Determining the post-operative opioid requirements of patients post total abdominal hysterectomy with a bupivacaine infusion in the incisional site

Samantha Lee Russell

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree

of

Master of Medicine

Johannesburg

2009

DECLARATION

I, Samantha Lee Russell, declare that this thesis is my own work. It is submitted for the admission to the degree of Master of Medicine by the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

_____day of _____, 2009

Presentations arising from this study

Presentation “Does a bupivacaine infusion in the incisional site post total abdominal hysterectomy reduce opioid requirements” at an Anaesthesiology combined departmental meeting at Charlotte Maxeke Academic Hospital, June 2009

Poster presentation “The use of a bupivacaine infusion into the wound for total abdominal hysterectomy” at the South African Society of Anaesthesiologists congress in Bloemfontein, March 2010

Abstract published in the SASA 2010 Main Conference Supplement

Preface

Postoperative pain is prevalent and not optimally managed in most patients. Pain can lead to adverse emotional and systemic consequences.

Numerous device orientated studies have been done in other countries looking at the effect of infusions of local anaesthetic at the wound site postoperatively via an elastomeric pump. There have however been no similar studies done in South Africa. The aims of this study was to assess whether the use of an incisional wound catheter and 0.39% bupivacaine infusion in patients post total abdominal hysterectomy for a 30 hour period will decrease opioid requirements compared to a control group having only systemic analgesia. Pain intensities were also documented at set observation periods.

The opioid requirements between the 2 groups were comparable however the participants who had the bupivacaine infusion in their incisional site had less pain intensity scores until 6 hours post operation and had less pain intensity on movement at 30 hours post operation.

A bupivacaine infusion in the incisional site decreases pain intensity in the above mentioned parameters but does not reduce opioid requirements.

Acknowledgements

I would like to acknowledge my supervisor, Professor Eva Fröhlich, Head of Department at the Helen Joseph and Rahima Moosa mother and child complexes. I was fortunate that her super-speciality is pain management and her guidance and insight was much appreciated.

I would like to thank the Helen Joseph Anaesthesiology Department for their assistance and the use of their departmental equipment and facilities.

I would like to thank Dr Pauline du Plessis for her continuous support throughout the clinical study. Her assistance and advice made this clinical study possible.

I would like to thank Mrs Juan Scribante for her endless assistance, expertise and patience in helping prepare this research report.

I would like to acknowledge Dr Brian Levy for his assistance in the approach to writing a research report.

I would like to acknowledge Mr Roche Swiegers of SA Biomedical-South Africa who supplied the elastomeric On-Q PainBuster^{R} Soaker^{TM} 6.5 pain relief systems.

I would like to thank Mrs Anke Breckon on her assistance and advice with regard to helping me in this research study.

I would like to acknowledge the assistance in the statistical analysis by Professor Piet Becker. I would like to acknowledge Mr Adam Martin who provided invaluable insight in the data analysis and assisted in providing concise and explanatory graphs and figures.

Table of Contents

List of Figures

List of Tables

1 Chapter One: Overview of the study

1.1 Introduction

In this chapter an overview of the study is provided. This includes the background to the study, the problem statement, the purpose, hypothesis, objectives, the importance of the study, relevant definitions, overview of methodology, validity and reliability and ethical considerations. The chapter concludes with a brief outline of the clinical study.

1.2 Background to the study

Pain is rated as a highly undesirable postoperative outcome (1). Post operative pain is often negligently overlooked and remains under-treated (1, 2). Postoperative pain, especially when poorly controlled, results in acute adverse physiologic responses and chronic effects (1). Inadequately controlled pain may extend the length of hospital stay and predispose to expensive, time-consuming complications. Control of acute postoperative pain, timing, duration, and fashion with which it is implemented, may be important in facilitating short and long-term patient convalescence after surgery (1).

The two modalities of pain relief are systemic (opioid and non-opioid) analgesia and regional analgesia (neuraxial and peripheral techniques). Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain (1). Intravenous patient controlled analgesia (PCA) optimises delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability among individual patients (1).

Compared with traditional 'as required' analgesic regimens, intravenous PCA provides superior postoperative analgesia, improves patient satisfaction and may decrease the risk of pulmonary complications (1). It also ensures that the patient controls the amount and therefore is independent on the nursing care to provide the necessary analgesia.

Another mode of pain relief is regional peripheral techniques. These techniques use local anaesthetics and additives to provide analgesia. Intrathecal and continuous epidural analgesia provide excellent postoperative analgesia but require extended patient monitoring (3).

Peripheral techniques may have several advantages over systemic opioids. Notably, superior analgesia, decrease in opioid-related adverse effects and avoidance of neuraxial complications (1).

Local analgesia is a well recognised component in multimodal analgesia. It is inexpensive, relatively safe and simple to use. Infusions of local anaesthetic through catheters are a new and evolving area of postoperative pain management (4, 5).

The measurement of pain is difficult as pain is a subjective experience with multimodal components making an objective measurement for a patient's pain difficult. There are numerous pain measurement tools. Self-reported unidimensional instruments include the visual analogue scale (VAS). This scale is a relatively simple and efficient instrument to administer (6).

In the international arena of postoperative pain control many protocols for pain control are used following total abdominal hysterectomy. The Procedure Specific Postoperative Pain Management (PROSPECT) website contains recommendations for several postoperative pain protocols for patients undergoing total abdominal hysterectomy (7).

This committee recommends from evidence from randomised control trials that postoperatively patients post total abdominal hysterectomy (TAH) should have "strong" opioids by intravenous PCA or fixed intravenous dosing, titrated to pain intensity. Continuous wound infiltration of local anaesthetic after closure is not recommended as currently there is limited procedure-specific evidence (8).

The standard drug against which other opioids are compared is morphine (9). Morphine is classed as a "strong" opioid. Morphine is a very efficient analgesic but has a number of adverse side effects. The large quantities of morphine required, can lead to pruritis, fatigue, gastrointestinal adverse effects (nausea, vomiting and ileus), urinary retention, and reduced ability to mobilize due to drowsiness (10, 11, 12). Respiratory depression is a potentially dangerous adverse effect (11).

Multimodal analgesia helps reduce opioid consumption and thus minimises opioid side effects (3, 9). This paradigm of multimodal analgesia has developed to attempt to reduce side effects of analgesic medication and provide satisfactory pain relief. Internationally this has led to research into which combination protocols are the most effective in relieving post operative pain.

In the South African context various pain relief protocols are implemented. In the setting of Rahima Moosa Mother and Child hospital two pain protocol options can be implemented. Firstly, patients can be prescribed 10 mg Omnopon-Fresenius^{R} (this is a combination of morphine hydrochloride, codeine hydrochloride and papaverine hydrochloride) eight hourly with paracetamol and ibuprofen tablets when patients can take fluids orally (usually 24 hours post operation). The other option, introduced in 2008, is an intravenous morphine PCA. The program for the morphine is intravenous 1mg morphine

bolus with a lockout time of 6 minutes. This service is run by the Department of Anaesthesiology and Pain Department of the Helen Joseph/Rahima Moosa Mother and Child Hospital Complex.

The pain relief of a local anaesthetic continuous infusion in the incisional site has not been used in a public hospital. Factors involved are the cost implications of the required equipment, as well as the lack of evidence of its efficiency in reducing patients' pain. This technique of acute pain management, has not been studied in a healthcare setting of a developing country such as South Africa, as seen by a PubMed MESH search in October 2008 of the following terms: "South Africa", "local anaesthetic infusions" and "postoperative pain management in South Africa". There were no research articles concerning the above terms in the two non-accredited appropriate journals, namely the South African Medical Journal and the South African Journal of Anaesthesia and Analgesia.

In our setting (a South African public hospital), we do not have the resources (nursing skills and financial means) to maintain an epidural service in the post operative surgical wards. It has been noted that our acute pain management in patients post operation is not optimal (13). Local anaesthetic infusions in the incisional site may improve the acute postoperative pain in these patients and be logistically possible as they are easier to manage and care for in the ward. Thereby increasing both patient and nurse satisfaction.

1.3 Problem Statement

At Rahima Moosa Mother and Child hospital it has been observed that pain is prevalent and poorly managed postoperatively in patients following total abdominable hysterectomy. A more effective pain management protocol needs to be introduced. Morphine patient controlled analgesia is an effective pain relief option, however there are concomitant opioid side effects. The question arises whether a new technique of bupivacaine infusion into the incisional site reduces pain and consequently decreases patients' opioid requirements and therefore opioid side effects.

1.4 Hypothesis

There is no decreased opioid consumption and/or decreased pain intensity in patients with bupivacaine infusions into the incisional site compared to the control group.

1.5 Aim

The aim of the study is to determine whether there is a reduction in patients' opioid requirements post total abdominable hysterectomy and a decrease in the patients' pain intensity with the use of a bupivacaine infusion into the incisional site.

1.6 Objectives

The aims of the study will be justified by the following objectives.

1.6.1 Primary Objectives

- To determine patients' opioid consumption post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site
- To determine opioid consumption in patients' post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site
- Compare the use of opioid consumption in the two above-mentioned groups of patients post total abdominal hysterectomy

1.6.2 Secondary Objectives:

- To determine patients' post operative pain dynamic visual analogue scale (VAS) scores in patients post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site at set time points
- To determine patients' post operative pain dynamic VAS scores in patients post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site at set time points
- To compare the dynamic VAS scores between the two above mentioned groups
- To determine patients' post operative pain static VAS scores in patients post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site at set time points
- To determine patients' postoperative static VAS scores in patients post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site at set time points
- To compare the static VAS scores in the two above mentioned groups

- To determine the incidence of opioid adverse effects in patients post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site at set time points
- To determine the incidence of opioid adverse effects in patients post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site at set time points
- To compare the incidence of opioid adverse effects in the two above mentioned groups

1.7 Location of the study

The study took place at the Rahima Moosa Mother and Child Hospital (formerly Coronation Hospital), Gauteng Province, South Africa.

Rahima Moosa Mother and Child Hospital is a woman and child hospital associated with the University of the Witwatersrand. It is a secondary regional hospital acting as a referral hospital for smaller hospital clinics.

1.8 Research assumptions and definitions

Throughout this research report the following assumptions with their definitions will be made as outlined in the table below:

Table 1.1: Research assumptions and definitions

Assumption	Definition
Bupivacaine	A local anaesthetic agent that produces reversible blockade of neural transmission (9).
Total abdominal hysterectomy	The whole uterus including the cervix is removed, with as little vagina as possible. The ovaries and tubes may or may not be removed depending on the indication (14).
Visual analogue scale	A graphic rating scale using the combination of rating on a line and by checking descriptive terms (15).
Dynamic pain intensity	The pain rating that the patient experiences on movement, deep breathing or coughing.
Static pain intensity	The pain rating that the patient experiences in bed at rest.

1.9 Ethical considerations

1.9.1 Authorisation

An approval to conduct the study was obtained from the Ethics Committee of the University of the Witwatersrand, clearance number M070701 (Appendix A).

Approval by the Postgraduate Committee of the University of Witwatersrand was granted.

Approval for the study was obtained by the hospital superintendent at the time and the Head Matron of Rahima Moosa Mother and Child Hospital (Appendix B).

1.9.2 Patient Consent

Patients who met the selection criteria for this study were given a verbal explanation of the study and follow-up requirements by the clinical investigator. Each patient was supplied with a copy of the Patient Information Form (Appendix D) and the Consent Form (Appendix E) which they read in their own time. If the patient was then willing to participate in this study they signed the informed consent document.

