose. Your treating doctor has indicated that you are to have abdominal surgery soon, so we propose to trickle local anaesthetic at the surgical site using a new device designed for this specific

INVITATION TO PARTICIPATE

We invite you to participate in a research project which we believe is of potential importance.
However, before you decide whether or not you wish to participate, we need to be sure that you understand
why we are doing it, and
what it would involve if you agreed.
We are therefore providing you with the following information.
Please read it carefully and be sure to ask any questions you have.
The Doctor conducting the research will be happy to discuss it with you and answer any questions that you may have.
You are also free to discuss it with outsiders if you wish. (i.e, family, friends and / or your local Doctor)
You do not have to make an immediate decision.
Your participation is purely voluntary.
Should you agree to enter the trial, you may change your mind and withdraw at any stage.

PROCEDURES AND TREATMENT

In addition to the surgery that you will be receiving as part of your clinical care, we would like you to consider a research study that includes the use of a local anaesthetic (pain killer) drug (called levobupivacaine, trade name Chirocaine®) that would be slowly trickled into the surgical site after the operation so as to numb the nerves that cause post-operative pain. This drug is currently widely used for this purpose, so is not a new drug. This drug will be delivered by a commercially available portable device called "Pain Buster". This device is not the reason for this research either, as it is already used in many hospitals around the world for managing pain after various types of surgery. The purpose of the research is to investigate whether this pain control system can be used safely and effectively for 4 days

after your surgery. It is hoped that this use will provide better pain management and require less use of other major pain killers (like morphine or fentanyl). As with any infusion device, there is a (low) incidence that it can become blocked, dislodged or suffer from other failure during the treatment period. In the event that this should occur, you will be withdrawn from this study and conventional pain management used to maintain your comfort level, as recommended by your doctor(s).

This study is being conducted as part of a new approach to surgery called "fast track" surgery where the aim is to reduce post-operative complications, reduce the length of hospital stay, and reduce the time taken for full recovery. This approach has been proved successful in hospitals in other countries. As a part of this approach, you MAY be asked (depending on specific aspects of your overall health status decided by your treating doctors) to drink a solution called Nutricia Pre-op (which is a high carbohydrate drink) before your operation (400ml the night before and 200ml 2 hours before) rather than the traditional total fasting from midnight on the day of your operation.

MEDICINES AND DRUGS

In addition to the medicines/drugs given as part of your normal surgical care, as mentioned above, we would use the local anaesthetic drug, levobupivacaine (also called Chirocaine®). This drug is not specifically the subject of this research, as it is already commonly used for similar clinical reasons following surgery. You may be aware of the use of this family of drugs called 'local anaesthetics' from visits to your dentist, where such drugs are used to numb the mouth to control pain.

PATIENT MANAGEMENT

The aim of this research is to consider the effectiveness of trickling levobupivacaine into the surgical site for 4 days after the surgery. However, you will also have available to you the usual pain management systems in the event that you should experience any pain/discomfort. This alternative is called, Patient Controlled Analgesia (PCA) and you will have available oral medication for pain management (this will happen whether you decide to participate in the research study, of not). So that the researchers can evaluate whether the local anaesthetic is more effective than the current PCA, some patients will receive saline infusion rather than local anaesthetic through the infusion device. Again, this would not be expected to result in any greater pain perception; rather, the researchers will be considering the differences in need and usage of the PCA between the local anaesthetic and control groups to assess outcome. To summarise, patients are NOT being denied the standard pain management (PCA), but rather the outcomes will be measured by the frequency at which the PCA is used.

TREATMENT GROUPS

There will be two different groups: a treatment group, which will consist of two-thirds of the patients and a control group, which will consist of one-third of the patients. You will be randomly allocated into either one. The treatment group will receive the local anaesthetic in the PainBuster and the control group will receive saline in the Painbuster. If you are in the saline group your pain management will not be compromised in any way as both groups will have readily available access to the PCA analgesia.

WHAT ARE THE DISCOMFORTS, RISKS AND SIDE EFFECTS?

With the administration of any drug, there is a possibility of side-effects. Published research has shown levobupivacaine to be amongst the safest local anaesthetic drugs currently available. Symptoms that have been associated with local anaesthetic drugs can range from more minor nervous effects through to more serious side effects at much higher doses (including effects on the cardiovascular system and central nervous system). The more serious side effects on heart or central nervous system are considered unlikely, based on our previous Pilot Study that included measurement of the amount of local anaesthetic absorbed from the infusion site into

the blood-stream when compared with published threshold concentrations associated with such adverse effects. The published adverse effects associated with high plasma concentrations are:
Cardiovascular: low or high blood pressure, fast or slow heart rate; or more rarely severe drop in blood pressure and slow heart rate, abnormal heart rhythm, and cardiac arrest.
Nervous system: Tingling in the lips, elevated temperature, chills, headache, dizziness, anxiety, and more rarely: muscle rigidity, twitching, unconsciousness, convulsions, low oxygen levels to organs, high carbon dioxide in the blood, and breathing disturbances.
Allergic reaction: rare with amide type local anaesthetics
Infection: there is potential for infection at the infusion site or blood sample catheter.