1.9.3 Confidentiality of Subject Records

Confidentiality of subject data was maintained at all times. Subject anonymity was guaranteed. All documentation relating to the subject was kept in a secure location. Subjects were made aware that clinical data was stored electronically.
Confidentiality will be guaranteed in any resulting publication. Subjects were made aware that data collected as part of this study may be published but anonymity was guaranteed.

1.9.4 Declaration of Helsinki

The World Medical Association Declaration of Helsinki and its subsequent amendments formed the accepted basis for the ethical conduct of this study (16).

1.10 Regulatory Requirements

Regulatory Approval was not required for this particular study as the infusion device and bupivacaine are commercially available.

1.11 Research methodology

1.11.1 Research design

This was a contextual, prospective, parallel, single blinded, randomised control trial.

1.11.2 Study population

The study population for this study were women undergoing total abdominal hysterectomy at the Rahima Moosa Mother and Child Hospital, Johannesburg.

1.11.3 Study Sample

1.11.3.1 Sample Statement

A biostatistician calculated that a sample size of at least 18 subjects per group will have power in excess of 90 % to detect a decrease of at least 20 milligrams over a time period of 48 hours in morphine use using a one-sided t-test. The standard deviation assumed was 20 units which is the range of expected morphine use (10 – 130mg) divided by 6. The latter assumes a symmetrical distribution, which is unlikely.

1.11.3.2 Sampling method

The study sample included all patients undergoing total abdominal hysterectomy during daytime hours. The patients all had a routine general anaesthetic and standard analgesia intraoperatively. Only patients who consented to take part in the study were included in the sample study.

A consecutive convenience sampling method was used in this study. The most readily accessible gynaecological patients who presented for surgery were included. It is noted that a convenience sample cannot fully represent the study population. However,

consecutive sampling is the most reliable for convenience sampling as research bias is limited (17).

Selection bias was avoided by having the control device inserted in alternate participants.

1.11.4 Selection criteria

1.11.4.1 Inclusion criteria

The following inclusion criteria were used for the study:

- ASA I-II patients
- Pfannenstiel incision only.
- Informed consent to participate in this clinical study

1.11.4.2 Exclusion criteria

The following exclusion criteria were used for the study:

- Contraindication to general anaesthesia
- Allergy to any of the study medications
- History of alcohol/drug abuse
- Major medical disease such as cardiovascular, pulmonary, metabolic, renal, neurological or psychiatric disease
- Patients with clinically significant bacterial infection

1.12 Methodology

Patients scheduled for a total abdominal hysterectomy were assessed by the investigator pre-operatively. If the inclusion criteria were met, an informed consent to participate in the trial was obtained.

Patients who consented to participate in this clinical study were randomly assigned to either receiving a bupivacaine infusion into their incisional site and a morphine patient controlled analgesia (PCA) pump, or to receive a morphine PCA pump only.

The opioid requirements as well as number of attempts for opioid administration were documented at set intervals together with patients' visual analogue scale (VAS) for pain intensities.

1.12.1 Data Analysis

Data analysis was done in consultation with the biostatistician. Descriptive statistics mean, standard deviation, median, range and 95% confidence intervals was employed to summarise the observed data that was opioid consumption and VAS scores at set time periods. Groups were compared using the two-sample t-test. Also a Mann-Whitney U-test was employed for the skewed data Testing was at the 0.05 level of significance. A statistician, assisted in the format and layout of the graphs and figures.

1.13 Significance of the study

The results of this study will be of primary interest to patients following total abdominal hysterectomy and to hospitals providing postoperative pain management. This study will prove to be valuable in determining whether local anaesthetic infusions in the surgical site will decrease opioid requirements and improve patient satisfaction. This could aid hospital management in determining whether this pain relief device is worth obtaining for patient care.

This study shall also be of interest to the South African Chapter of the International Association of the Study of Pain (IASP). This study shall also be of interest to the South African Society of Anaesthesiologists (SASA), and the South African Journal of Regional Anaesthesia, which as a body proposes protocols/guidelines for the safe practice of anaesthesia and pain management.

1.14 Validity

The visual analogue scale is a well documented tool in measuring pain as a single quality that only varied in intensity. The average group scores can be treated as ratio data and there is good evidence for validity (6).

The morphine PCA pumps were all programmed identically for the study patients. The pumps program was locked and was not adjusted while the participant was in the trial.

The anaesthetic and surgical technique was a standardised procedure. The validity was confirmed by the researchers who checked the surgical notes and anaesthetic charts postoperatively.

1.15 Reliability

The data was collected consistently within the given time periods by two researchers to ensure reliability.

Quality control was achieved with the use of new morphine PCA pumps of the same make, the CADD-Legacy PCA Pump Model 6300 (Smith Medical). The PCA pumps were only

used on the clinical study participants during the clinical study. They had all been calibrated and serviced appropriately for the clinical study to ensure reliability.

The amounts in milligrams of morphine given and the patients attempted boluses (that been the number of times the participant pressed the button for a morphine bolus for breakthrough pain but was not delivered as the lockout time was not exceeded) were recorded from the PCA computer which automatically records the number of attempts and amount of doses that the pump gave to the patient.

The participants were operated on by different teams of surgeons and anaesthesiologists. The surgeons reliably preformed the total abdominal hysterectomy with a uniform surgical technique. The group of anaesthesiologists who provided the general anaesthetic for the study participants gave a uniform general anaesthesia with only opioid analgesia. This was ensured with regular interactions with the researches and presentations at departmental meetings. This ensured reliability in surgical and anaesthetic techniques of the study participants.

1.16 Potential limitations

The following limitations of this study have been identified:

The study population may not be representative of the national group of women undergoing total abdominal hysterectomy but addresses a clinical setting relevant locally.

The pain evaluations during the postoperative days were not performed under blinded conditions because of the clinical setting of this study. Rigorous scientific methods require

placing a subfascial catheter to all patients. Evident ethical reasons restrain our application of this method. Bias may occur due to the design of the trial, not being double-blinded. These limitations will be acknowledged as part of the discussion of the study's results.

1.17 Overview of the study

This study will be presented as follows:

Chapter 1: Overview of the study

Chapter one will provide an introduction for the study and will include the background to the study, the problem statements, aim and objectives. This chapter will also include the research assumptions, demarcation of the study and its purpose. It will contain a brief explanation of the research methodology and limitations.

Chapter 2: Literature review

This chapter will be a review of the literature relevant to this clinical study.

Chapter 3: Research methodology

Chapter three will contain the research methodology used, including the research design, the study setting, randomisation of trial participants, data collection procedures, validity and reliability of the study and ethical considerations.

Chapter 4: Data analysis and discussion of results

In this chapter the results, including the visual analogue scale scores, opioid consumption and the incidence of opioid adverse effects, of the two groups will be analysed. In addition this chapter will contain the descriptive statistics analysis and the analysis for statistical differences between the two clinical study groups.

Chapter 5: Summary, conclusions, limitations and recommendations.

In this chapter a summary and the conclusions from the main findings are presented, followed by a discussion of the limitations of the study and recommendations for clinical practise and for further research in this area.

1.18 Summary

Postoperative pain is prevalent and not optimally managed in most patients. Pain can lead to adverse emotional and systemic consequences.

Numerous device orientated studies have been done in other countries looking at the effect of infusions of local anaesthetic at the wound site postoperatively via an elastomeric pump. There have however been no similar studies done in South Africa. Knowledge of whether these pain relief devices are effective in patients following total abdominal hysterectomy in Rahima Moosa Mother and Child hospital could increase our choice of pain relief options in these patients.

2 Chapter Two: Literature Review

2.1 Introduction

In this chapter a review of the relevant literature is presented. The review begins with a discussion on postoperative pain and its associated problems. This will be followed by a review of pain relief options. The tools for monitoring and measuring pain will be discussed. Pain relief options for patients post total abdominal hysterectomy will be reviewed both in the international setting as well as the setting at Rahima Moosa Mother and Child hospital.

2.2 Postoperative Pain

2.2.1 Prevalence

Pain is rated as a highly undesirable postoperative outcome (1). Post operative pain is often negligently overlooked and remains under-treated (1, 3). In an audit at a public hospital a large proportion (37%) of patients will suffer severe pain 24 hours after surgery. After 24 hours, 43% of the patients had a pain score higher than 4 (out of 10) on movement (13). The same audit showed that only 14% of patients received their pain medication as prescribed at 24 hours. This trend continued at 48 and 72 hours, with respectively 18% and 21% of prescriptions being followed (13).

There is great variability in the rate of resolution of surgical pain (1). In one study 26% of surgical patients reported experiencing severe pain after 72 hours (13).

2.2.2 Complications of postoperative pain

Postoperative pain, especially when poorly controlled, results in acute adverse physiologic responses and chronic effects (1). Uncontrolled postoperative pain activates the sympathetic nervous system, which may contribute to morbidity or mortality. Activation of the sympathetic nervous system causes an increase in myocardial oxygen consumption, which may be significant in the development of myocardial ischemia and infarction. Sympathetic activation may also delay return of postoperative gastrointestinal motility and may develop into paralytic ileus (1). Unrelieved pain increases the stress response and aggravates wound healing (18). Beneficial effects of analgesia on functional rehabilitation and the duration of convalescence have been suggested repeatedly (19). Preclinical studies show that neuronal expression of new genes – the basis for neuronal sensitisation and remodelling, occurs within 20 minutes of injury resulting in increased sensitisation to chronic pain syndromes (20). Even brief intervals of acute pain can induce long-term neuronal remodelling and sensitisation ("plasticity"), chronic pain and lasting psychological distress (20, 21). This nociceptive process is not a hard-wired characteristic but is a plastic and dynamic process. Clinical studies also suggest that intensity and duration of acute postoperative pain are significant predictors of chronic pain development. In commonly used animal models for neuropathic pain, both spontaneous activity and pain behaviours appear within the first 12 hours to 2 days post-injury (22). Inadequately controlled pain may extend the length of hospital stay and predispose to expensive, time-consuming complications. Recognition of economical and humanitarian benefits of pain

control has prompted worldwide attention from professional group insurers, and governments (20).

2.3 Pain management

Control of acute postoperative pain, timing, duration, and fashion with which it is implemented, may be important in facilitating short and long-term patient convalescence after surgery (1).

There is no consensus on the best method for controlling pain (18).

Many options are available for the treatment of postoperative pain. Broadly there are two main options:

- Systemic (opioid and non-opioid) analgesia
- Regional analgesia (neuraxial and peripheral techniques).

2.3.1 Systemic analgesia

One of the main groups of systemic analgesia is the opioids. The standard drug against which other opioids are compared is morphine (9). Morphine is classed as a "strong" opioid. Morphine is a very efficient analgesic but has a number of adverse side effects. These are pruritis, fatigue, gastrointestinal adverse effects (nausea, vomiting and ileus), urinary retention, and reduced ability to mobilize due to drowsiness (10, 11, 12).

Respiratory depression is a potentially dangerous adverse effect (11).

Intravenous patient controlled analgesia (PCA) optimises delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability among individual patients (1). Compared with traditional 'as required' analgesic regimens,

intravenous PCA provides superior postoperative analgesia, improves patient satisfaction and may decrease the risk of pulmonary complications (1). It also ensures that the patient controls the amount and therefore is independent on the nursing care to provide the necessary analgesia.

Multimodal analgesia helps reduce opioid consumption and thus minimises opioid side effects (3, 23, 24). This paradigm of multimodal analgesia has developed to attempt to reduce side effects of analgesic medication and provide satisfactory pain relief. Principles of multimodal strategy require multidisciplinary collaboration and change in the traditional principles of postoperative care. Additional resources and expansion of the traditional acute pain service might be difficult in the current economic climate (1).

2.3.2 Non-systemic analgesia

Regional and peripheral techniques can provide superior analgesia, particularly when local anaesthetics are used, compared with systemic opioids. The use of these techniques may even reduce morbidity and mortality (1, 25, 26). Intrathecal and continuous epidural analgesia provide excellent postoperative analgesia but require extended patient monitoring (27, 28).

Epidural analgesia is associated with: hypotensive episodes (incidence up to 7%), motor block (2-3%), nausea and vomiting (20-30%) and urinary retention (18 – 80%). The dangerous complication of a spinal haematoma has an incidence of 1 in 3100 for postoperative epidural analgesia in certain groups of patients (1).

Peripheral techniques may have several advantages over systemic opioids notably, superior analgesia and a decrease in opioid-related adverse effects. Peripheral techniques also avoid neuraxial complications (1).

2.3.3 Local anaesthesia

Local anaesthesia is a well recognised component in multimodal analgesia. Local anaesthetics have an opioid sparing effect thereby decreasing opioid adverse effects (18). Local anaesthetics have multiple molecular and cellular actions (29).

Local anaesthetics block sensory inflow and can completely stop nociceptive transmission. It is also possible that repeated local anaesthetic wound instillation could decrease/modulate injury induced C-fibre activity with consequent attenuation of peripheral and central sensitisation and possibly decrease the incidence of hyperalgesia (24, 28).

Local anaesthetics provide good analgesia. In addition, they are inexpensive, relatively safe and simple to use. They are locally anti-inflammatory (24, 30) and have bacteriostatic and antimicrobial effects (30).

Local anaesthetics can be applied topically, subcutaneously or infiltrated into surgical sites. It is simple to inject local anaesthetics into the surgical wound and can be very efficacious (1, 12, 31, 32). They can also be used for single shot blocks for abdominable surgery such as the transverses abdominal plane block (33). However a single shot of local anaesthetic in the abdominal wall post total abdominal hysterectomy has shown no opioid-sparing effect (34). They can also be infused into the operative site via a pump (10, 21). This drug delivery system can give prolonged analgesia with few adverse effects, increased patient satisfaction and possibly expedite recovery (18). The technological improvements in the

needles and catheter insertion technique with practical drug delivery systems have increased the use of this modality for analgesia (18).

2.3.3.1 Local anaesthetic infusions

Infusions of local anaesthetic through perineural, incisional and intra-articular catheters are a new and evolving area of postoperative pain management (35, 36). The data for optimal parameters, that is local anaesthetic concentration, use of adjuvants (for example opioids) and continuous versus PCA or intermittent boluses for peripheral analgesia have not been determined (1, 11, 28, 37). In one study it was shown that 0.5% bupivacaine infiltrate infusion gave better analgesia than a 0.25% bupivacaine solution (12). The strengths of bupivacaine used in clinical studies are from 0.1 - 0.5% (18, 28).

There are 2 types of infusion pumps:

1) Elastomeric or spring- activated pumps

2) Battery powered electronic pumps

The elastomeric pump has simple equipment and technology and therefore needs a simple explanation concerning the equipment to patients and caregivers. The balloon pumps supply the required force to deliver anaesthetic agents to the surgical site and therefore needs no manual compression (18). Disadvantages are that their have inaccurate infusion rates and no ability to adjust/customise the infusion rate or provide boluses. The accuracy (infusion at affixed rate) and consistency (the majority of time at a fixed rate) depends on the location of catheter system and concentration and amount of local anaesthetic. The infusion rate is regulated by the temperature detection devices which are calibrated to skin. Complications regarding the local anaesthetic infusions are local anaesthetic toxicity especially if the catheter migrates into the intravascular space (18). Clinical impact of long

term myotoxic effects still have to be assessed especially regarding calcific myonecrosis (38). Controversies regarding local anaesthetics and neurotoxicity, myotoxicity and cartilage toxicity are present (38). The extent of muscle injury seems to be directly related to the dose and number of drug administrations. In the clinical setting local anaesthetic-induced myotoxicity seems to be rare (28, 37, 39). This is probably because local anaesthetic-induced analgesia and anaesthesia is achieved at a dosage insufficient to produce clinically recognisable myotoxicity (37).

Some clinicians have a preference for incisional catheter techniques because of their simplicity and safety over perineural catheters (36). Liu et al published a meta-analysis of trials using continuous infusions through wound catheters for postoperative analgesia. The outcome showed reduced pain scores and/or opioid consumption. Procedures included orthopaedic surgery, abdominal surgery, cardiothoracic surgery and gynaecological surgery. In general there was a 32% reduction of pain scores at rest and movement, 25% decreased need for opioids, 15% decreased risk of post operative nausea and vomiting and 30% increase in patient satisfaction. There was also a one day reduction of hospitalisation but the data were from limited number of patients (24, 40). These results were especially noted in orthopaedic patients. No cases of systemic toxicity or wound infection were reported (24). The meta-analysis found that randomised controlled trials involving gynaecological procedures showed a slight majority (5/9) of improved analgesic efficacy especially pertaining to the immediate postoperative period (24). Positive results were also noted in a study in patients who had an infusion of local anaesthetic in their incisional wound post median sternotomy (12) and inguinal hernia repair (41).

Current evidence from Canada and Sweden suggests that infusions of local anaesthetic techniques are effective, feasible and safe in the home environment if appropriate patient selection, routines and organization for follow-up are in place (24, 30, 40, 42). The local anaesthetic is infused into the operative site by a pump. Benefits include quicker recovery, decreased complications associated with narcotics and possibly a reduction in treatment costs (40). In the study by Gupta et al regarding gynaecological operations and intraperitoneal local anaesthetic infusion, it was noted that in addition to the reduced postoperative pain and opioid-sparing effects, there were no signs or symptoms of local anaesthetic toxicity and no clinical or laboratory evidence of infection in any of the trial groups (10). A similar study was done to evaluate the efficacy and patient satisfaction with incisional analgesia with a subfascial catheter compared to epidural analgesia for pain relief following caesarean section. The subfascial catheter provided satisfactory pain relief with patient satisfaction similar to that seen with epidural analgesia (43). This is in contrast to the study of postoperative pain in patients post caesarean section comparing systemic morphine, Ketorolac and a subcutaneous saline placebo infusion with a levobupivacaine subcutaneous infusion. In this study there was significantly less pain shown by the VAS scores in the group receiving systemic analgesia (44).

Problems (40 cases) that have been reported from the use of these catheter devices to the US Food and Drug Administration have been reported from surgeries and are possibly isolated incidents or sentinel events these are tissue necrosis, surgical wound infection and cellulitis. Tissue necrosis could be the result of using adrenaline in the local anaesthetic mixture (45).

2.4 Pain measurement tools

The measurement of pain is difficult as pain is a subjective experience with multimodal components including individual, genetic, cultural and sociological factors. This makes an objective measurement for a patient's pain difficult. There are numerous pain measurement tools. Self-reported unidimensional instruments include the visual analogue scale. This scale is a relatively simple and efficient instrument to administer especially for acute pain (6). Other measurements for acute pain are the intensity described in words or indirectly by opioid consumption, patients' satisfaction in analgesic protocols and the patients' mobility (46).

2.5 Post operative pain relief for total abdominal hysterectomy

In the international arena of postoperative pain control many protocols for pain control are used following total abdominal hysterectomy. The Procedure Specific Postoperative Pain Management (PROSPECT) website contains recommendations for several postoperative pain protocols for patients undergoing total abdominal hysterectomy. The committee recommends pain management options after evaluating information from a systematic review in addition to transferable evidence and expert knowledge. These recommendations are graded based on the level of evidence from studies in accordance with the Oxford Centre for evidence based medicine (7).

This committee recommends (evidence from randomised control trials), that postoperatively patients post total abdominal hysterectomy should have "strong" opioids by intravenous PCA or fixed intravenous dosing, titrated to pain intensity. Cyclo-oxygenase 2

(COX- 2) selective inhibitors and conventional non-steroidal anti-inflammatory drugs (NSAIDS) should be used in combination with opioids for analgesia. Paracetamol should be used in combination with NSAIDS in moderate to low intensity of pain. Moderate pain is defined as pain with a VAS >30/100 but <50/100. Low intensity pain is defined as pain with a VAS <30/100 (7).

Continuous wound infiltration of local anaesthetic after closure is not recommended as currently there is limited procedure-specific evidence. (8)

Literature shows that patients post total abdominable hysterectomy on average require 70mg of morphine over a 24 hour period (47).

2.5.1 Current practice for pain relief post total abdominal hysterectomy

In the South African context various pain relief protocols are implemented. In the setting of Rahima Moosa Mother and Child hospital two pain protocol options can be implemented. Firstly, patients can be prescribed 10 mg Omnopon-Fresenius^{R} (this is a combination of morphine hydrochloride, codeine hydrochloride and papaverine hydrochloride) eight hourly with paracetamol and ibuprofen tablets when patients can take fluids orally (usually 24 hours post operation). The other option, introduced in 2008, is an intravenous morphine PCA. The program for the morphine is IV 1mg morphine bolus with a lockout time of 6 minutes. This service is run by the Department of Anaesthesiology and Pain Department of the Helen Joseph/Rahima Moosa Mother and Child Hospital Complex.

2.6 Summary

This chapter has been a discussion of current literature relevant to the study.

Post operative pain is prevalent and not optimally managed. There are many modalities for pain control. The technique of a local anaesthetic continuous infusion in the incisional site for pain relief has not been used in South African public hospitals, one of the reasons being paucity of clinical evidence with this device. Local anaesthetic infusions in the incisional site may improve the acute postoperative pain in these patients and be logistically possible as they are easier to manage and care for in the ward, compared to an epidural service.

3 Chapter Three: Research Methodology

3.1 Introduction

In this chapter a detailed discussion of the methodology will be given. Points of discussion included are: problem statement, hypothesis, aim and objectives, ethical considerations, research methodology, financial considerations, the reliability and validity of the clinical study.

3.2 Problem statement

At Rahima Moosa Mother and Child hospital it has been observed that pain is prevalent and poorly managed postoperatively in patients following total abdominable hysterectomy. A more effective pain management protocol needs to be introduced. Morphine patient controlled analgesia is an effective pain relief option however there are concomitant opioid side effects. The question arises whether a new technique of a bupivacaine infusion into the incisional site reduces pain and consequently decreases patients' opioid requirements and therefore opioid side effects.

3.3 Hypothesis

There is no decreased pain intensity and/or decreased opioid consumption in patients with bupivacaine infusions into the incisional site compared to the control group.

3.4 Aim

The aim of the study is to determine whether there is a reduction in patients' opioid requirements post total abdominable hysterectomy and a decrease in the patients' pain intensity with the use of a bupivacaine infusion into the incisional site.

3.5 Objectives

The aims of the study will be justified by the following objectives.

3.5.1 Primary Objectives:

- To determine patients' opioid consumption post total abdominal hysterectomy in the presence of a local bupivacaine infusion incisional site
- To determine opioid consumption in patients' post total abdominal hysterectomy without the presence of a local bupivacaine infusion in the incisional site
- Compare the use of opioid consumption in the two above-mentioned groups of patients post total abdominal hysterectomy

3.5.2 Secondary Objectives

- To determine patients' post operative pain dynamic visual analogue scale (VAS) scores in patients post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site at set time points

- To determine patients' post operative pain dynamic VAS scores in patients post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site at set time points
- To compare the dynamic VAS scores between the two above mentioned groups
- To determine patients' postoperative pain static VAS scores in patients post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site at set time points
- To determine patients' postoperative static VAS scores in patients post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site at set time points
- To compare the static VAS scores in the two above mentioned groups
- To determine the incidence of opioid adverse effects in patients post total abdominal hysterectomy in the presence of a bupivacaine infusion in the incisional site at set time points
- To determine the incidence of opioid adverse effects in patients post total abdominal hysterectomy without the presence of a bupivacaine infusion in the incisional site at set time points
- To compare the incidence of opioid adverse effects in the two above mentioned groups

3.6 Ethical considerations

3.6.1 Authorisation

An approval to conduct the study was obtained from the Ethics Committee of the University of the Witwatersrand, clearance number M070701 (Appendix A).