If you should experience any symptoms during your stay in hospital, then you should immediately advise the nurses or doctors caring for you.

The trickle of levobupivacaine will be stopped 4 days after your operation, or at such earlier time your doctor may decide, and standard established pain management procedures used for your comfort.

So that the researchers can establish scientific facts, we also plan to draw blood samples from you to measure the concentration of levobupivacaine in your blood. By knowing this concentration, we can compare your results with those published in the medical journals as evidence of safety margins. This will include a total of 80ml (about quarter of a cup) over a period of 4 days while you are in hospital. There is discomfort associated with blood collection, but we will do our best to minimise this for you by using a catheter (called a Jelco) in your arm vein for the early blood collections, this should reduce the number of jabs required.

WHAT WILL HAPPEN TO THE INFORMATION COLLECTED?

The information that is collected from the blood tests and from your participation will be added to that from other patients who have had the same treatment after their surgery. Your participation will be held as **strictly confidential** to the researchers and staff directly involved in your care. You will not be identified in any way in results that are presented or published in medical journals.

WHAT ARE MY RIGHTS?

You are free to participate, or not, in this research study. Your decision whether to participation will **not** affect your continuing care at TQEH in any way. You are free to ask questions of the doctors and surgeons involved in this research, or discuss the study with your own doctor, family members or friends before making your decision. If English is not your first language, the researchers can arrange to have the study explained to you in a language of your choice by a professional medical interpreter. You should not feel in any way pressured to participate, as this study is voluntary. You are also free to withdraw your consent at any time.

Contact details for the Researchers:
Mr Peter Hewett (Colorectal Surgeon): phone number: 8222 6248
Mr David Rodda (Colorectal Surgeon): phone number: 8222 6750
A/Prof Ray Morris (Chief Medical Scientist): phone number: 8222 6753

IS THERE ANY PAYMENT FOR PARTICIPATION?

Current medical research guidelines do not allow payment as this can be seen as an inducement to participate. As the study will be undertaken during your stay in hospital, we do not anticipate that there will be any "out-of-pocket" expenses that would need to be reimbursed.

FUNDING FOR THE STUDY

Support for this study has been offered by the PainBuster device company (represented in Australia by Surgical Synergies) by providing gratis PainBuster devices.
The senior researchers receive no reimbursement from this sponsoring company for undertaking in this study. Any other reimbursement offsets the cost of research staff employed for this study. Any surplus funds contribute to research in the Researchers' Units.

CONSENT

I, the undersigned .....

hereby consent to my involvement in the research project explained above.
I have read the information sheet, and I understand the reasons for this study.
The ways in which it will affect me have been explained by the research worker.
My questions have been answered to my satisfaction.
My consent is given voluntarily.
I understand that the purpose of this research project is to improve the quality of medical care, but my involvement may not be of benefit to me.
I have been given the opportunity to have a member of family or a friend present while the project was explained to me.
The details of the research project have been explained to me, including:
the expected time it will take
the nature of the procedures to be performed
the nature of any medication I may be given
any risks/discomforts which I may experience
I understand that I am free to withdraw from the project at any stage without having to give any reasons, and that if I withdraw from the project it will not affect my treatment at this hospital in the future.

What if I have a question about the study?
The Central Northern Adelaide Health Service Ethics of Human Research Committee has approved this study.
Should you wish to speak to a person not directly involved in the study in relation to matters concerning policies,
information about the conduct of the study, policies and procedures
your rights as a participant, or
should you wish to make a confidential complaint, you may contact The Executive Officer of this Committee, on (08) 8222 6841

SIGNED

.....

ADDRESS

.....

(please print)

.....

RESEARCH WORKER

.....

DATE

Appendix 4

ACUTE PAIN SERVICE

November 2007

Patient controlled oral analgesia

NOTE:
This appendix is included on pages 266 - 267 of the print copy of the thesis held in the University of Adelaide Library.

Appendix 5

Cortisol (COR) CE

Indicates Revised Information

Assay Summary

Sample Type	*Serum, Urine*
Sample Volume	*20 µL*
Calibrator	*E*
Sensitivity and Assay Range	*0.20 – 75 µg/dL (5.5 – 2069 nmol/L)*

Contents

REF	Contents	Number of Tests
04344187 (110776)	5 ReadyPack® primary reagent packs containing ADVIA Centaur® COR Lite Reagent and Solid Phase ADVIA Centaur COR Master Curve card	250
or		
01071457 (110775)	1 ReadyPack primary reagent pack containing ADVIA Centaur COR Lite Reagent and Solid Phase ADVIA Centaur COR Master Curve card	50

For a definition of symbols used in product labeling, please refer to *Understanding the Symbols* in Appendix D.