Approval by the Postgraduate Committee of the University of Witwatersrand was granted (Appendix B).

Approval for the study was obtained by the hospital superintendent at the time and Head Matron of Rahima Moosa Mother and Child Hospital (Appendix C).

3.6.2 Patient Consent

Patients who met the selection criteria for this study were given a verbal explanation of the study and follow-up requirements by the clinical investigator. Each patient was supplied with a copy of the Patient Information Form (Appendix D) and the Consent Form (Appendix E) which they read in their own time. Any questions and queries raised by the patient were answered appropriately by the researcher obtaining consent. Patients that agreed to take part in the study gave written consent.

The participants were made aware that participation/non-participation was not going to disadvantage them, directly or indirectly, in any way.

3.6.3 Confidentiality of Subject Records

Confidentiality of subject data was maintained at all times. Subject anonymity was guaranteed. All documentation relating to the subject was kept in a secure location.

Subjects were made aware that clinical data was stored electronically.

Confidentiality was guaranteed for any resulting publication. Subjects were made aware that data collected as part of this study may be published but anonymity was guaranteed.

3.6.4 Declaration of Helsinki

The World Medical Association Declaration of Helsinki and its subsequent amendments formed the accepted basis for the ethical conduct of this study (16).

3.6.5 Regulatory requirements

Regulatory approval was not required for this study as the infusion device and bupivacaine are commercially available.

3.7 Research methodology

3.7.1 Research design

This was a contextual, prospective, parallel, single blinded, randomised control trial.
The study was contextual in nature as it was conducted in the Rahima Moosa Mother and Child Hospital. It was prospective as the study examined the opioid consumption and visual analogue scale scores of women post total abdominable hysterectomy after participants gave their informed consent. The design was single blinded as the clinical providers and not the study participants knew who the control or trial participants were.

3.7.2 Study population

The study population for this study were women undergoing total abdominal hysterectomy at the Rahima Moosa Mother and Child Hospital, Johannesburg.

3.7.3 Study Sample

3.7.3.1 Sample Statement

A biostatistician calculated that a sample size of at least 18 subjects per group would have power in excess of 90 % to detect a decrease of at least 20 milligrams over a time period of 48 hours in morphine use using a one-sided t-test. The standard deviation assumed was 20mg which is the range of expected morphine use (10 – 130mg) divided by 6. The latter assumes a symmetric distribution, which is unlikely in this clinical study.

3.7.3.2 Sampling method

A consecutive convenience sampling method was used in this study. The most readily accessible elective gynaecological patients presenting for total abdominal hysterectomy surgery were included. It is noted that a convenience sample cannot fully represent the study population. The patients all had a routine general anaesthetic and standard analgesia intraoperatively.

Every patient suitable for the clinical study who presented for the operation was invited to participate in the study. Only patients who consented to take part in the study were included in the sample study. Consecutive sampling is the most reliable for convenience sampling as research bias is limited (17).

3.7.4 Selection criteria

Inclusion criteria

- The following inclusion criteria were used for the study:
- ASA I-II patients
- Pfannenstiel incision only
- Informed consent to participate in this clinical study

Exclusion criteria

The following exclusion criteria were used for the study:

- Contraindication to general anaesthesia
- Allergy to any of the study medications
- History of alcohol/drug abuse
- Major medical disease such as cardiovascular, pulmonary, metabolic, renal, neurological or psychiatric disease
- Patients with clinically significant bacterial infection

3.7.5 Clinical Methodology

Patients scheduled for a total abdominal hysterectomy were assessed by the investigator pre-operatively. If the inclusion criteria were met, an informed consent to participate in the trial was obtained.

Patients who consented to participate in this clinical study were randomly assigned to either receiving a bupivacaine infusion into their incisional site and a morphine patient controlled analgesia (PCA) pump, or to receive a morphine PCA pump only.

Preoperatively

The patients were preoperatively assessed the day before. The anaesthetic orders were that the patient was to be starved appropriately and given no analgesic premedication.

Intraoperatively

The group of anaesthesiologists from the Helen Joseph/Rahima Moosa Mother and Child Hospital Anaesthetic Department, who provided the general anaesthetic for the study participants gave a uniform general anaesthesia with only opioid analgesia. This was ensured with regular interactions with the researchers and presentations at departmental meetings.

All patients had the standard monitors applied. Monitoring included non-invasive arterial blood pressure, heart rate, peripheral oxygen saturation, end-tidal gas monitoring and electrocardiogram. After intravenous cannulation, anaesthesia was induced with opioids and propofol until loss of consciousness. The opioids used were either fentanyl or alfentanil depending on the anaesthesiologist's discretion. The doses used were titrated to effect on the patient and varied accordingly. Tracheal intubation was performed after muscle relaxation with a non depolariser muscle relaxant of the anaesthetists' choice. Anaesthesia was maintained by an inhalational anaesthetic. Air and oxygen were used and the inhalational anaesthetic was either isoflurane or sevoflurane depending on the anaethesiologist's discretion. Mechanical ventilation was used in a low-flow system to maintain an end-tidal carbon dioxide of 35 – 45 mmHg. Only opioids, namely fentanyl and morphine, were given for analgesia. Doses were titrated accordingly to the patients body mass and effect. At the end of the operation, muscle relaxation was reversed with

glycopyrrolate and neostigmine in adequate doses and the inhalational anaesthetic was turned off. After satisfactory spontaneous ventilation and awakening, the patient was extubated and transferred to the recovery area for further standard post-operation observations and facemask oxygen via a Venturi mask. Once the recovery sisters were satisfied with the patients' condition they discharged the patient to the ward where standard post operative observations were performed by the nursing staff.

Surgery was performed by surgeons of five different surgical teams. Surgery was preformed in a standardised manner using a Pfannenstiel incision, approximately 10-15cm depending on the patients body habitus. Surgical procedures were either a total abdominable hysterectomy with or without salpingo-oophorectomy. None of the participants had extensive blood loss requiring blood transfusion.

The patients who were study participants had an On-Q PainBuster^{R} Soaker^{TM} 6.5 pain relief system (all within their expiry date) inserted. At wound closure, a multi-holed catheter (On-Q PainBuster^{R} Soaker^{TM} 6.5 pain relief system, 270ml volume, 4ml/hr, I-Flow Corporation, USA) was inserted by the gynaecologist along the length of the incisional site under the abdominal fascia. Prior to the placement of these catheters 1-2ml bolus of 0.5% bupivacaine was injected into each catheter to prime them. The placement method was as follows, the introducer needles were tunnelled 3-5cm lateral to the incision using a Z-track method. A catheter was threaded through the introducer into the subfascial space. The T-peel was pulled out of the insertion site completely before been peeled away. The catheter was brought out approximately 2cm away from the wound site. The fascial layer was closed with sutures over this catheter, after closure of the fascia the second catheter was inserted in a similar manner as the subfascial catheter but from the opposite side and above

the subfascial catheter. Once the skin had been closed, 5ml bolus of 0.5% bupivacaine was injected through each catheter thus infiltrating the incision. The catheters were secured by been coiled and taped to the skin with a dressing. Using an aseptic technique, these catheters were then connected to a 270ml elastomeric disposable balloon pump with the appropriate volume of the study drug (192ml of 0.39% bupivicaine). The drug infusion was started by opening the clamps on the catheter. The bupivacaine was obtained from the pharmacy in a concentration of 0.5% (volume, 10ml/ampoule) all were within their expiry date. This infusion was made up of 150ml of 0.5% bupivacaine (750mg) which was mixed with 42ml of 0.9% saline to provide 750mg bupivacaine in 192ml of 0.9% saline making up a concentration of 3.9mg/ml. This was infused at 4ml/hr (15.6mg/hr) for 30hours. An additional 10ml of 0.5% bupivacaine solution (50mg) was bolused down the catheters. The total amount of bupivacaine injected during the 30 hours was 468mg which was within the manufacturers' recommended dose of 400mg bupivacaine in a 24 hour period.

The control participants had after placing a sterile bandage over the wound site a catheter placed on top of the bandage and coiled and connected to apparatus similar to the trial group. The catheter was taped and covered by another bandage. The catheter neither penetrated the wound site nor infused any substance. Both groups had the pump apparatus concealed in an On-Q painbuster black bag.

Postoperatively

After surgery, all patients were connected to morphine CADD-Legacy PCA Pump Model 6300s (Smith Medical). The PCA protocol was one milligram (1mg) morphine bolus dose with a lock-out of 6 minutes for breakthrough pain. Maximum dose of morphine was 10 milligrams per hour. This concentration was made up from 90mg morphine diluted to

22ml of 0.9% saline making up a concentration of 4mg/ml. This patient controlled analgesia (PCA) pump was for breakthrough pain. The patients were instructed in its use before surgery. No other pain analgesia was prescribed. If patients complained of nausea or vomiting, prochlorperazine 12,5mg intramuscularly was administered. Promethazine 25mg intramuscularly (8 hourly) was prescribed for patients with itchiness.

After thirty hours, the catheter was withdrawn and the intravenous line was taken down together with the morphine PCA pump. Regular diclofenac suppositories (100mg eighteen hourly) and paracetamol (1gr orally 6 hourly) was then prescribed for analgesia.

The patients were discharged by the surgical team.

3.7.6 Data collection

Postoperative evaluations were performed by two assessors only (the researcher and an anaesthestic consultant) at 1 hour, 6, 24 and 30 hours post operation. For all measurements, the time at which the study drug infusion was started was considered to be Time 0.

The following postoperative evaluations at the set times were made: Visual analogue pain scale (VAS) scores were for:-

- The worst pain experienced since the last observation
- Static pain intensity at the time of observation
- Dynamic pain intensity at the time of observation

Opioid adverse effects, namely nausea, vomiting and itchiness were asked about at the set times post operation.

Total morphine consumption and the number of attempts for morphine boluses were recorded for the periods: 0-1hr, 1-6hrs, 6-24hrs and 24-30 hours post operation. Patient and nurse satisfaction with the catheter was also asked at each set time post operation. The day of discharge and any perioperative complications were noted. Data was collected by the investigator in copy and compiled on a Microsoft Excel (2003) data table.

3.7.7 Data Collection Tool

The data sheet consisted of 2 sections (APPENDIX F):

Section A: the demographic survey section included subcategories within the study sample by which data was analysed. These subcategories were age and if the participants had previous Caesarean section(s).

Section B: the subcategories were as follows - the worst pain intensity score felt since the previous set observation point, pain intensity scores when lying quietly (static VAS) and on movement (dynamic VAS), presence of adverse side-effects of morphine (itchiness, nausea and vomiting), any complications with the catheter, the patient's satisfaction with the device, the nurses' satisfaction with the device, day of hospital discharge and perioperative complications.

3.7.8 Study Devices

3.7.8.1 On-Q PainBusterR SoakerTM 6.5 pain relief system (figure 3.1)

On-Q PainBuster^{R} Soaker^{TM} 6.5 pain relief system delivered the bupivacaine infusion in the incisional site as per the manufacturer's guidelines. The infusion continued for a 30 hour period at 4ml per hour.

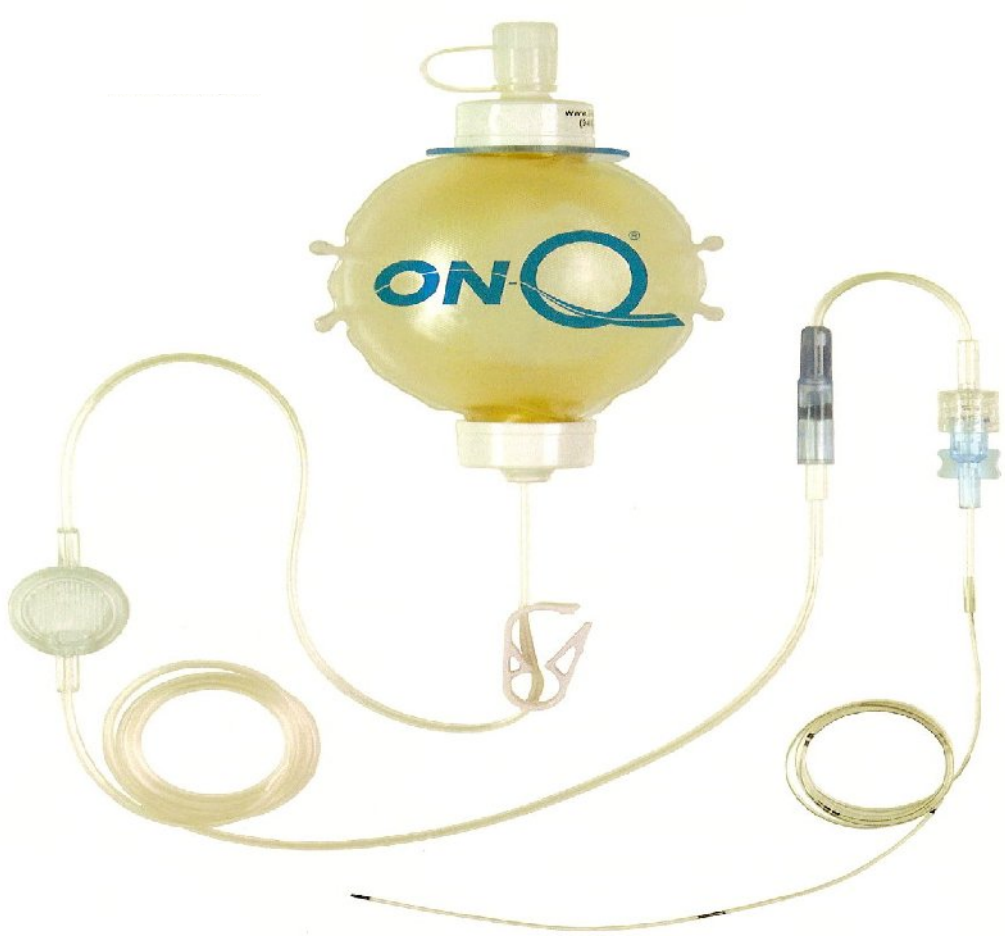

Figure 3.1: ON-Q Pain Buster^{R} Soaker^{TM} 6.5 pain relief system (47)

3.7.8.2 CADD-Legacy PCA Pump Model 6300 (Smith Medical)

All participants were connected to a morphine CADD-Legacy PCA Pump Model 6300 (Smith Medical) as per the morphine PCA protocol.

3.7.9 Data Analysis

Data analysis was done in consultation with the biostatistician. Descriptive statistics mean, standard deviation, median, range and 95% confidence intervals was employed to summarise the observed data that was morphine use and VAS scores. Groups were compared using the two-sample t-test. Also a Mann-Whitney U-test was employed for the skewed data Testing was at the 0.05 level of significance. A statistician assisted with the presentation and further analysis of the data collected.

3.7.10 Statistical considerations

Function evaluation served as the basis for evaluating the clinical results of the subjects.

3.8 Costs

The participants in this study did not incur any extra costs. Non-participation did not disadvantage participants in any way.

SA Biomedical Pty Ltd. supplied the 20 On-Q PainBuster^{R} Soaker^{TM} 6.5 pain relief systems. The analgesics were provided by the hospital pharmacy.

The CADD-Legacy PCA Pumps were the property of the Anaesthetic Department of the Rahima Moosa Mother and Child Hospital. The components for the functioning of the morphine CADD-Legacy PCA Pump Model 6300 (Smith Medical) were provided by the hospital.

Administrative costs were incurred by the Department of Anaesthesiology, Helen Joseph/Rahima Moosa Mother and Child Hospital Complex.

3.9 Validity

The visual analogue scale is a well documented tool in measuring pain as a single quality that only varies in intensity. The average group scores can be treated as ratio data and there is good evidence for validity (6). In this study the individual scores were treated as ratio data.

3.10 Reliability

The morphine PCA pumps were all programmed identically for all the study participants. The pumps programme was locked and was not adjusted while the participants were in the trial.

The On-Q PainBuster^{R} Soaker^{TM} 6.5 pain relief systems delivered the bupivacaine infusion in the incisional site as per the manufacturer's guidelines. The infusions were mixed and drawn up by only the two clinical investigators to ensure reliability.

The data collection was collected consistently within the set data collection times. The data was collected by only two investigators to ensure reliability.

The amounts of morphine given and attempted were recorded from the morphine PCA computer which automatically recorded the number of attempts and amount of doses that the pump gave to the patient.

3.11 Summary

The study design allowed for an assessment of the pain intensities of the study participants postoperatively in a single blinded fashion. The data collection sheet was a valid tool with increased standardisation as the data collected was by two assessors only. Thus allowing a comparison between the two groups in order to prove or disprove the hypothesis that there is no decreased pain intensity and/or decreased opioid consumption in patients with local bupivacaine infusions into the incisional site compared to the control group.

4 Chapter Four: Results and statistical analysis

4.1 Introduction

This chapter begins with the comparison of the demographic data between the two clinical trial groups. It then continues with the results of the data collection and the statistical analysis. The statistical analyses pertain to the two groups. The results are the visual analogue scores and opioid consumption of the two groups at the set observation periods and the opioid adverse side effects at the set observation periods. This is followed by the comparison of the two groups for statistical differences with one another.

4.2 Data Collection Results

4.2.1 Demographic Data and Analysis

The demographic data of the 2 groups illustrating the participants' age, race, type of operation and body mass index follows.

4.2.1.1 Age

The means, confidence intervals and standard deviations of the study participants' ages are listed in Table 4.1. These were for the control group 42.55 years of age, 38.21-46.80 and 9.77 respectively. The values for the device group were as follows 43.61 years of age,

39.96-47.26 and 7.34. There were no missing values. The two sample t test with unequal variance result is 0.652. This shows there was no statistical significance between the groups and their ages.

4.2.1.2 Racial comparison

The clinical data pertaining to the race group of the study participants is tabulated in Table 4.2. In the control group there were 15 Blacks, 6 "Coloureds", 1 Indian making the number of 22 participants. In the device group there were 12 Blacks, 4 "Coloureds" 1 Malay and 1 White participant making up the number of 18 participants. There were no missing values. The Fisher's exact test result of 0.691 is noted. This indicates no statistical significance between the two groups.

4.2.1.3 Operations of the study participants

The clinical data pertaining to the specific operations performed on the study participants is tabulated in Table 4.3. In the control group there was 14 total abdominal hysterectomies (TAH), 7 total abdominal hysterectomies and bilateral salpingoophectomy (TAH and BSO), 1 myomectomy. In the device group there were 10 TAHs, 7 TAH and BSO and 1 total abdominal hysterectomy and unilateral salpingoophectomy (TAH and USO). The Fisher's exact test result of 0.721 is noted indicating no statistical significance between the two groups.

4.2.1.4 Body mass index

The means, confidence intervals and standard deviations of the study participants' ages are listed in Table 4.4. These values in the control group were 28.79, 25.54-32.04 and 7.34 respectively. The values for the device group were as follows 31.12, 28.51-33.73 and 5.25. There were no missing values. The two sample t test with unequal variance result is 0.25. This test indicates no statistical difference between the two groups' body mass indexes.

Table 4.1: Age comparison between the 2 groups

Group	Observations	Mean	Standard error	Standard deviation	95% confidence interval (lower limit)	95% confidence interval (upper limit)
Control	22	42.55	2.08	9.77	38.21	46.80
Device	18	43.61	1.73	7.34	39.96	47.26
Combined	40	43.03	1.37	8.67	40.25	45.79
Difference		-1.07	2.71		-6.54	4.41

Table 4.2: Racial comparison between the 2 groups

Race	Control	Device	Total
Black	15	12	27
Coloured	6	4	10
Indian	1	0	1
Malay	0	1	1
White	0	1	1
Total	22	18	40

Table 4.3: Operation comparison between the 2 groups

Operation	Control	Device	Total
TAH	14	10	24
TAH & BSO	7	7	14
TAH & USO	0	1	1
Myomectomy	1	0	1
Total	22	18	40

TAH: total abdominal hysterectomy

TAH & BSO: total abdominal hysterectomy and bilateral salpingoophectomy

TAH & USO: total abdominal hysterectomy and unilateral salpingoopherectomy

Table 4.4: Body Mass Index

Group	Observations	Mean	Standard error	Standard deviation	95% confidence interval (lower limit)	95% confidence interval (upper limit)
Control	22	28.79	1.56	7.34	25.54	32.04
Device	18	31.12	1.24	5.25	28.51	33.73
Combined	40	29.84	1.03	6.51	27.76	31.92
Difference		-2.33	1.99		-6.365	1.70

4.2.1.5 Analysis of demographic data

The comparison of demographical information between the two groups and associated parametric and non parametric testing indicate there was no statistical difference between these two groups improving the validity of the results comparing the measured variables.

4.3 Descriptive statistical analysis of the data

The descriptive analyses will include the measured variables grouped at the set observation periods.

4.3.1 Opioid consumption in the control group

The means, confidence intervals and standard deviations of the opioid consumption of participants post total abdominal hysterectomy (TAH) without the device at the 4 different set observation periods are listed in Table 4.5. There were no missing values. The values for the Period 0-1 hour post operation are 4.89mg, 3-29-6.49mg and 3.6 mg respectively. The values for Period 1-6 hours post operation are 8.22mg, 5.43-11.02mg and 6.30mg respectively. The values for Period 6-24 hours post operation are respectively 24.67mg, 20.25-29.08mg and 9.70mg. In the last period from 24 – 30 hours post operation the values are respectively 8.33mg, 6.12-10.49mg and 4.74mg.

4.3.2 Opioid consumption in the device group

The means, confidence intervals and standard deviations of the opioid consumption of participants post TAH with the device at the 4 different set observation periods are listed in Table 4.6. There were no missing values. The values for the Period 0-1 hour post operation are 3.35mg, 1.98-4.72mg and 2.67mg respectively. The values for Period 1-6 hours post operation are 10.83mg, 6.43-15.24mg and 8.86mg respectively. The values for Period 6-24 hours post operation are respectively 25.11mg, 16.80-33.42mg and 16.71mg. In the last period from 24 – 30 hours post operation the values are respectively 5.78mg, 3.52-8.03mg and 4.53mg.

4.3.3 Dynamic visual analogue scale (VAS) scores in the device group

The means, confidence intervals and standard deviations of the dynamic VAS scores of participants post TAH with the device at the 4 different set observation periods are listed in Table 4.7. There were no missing values. The values for the Period 0-1 hour post operation are 39.42, 21.36-57.47 and 36.31 respectively. The values for Period 1-6 hours post operation are 33.97, 18.37-49.58 and 31.37 respectively. The values for Period 6-24 hours post operation are respectively 39.17, 25.16-53.17 and 28.16. In the last period from 24 – 30 hours post operation the values are respectively 32.56, 19.49-45.62 and 26.28.