Intended Use

For *in vitro* diagnostic use in the quantitative determination of cortisol in serum or urine using the ADVIA Centaur® System.

Materials Required But Not Provided

REF	Description	Contents
03283109 (672184)	Calibrator E	6 vials of low calibrator CAL L 6 vials of high calibrator CAL H
or		
09689166 (672169)	Calibrator E	2 vials of low calibrator CAL L 2 vials of high calibrator CAL H

Optional Reagents

REF	Description	Contents
05389133 (110315)	ADVIA Centaur Multi-Diluent 3 M-DIL	2 ReadyPack ancillary reagent packs containing 5 mL/pack
06223468 (672192)	Multi-Diluent 3 M-DIL	50 mL/vial
07642456 (986000)	Ligand Plus 1, 2, 3 quality control material	5 x 5 mL CONTROL 1 5 x 5 mL CONTROL 2 5 x 5 mL CONTROL 3
07377973 (986400)	Ligand Plus 1, 2, 3 barcode labels	60/level
672409	COR Master Curve Material	7 x 1 mL

Summary and Explanation of the Test

Cortisol is the primary glucocorticoid hormone synthesized and secreted by the adrenal cortex. Cortisol is essential for life, regulating carbohydrate, protein, and lipid metabolism, maintaining normal blood pressure, and inhibiting allergic and inflammatory reactions.[1] Cortisol is synthesized and secreted by the cortex of the adrenal gland under the direction of adrenocorticotropic hormone (ACTH). ACTH is secreted in a circadian pattern by the anterior lobe of the pituitary gland in response to corticotropin releasing hormone (CRH) secretion by the hypothalamus. Increased ACTH levels stimulate cortisol secretion. The increased cortisol levels inhibit CRH secretion, which subsequently inhibits ACTH secretion. This negative feedback mechanism results in decreased cortisol levels.[2]

Circulating cortisol levels follow a diurnal pattern in healthy individuals. Levels are highest in the morning after waking and lowest in the evening. Disorders of the hypothalamic-pituitary-adrenal axis override this diurnal pattern. Decreased cortisol levels are induced by either primary or secondary adrenal insufficiency.[3] Addison's disease is caused by primary adrenal insufficiency due to metabolic errors or destruction of the adrenal cortex. Secondary adrenal insufficiency is caused by pituitary destruction or failure, resulting in loss of ACTH stimulation of the adrenal gland. Cushing's syndrome is caused by increased levels of cortisol due to either primary or secondary adrenal hyperfunction.[4] Causes of primary adrenal hyperfunction are adrenal tumors and nodular adrenal hyperplasia. Secondary adrenal hyperfunction is caused by pituitary overproduction of ACTH or ectopic production of ACTH by a tumor. Increased cortisol levels are induced by pregnancy and by stress due to depression, trauma, surgery, hypoglycemia, alcoholism, uncontrolled diabetes, and starvation.

Due to the diurnal pattern of secretion, an assessment of serum cortisol levels at a single timepoint is of little diagnostic value. Cortisol is often measured in combination with dynamic function testing.[2-4] These tests provide diagnostic tools to determine the etiology of glucocorticoid reserve or excess. The ACTH stimulation test is used to evaluate Addison's disease. The dexamethasone suppression test is used to diagnose Cushing's syndrome or depression due to neuroendocrine disorders.

A 24-hour urinary cortisol measurement is the method of choice in the initial screening for Cushing's syndrome because it provides the best assessment of cortisol production. Urinary cortisol is not subject to the diurnal pattern of secretion and accurately differentiates healthy persons from patients with Cushing's syndrome.[4]

Assay Principle

The ADVIA Centaur Cortisol assay is a competitive immunoassay using direct chemiluminescent technology. Cortisol in the patient sample competes with acridinium ester-labeled cortisol in the Lite Reagent for binding to polyclonal rabbit anti-cortisol antibody in the Solid Phase. The polyclonal rabbit anti-cortisol antibody is bound to monoclonal mouse anti-rabbit antibody, which is covalently coupled to paramagnetic particles in the Solid Phase.

The system automatically performs the following steps:

- dispenses 20 µL of sample into a cuvette
- dispenses 50 µL of Lite Reagent and 250 µL of Solid Phase and incubates for 5.0 minutes at 37°C
- separates, aspirates, and washes the cuvettes with reagent water[5]
- dispenses 300 µL each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction
- reports results according to the selected option, as described in the system operating instructions or in the online help system