4.3.4 Dynamic VAS scores in the control group

The means, confidence intervals and standard deviations of the dynamic VAS score of participants without the device at the 4 different set observation periods are listed in Table 4.8. There were no missing values. The values for the Period 0-1 hour post operation are 67.17, 54.20-80.13 and 28.49 respectively. The values for Period 1-6 hours post operation are 48.73, 35.23-62.23 and 30.44 respectively. The values for Period 6-24 hours post operation are respectively 60.89, 48.62-73.14 and 26.94. In the last period from 24 – 30 hours post operation the values are respectively 54.31, 40.07-68.54 and 31.28.

4.3.5 Static VAS scores in the device group

The means, confidence intervals and standard deviations of the static pain VAS score of participants with the device at the 4 different set observation periods are listed in Table 4.9. There were no missing values. The values for the Period 0-1 hour post operation are 34.89,

17.27-52.51 and 35.44 respectively. The values for Period 1-6 hours post operation are 26.89, 13.20-40.58 and 27.52 respectively. The values for Period 6-24 hours post operation are respectively 22.53, 14.46-30.59 and 16.22. In the last period from 24 – 30 hours post operation the values are respectively 20.06, 8.54-31.57 and 23.16.

4.3.6 Static VAS scores in the control group

The means, confidence intervals and standard deviations of the static pain VAS score of participants without the device at the 4 different set observation periods are listed in Table 4.10. There were no missing values. The values for the Period 0-1 hour post operation are 59.25, 43.41-75.09 and 35.72 respectively. The values for Period 1-6 hours post operation are 25.80, 17.59-34.00 and 18.51 respectively. The values for Period 6-24 hours post operation are respectively 28.69, 15.69-41.69 and 28.56. The last period from 24 – 30 hours post operation the values are respectively 27.23, 16.75-37.72 and 23.03.

4.3.7 VAS scores of the worst pain since the last time seen in the control group

The means, confidence intervals and standard deviations of the worst pain VAS score of participants without the device at the 4 different set periods are listed in Table 4.11. There were no missing values. The values for the Period 0-1 hour post operation are 72.45, 60.12-84.79 and 27.83 respectively. The values for Period 1-6 hours post operation are 60.43, 46.61-74.45 and 31.62 respectively. The values for Period 6-24 hours post operation are respectively 54.31, 41.24-67.38 and 28.72. The last period from 24 – 30 hours post operation the values are respectively 45.90, 30.01-61.80 and 34.92.

4.3.8 VAS scores of the worst pain since the last time seen in the device group

The means, confidence intervals and standard deviations of the worst pain VAS score of participants with the device at the 4 different set periods are listed in Table 4.12. There were no missing values. The values for the Period 0-1 hour post operation are 46.89, 32.17-61.61 and 29.61 respectively. The values for Period 1-6 hours post operation are 35.86, 19.34-52.38 and 33.22 respectively. The values for Period 6-24 hours post operation are respectively 50.53, 34.39-66.67 and 32.46. The last period from 24 – 30 hours post operation the values are respectively 41.67, 23.94-59.39 and 35.64.

4.3.9 Opioid adverse effects in the device group and control group

The number of participants with opioid adverse effects namely nausea, vomiting and itchiness in the patients post TAH with the device. The clinical data is tabulated in table 4.13 with regard to the participants in the device group. The clinical data is tabulated in the table 4.14 with regard to the participants in the control group. In the first period 2 participants from the device group complained of nausea or/and vomiting versus 4 control participants in the same period. In the second period 6 participants in the device group complained of nausea and/or vomiting which was the same number in the control group. In the third period 5 participants in the group with the device complained of nausea and/vomiting compared to 8 participants in the control group. The last period 1 participant in the device group compared to 5 participants in the control group complained of nausea and/or vomiting.

In the first period 3 participants of the group with the device complained of itchiness compared to 1 participant in the control group. In the second period 5 participants complained of itchiness compared to 1 participant in the control group. In the third period 8 participants from the device group compared to 10 participants in the control group complained of itchiness. In the last period 10 participants from the device group compared to 11 participants in the control group complained of itchiness.

Table 4.5: Descriptive statistics of opioid consumption in the control group

	Statistic	Standard error
Period 0-1h mean	4.89mg	0.77
Standard deviation	3.60mg	
95% Confidence level lower limit	3.29mg	
upper limit	6.49mg	
Period 1-6h mean	8.22mg	1.34
Standard deviation	6.30mg	
95% Confidence level lower limit	5.43mg	
upper limit	11.02mg	
Period 6-24h mean	24.67mg	2.12
Standard deviation	9.70mg	
95% Confidence level lower limit	20.25mg	
upper limit	29.08mg	
Period 24-30h mean	8.33mg	1.03
Standard deviation	4.74mg	
95% Confidence level lower limit	6.12mg	
upper limit	10.49mg	

Table 4.6: Descriptive statistics of opioid consumption in the device group

	Statistic	Standard error
Period 0-1h mean	3.35mg	0.65
Standard deviation	2.67mg	
95% Confidence level lower limit	1.98mg	
upper limit	4.72mg	
Period 1-6h mean	10.83mg	2.1
Standard deviation	8.8g6m	
95% Confidence level lower limit	6.43mg	
upper limit	15.24mg	
Period 6-24h mean	25.11mg	3.94
Standard deviation	16.71mg	
95% Confidence level lower limit	16.80mg	
upper limit	33.42	
Period 24-30h mean	5.78	1.07
Standard deviation	4.53	
95% Confidence level lower limit	3.52	
upper limit	8.03	

Table 4.7: Descriptive statistics of dynamic VAS scores in the device group

	Statistic	Standard error
Period 0-1h mean	39.42	8.56
Standard deviation	36.31	
95% Confidence level lower limit	21.36	
upper limit	57.47	
Period 1-6h mean	33.97	7.40
Standard deviation	31.37	
95% Confidence level lower limit	18.37	
upper limit	49.58	
Period 6-24h mean	39.17	6.63
Standard deviation	28.16	
95% Confidence level lower limit	25.16	
upper limit	53.17	
Period 24-30h mean	32.56	6.19
Standard deviation	26.28	
95% Confidence level lower limit	19.49	
upper limit	45.62	

Table 4.8: Descriptive statistics of dynamic VAS scores in the control group

	Statistic	Standard error
Period 0-1h mean	67.17	6.21
Standard deviation	28.49	
95% Confidence level lower limit	54.20	
upper limit	80.13	
Period 1-6h mean	48.73	6.49
Standard deviation	30.44	
95% Confidence level lower limit	35.23	
upper limit	62.23	
Period 6-24h mean	60.89	5.88
Standard deviation	26.94	
95% Confidence level lower limit	48.62	
upper limit	73.14	
Period 24-30h mean	54.31	6.82
Standard deviation	31.28	
95% Confidence level lower limit	40.07	
upper limit	68.54	

Table 4.9: Descriptive statistics of the static VAS scores in the device group

	Statistic	Standard error
Period 0-1h mean	34.89	8.35
Standard deviation	35.44	
95% Confidence level lower limit	17.27	
upper limit	52.51	
Period 1-6h mean	26.89	6.49
Standard deviation	27.52	
95% Confidence level lower limit	13.20	
upper limit	40.58	
Period 6-24h mean	22.53	3.82
Standard deviation	16.22	
95% Confidence level lower limit	14.46	
upper limit	30.59	
Period 24-30h mean	20.06	5.46
Standard deviation	23.16	
95% Confidence level lower limit	8.54	
upper limit	31.57	

Table 4.10: Descriptive statistics of static VAS scores in the control group

	Statistic	Standard error
Period 0-1h mean	59.25	7.62
Standard deviation	35.72	
95% Confidence level lower limit	43.41	
upper limit	75.09	
Period 1-6 mean	25.80	3.95
Standard deviation	18.51	
95% Confidence level lower limit	17.59	
upper limit	34.00	
Period 6-24h mean	28.69	6.23
Standard deviation	28.56	
95% Confidence level lower limit	15.69	
upper limit	41.69	
Period 24-30h mean	27.23	5.03
Standard deviation	23.03	
95% Confidence level lower limit	16.75	
upper limit	37.72	

Table 4.11: Descriptive statistics of the VAS score of the worst pain since the last time seen in the control group

	Statistic	Standard error
Period 0-1h mean	72.45	5.93
Standard deviation	27.83	
95% Confidence level lower limit	60.12	
upper limit	84.79	
Period 1-6h mean	60.43	6.74
Standard deviation	31.62	
95% Confidence level lower limit	46.41	
upper limit	74.45	
Period 6-24h mean	54.31	6.27
Standard deviation	28.72	
95% Confidence level lower limit	41.24	
upper limit	67.38	
Period 24-30h mean	45.90	7.62
Standard deviation	34.92	
95% Confidence level lower limit	30.01	
upper limit	61.80	

Table 4.12: Descriptive statistics of the VAS score of the worst pain since the last time seen in the device group

	Statistic	Standard error
Period 0-1h mean	46.89	6.98
Standard deviation	29.61	
95% Confidence level lower limit	32.17	
upper limit	61.61	
Period 1-6h mean	35.86	7.83
Standard deviation	33.22	
95% Confidence level lower limit	19.34	
upper limit	52.38	
Period 6-24h mean	50.53	7.65
Standard deviation	32.46	
95% Confidence level lower limit	34.39	
upper limit	66.67	
Period 24-30h mean	41.67	8.40
Standard deviation	35.64	
95% Confidence level lower limit	23.94	
upper limit	59.39	

Table 4.13: Opioid adverse effects in the device group

	Nausea/vomiting		Itchiness		total
	No	Yes	No	Yes	
Period 0 -1h	16	2	15	3	18
Period 1-6h	12	6	13	5	18
Period 6 – 24h	13	5	10	8	18
Period 24 – 30h	17	1	8	10	18

Table 4.14: Opioid adverse effects in the control group

	Nausea/vomiting		Itchiness		total
	No	Yes	No	Yes	
Period 0-1h	18	4	21	1	22
Period 1-6h	16	6	20	2	22
Period 6–4h	13	8	11	10	21
Period 24–30h	16	5	10	11	21

4.4 Analysis for statistical differences between the control and device groups

The opioid consumption of the two groups and the VAS scores of the two groups at set observation periods were tested with the two sample t test with unequal variances and two-sample Wilcoxon rank-sum (Mann-Whitney) tests. They were both used to increase the reliability of the results. The measured variables were analysed and illustrated in the following order: opioid consumption between the control and device group, dynamic VAS scores between the control and device groups, the static VAS scores between the control and device group and the worst VAS score since the last time seen since the control and device group.

The non continuous variables namely the opioid adverse effects (nausea, vomiting and itchiness) were tested with the Fischer exact test. The data is analysed following the continuous variable data analysis. The comprehensive statistical data and tables are in Appendix H.

4.4.1 Opioid consumption between the control and device groups

Analysis of the opioid consumption was performed. There was no statistical difference between the two groups. The following p values are when equal variance is assumed and then tested again for unequal variance respectively. The p value at the first set period was 0.134 and 0.145. The p value at the second set period was 0.302 and 0.369. At the third set period the p value was 0.922 and 0.544 and the last set period the p values were 0.094 and 0.090 respectively. Figure 4.1 is a line graph illustrating the differing opioid consumption of the participants at the set observation periods.

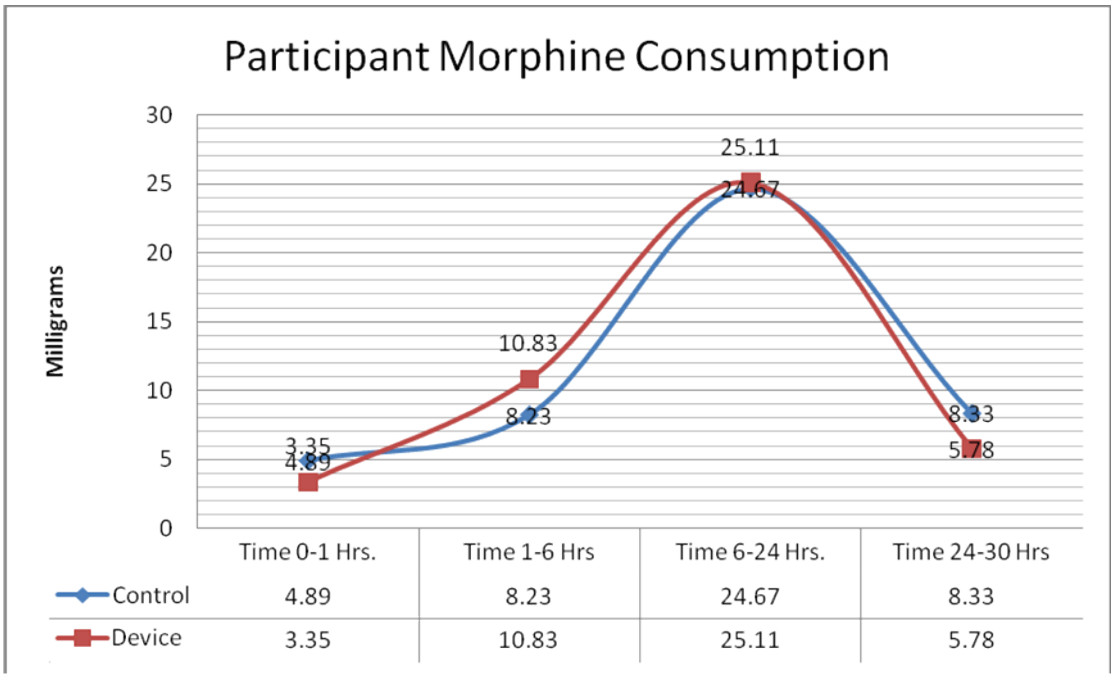

Figure 4.1: Comparison of morphine consumption between the device and control groups

4.4.2 **Dynamic VAS scores between the control and device groups**

Analysis for statistical difference between the dynamic VAS scores of the two groups was performed. First, equal variance was assumed and then the data was tested for unequal variance. There was a statistical difference between the two groups at the first, third and fourth set observation period. The p value at the first set period was 0.013 and 0.021. The p value at the second set period was 0.142 and 0.097. At the third set period the p values were 0.019 and 0.022 and the last set period the p values were 0.023 and 0.047. This is illustrated in Figure 4.2 with the significant p values asterisked.

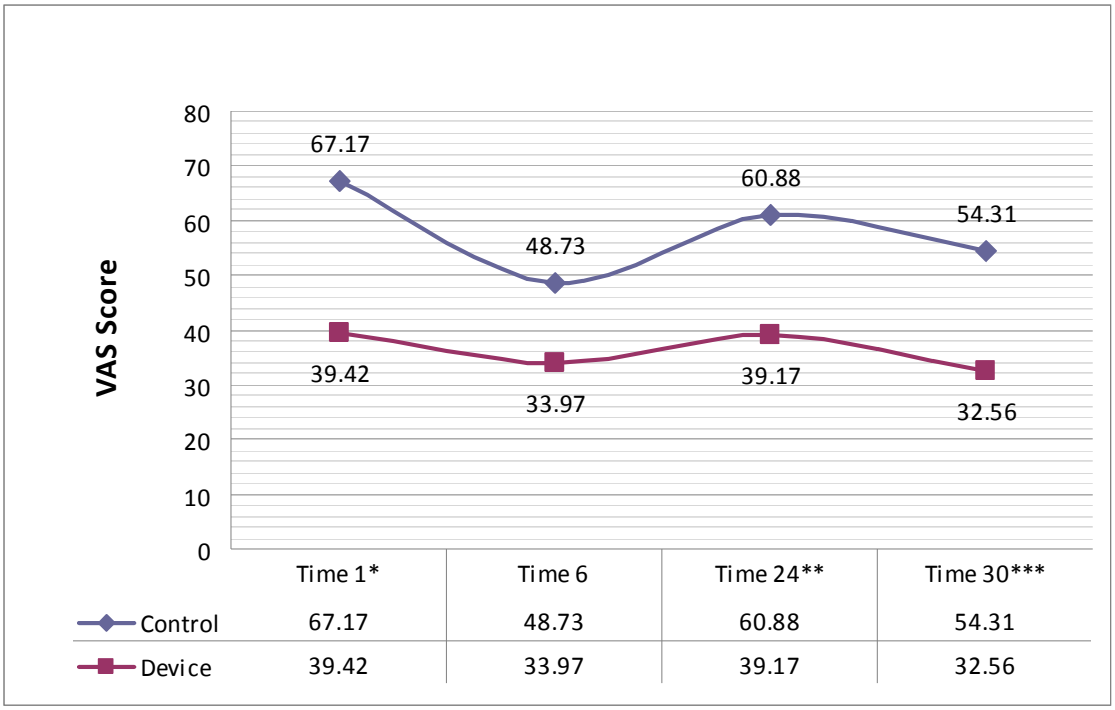

Figure 4.2: Dynamic VAS scores in the two groups
*p=0.013 **p=0.019 ***p=0.023

4.4.2 Static VAS scores between the control and device group

Analysis of the static VAS scores was performed. First, equal variance was assumed and then the data was tested for unequal variance. There was a statistical difference between the two groups at the first set observation period. The p value at the first set observation period was 0.038 and 0.048. The p value at the second set period was 0.887 and 0.596. At the third set period the p value was 0.405 and 0.921 and the last set period the p values were 0.339 and 0.231. These numbers are depicted in the Figure 4.2 below with the statistically significant p value asterisked.

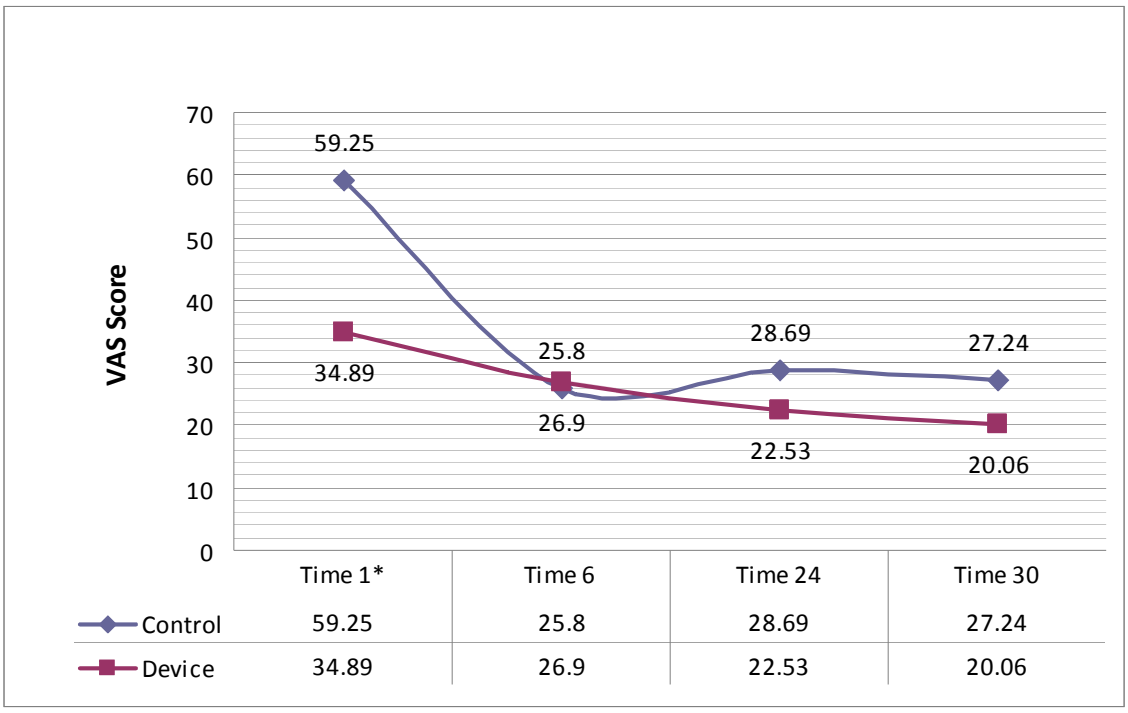

Figure 4.3: Static VAS scores of the control and device groups
*p=0.038

4.4.3 Worst VAS since the last time seen between the device and control groups

Analysis of the worst VAS scores since the last time observed was done. Equal variance was first assumed and then the data was tested for unequal variance. There was a statistical difference between the two groups at the first and second set periods. The p value at the first set period was 0.008 and 0.010. The p value at the second set period was 0.023 and 0.020. At the third set period the p value was 0.704 and 0.583 and the last set period the p values were 0.711 and 0.693 respectively. This data is illustrated in Figure 4.4 with the significant p values asterisked.

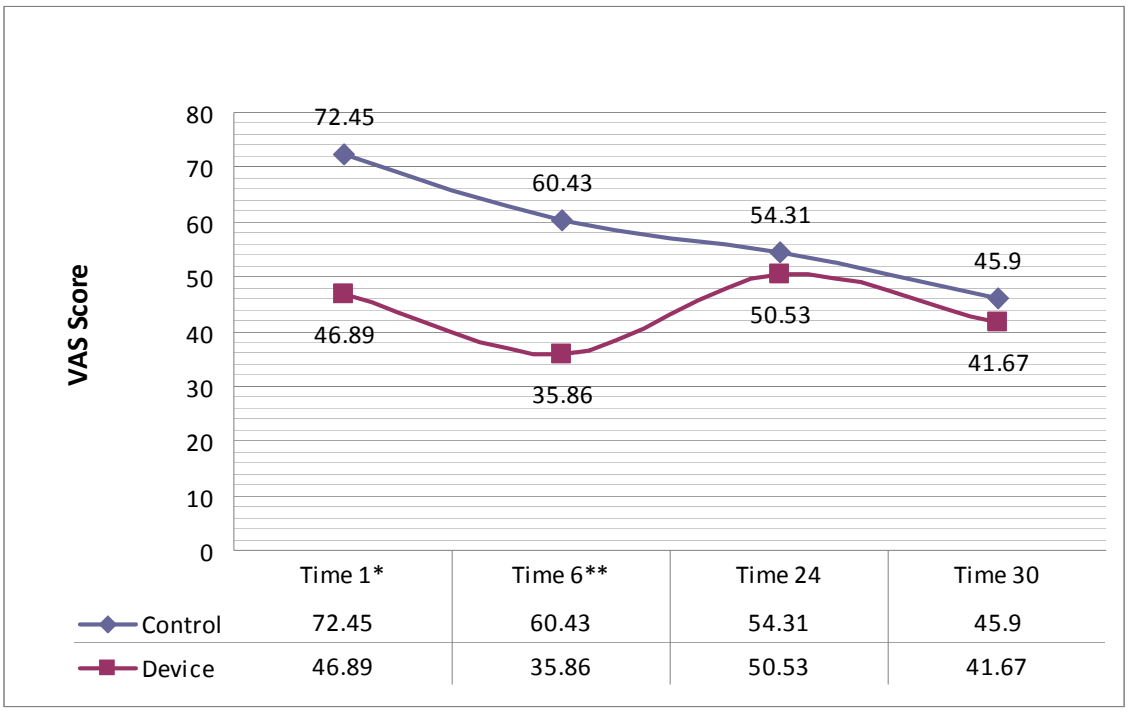

Figure 4.4: VAS for the worst pain experienced since last seen between the device and control groups
* p= 0.008 **p=0.023

4.4.4 Opioid adverse effects between the control and device groups

This categorical data between the device and control groups was analysed with the Fischer's exact test.

4.4.4.1 Nausea and vomiting between the control and device groups

The incidence of nausea and vomiting between the two groups showed no statistical difference. The Fischer's exact test at the first set period was 0.673, the second set observation period 0.738, third set observation period 0.734 and fourth set observation period was 0.190.

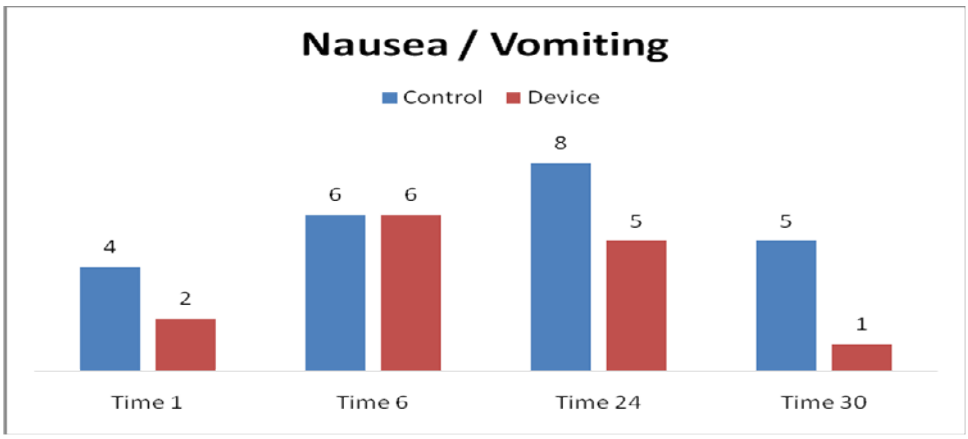

Figure 4.5: Comparison of the two groups: incidence of nausea and vomiting

4.4.4.2 Itchiness between the control and device groups

There was no statistical difference between the two groups. The Fischer's exact test at the first set period was 0.310, second period 0.211, third period 1.000 and fourth set period was 1.000.

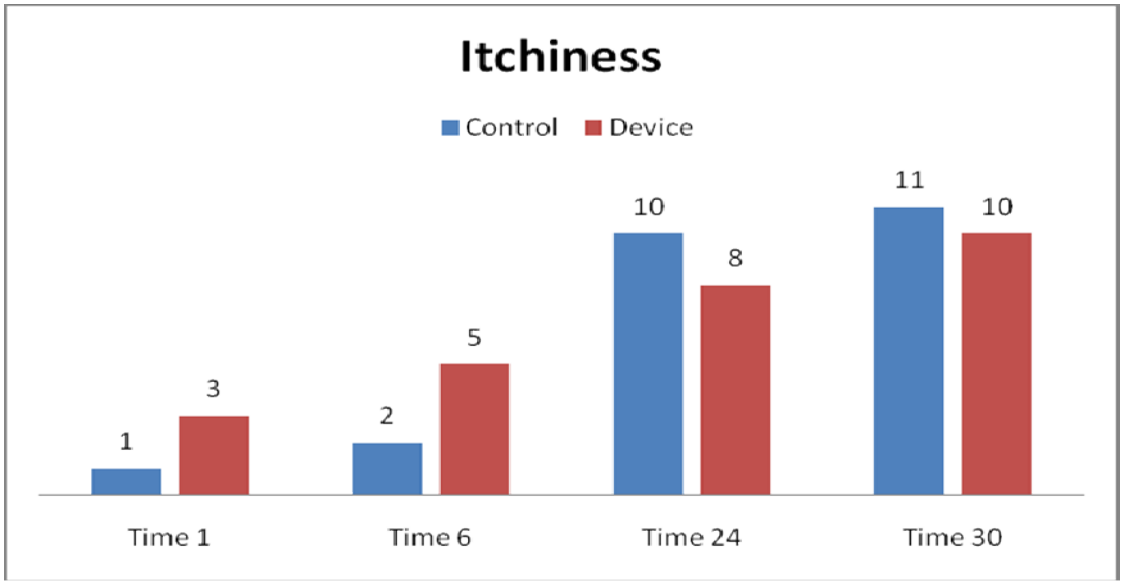

Figure 4.6: Comparison of the two groups: incidence of itchiness

4.5 Conclusion

Chapter four gives a comprehensive analysis of the data obtained in this clinical study. The analysis was performed in a manner to answer the primary and secondary objectives of this study.

In summary, the two groups had a similar demographic profile to ensure validity of the study findings. Statistical differences were seen between the control and device groups' VAS scores in the first period and worst VAS scores in the second set observation period. There were statistically lower dynamic VAS scores in the device group compared to the control group in the third and fourth set periods.

There was no statistical difference between the two groups' opioid consumption and adverse side effects.

Chapter 5 will follow with the discussion and recommendations of the findings of this chapter.

5 Chapter 5: Discussion and Recommendations

5.1 Introduction

This chapter has a detailed discussion on the results and findings of the clinical study. From this is a discussion on the implications of daily practise and further research. Following this is the conclusion regarding the hypothesis of decreased pain intensity and/or opioid consumption in patients with bupivacaine infusions into the incisional site post total abdominal hysterectomy.

5.2 Discussion of statistical results

The two clinical study groups had a similar demographic profile to ensure validity of the measured study findings.

Statistical differences were seen between the two groups' dynamic VAS scores in the first (1 hour post operation), third (24 hours post operation) and fourth (30 hours post operation) observation periods. There was also a statistical difference in the static VAS score in the first observation period. Thirdly there was a statistical difference in the worst VAS scores in the first and second observation periods.

The mean dynamic VAS score of the device group in the first, third and fourth periods were 39.42, 39.17 and 35.36 respectively. This is in comparison with the mean dynamic

VAS scores of the control group in the first, third and fourth periods which were 67.17, 60.89 and 54.31 respectively. The p values were 0.013, 0.019 and 0.023 respectively.
The mean worst VAS score of the control group in the first and second observation period was 72.45 and 60.43 respectively, this is compared with the mean worst VAS score of the device group of 46.89 and 35.86 respectively. The p values were 0.008 and 0.023 respectively making these results statistically significant.
The mean static VAS score of the device group in the first period was 34.89 compared to the mean static VAS score of the control group as 59.25. This resulted in a statistically significant p value of 0.038.
Movement of a patient elicits somatic pain more than visceral pain. The decrease in dynamic VAS scores could reflect that the bupivacaine infusion decreased the somatic pain from the incisional site. In contrast, the static VAS scores were not different from 6 hours post operation as the bupivacaine infusion did not provide any pain relief from the visceral component originating mainly from the peritoneum.

There was no statistical difference between the two groups' opioid consumption and adverse side effects namely nausea, vomiting and itchiness.

The mean opioid consumption in the device group in the first, second, third and fourth periods was the following 3.35mg, 10.83mg, 25.11mg and 5.78mg. This is compared to the mean opioid consumption in the control group of the respective observation periods as been 4.89mg, 8.22mg, 24.67mg and 8.33mg.

The reason for the difference between the two trial groups in their VAS scores but similar opioid consumption could be speculated that the bupivacaine infusion helped relieve somatic pain from the incisional site but not the visceral component of pain post operation which needed morphine boluses to help ease. In addition, the morphine PCA is still a relatively novel device in the government setting, and nurses might be overenthusiastic in their instruction to the patients to "push the button". Finally, communication between the researchers and patients of different home languages could have caused differences in understanding of when to push the button for pain relief.

The documented occurrence of the opioid adverse effects namely itchiness, nausea and vomiting, between the two groups was also not statistically different either. However, the sample size is small and so the number of participants (that is the counts) were used and not the percentages.

The visual analogue scale score is an unidimensional instrument using the patients' self-reported assessment of the intensity of pain. This pain measurement tool indicated that patients in the device group reported less intensity of pain in the above mentioned set periods than the participants in the control group. The VAS score did not correlate with the participant's opioid consumption. There was no significant difference between the groups' morphine consumption and the incidence of morphine's adverse effects.

5.3 Discussion of limitations and logistical issues

The study population was not representative of the national group of women undergoing total abdominal hysterectomy in South Africa. However the study sample addressed a clinical setting that is relevant locally, that is the Rahima Moosa Mother and Child Hospital. This is a public hospital in central Johannesburg surrounds.

The clinical setting of the study resulted in single blinded conditions whilst evaluations were performed. That is the patients did not know whether they had the bupivacaine infusion in their incisional site or not (as all participants had the same external apparatus), however the researchers and surgeon did. Scientific methods required placing a subfascial catheter in all participants, evident ethical reasons restrained our application of this method. Bias may have occurred due to the design of the trial, not been double-blinded.

The application of the subfascial catheter prolonged the anaesthetic time minimally and the surgeons found the technique of inserting the catheters simple. The time required in insertion of these catheters was less than five minutes. There was one complication with the subfascial catheter and this was that on insertion of the first catheter the surgeon transacted it with the scalpel. It was noted immediately and the catheter parts were removed and replaced with a complete catheter with no further problems.

The participants were strongly positive concerning their pain relief management plan especially the high level of satisfaction obtained with the self administration of opioid boluses for their pain relief. Three participants complained of only back pain (two device

participants, one control participant). A participant in the device group commented: “I don’t know what it is but it is fantastic”.

The device group reported no adverse effects or hindrances regarding the elastomeric pump. The nursing staff in the recovery holding area and wards required only basic education and training in the use of these pumps. They were highly satisfied with the use of these elastomeric pumps and required minimal re-education. The nurses on the whole felt that the standard of patient care of the participants was increased and felt that there was no extra nursing burden concerning the care of the elastomeric pumps and its application. The application of these elastomeric pumps did not require similar extensive training or more nursing requirements for patient care such as in situations when neuroaxial analgesia is been performed.

Technical problems of running an intravenous line for adequate PCA management occurred. These were rectified easily by either of the two researchers or nursing staff but did require a delay in administered morphine boluses. These were: high pressure alarms - the PCA clamp had been mistakenly clamped (two incidents), leaking of the intravenous lines - managed successfully with tightening of the intravenous connections (two incidents), dislodgement and blocking of the intravenous access port which required resiting of the intravenous line. In total eight intravenous lines needed to be resited due to migration of catheters into subcutaneous tissues.

Participants were mobilised as soon as possible and all participants were mobilised twenty-four hours post operation. The participants found the intravenous line administration set and the PCA pump itself as bulky equipment and cumbersome. Some participants commented that this was a hindrance to mobilisation.

The intravenous fluid administration was continued to prevent the line becoming blocked. The intravenous fluid was not administered at a strict flow rate, this could have resulted in excess fluid given and three participants (2 controls) complained of excessive urinary micturition. The routine management plan for these patients post total abdominal hysterectomy in this hospital was that the intravenous line was removed twenty-four hours post operation. Due to the circumstances of the study the intravenous line remained so the PCA pump could be continued. Four participants were unhappy or complained of pain due to the intravenous access.

The incidence of adverse effects of opioids was overall low but two participants in the control group complained of itchiness severe enough to be treated with a promethazine injection.

Generally the surgical teams were happy with the patient outcomes regarding postoperative pain. A feedback questionnaire (appendix G) was distributed after the completion of the clinical study. The surgical teams consisted of consultants, registrars and interns. They all thought that the PCA pumps benefited the patients with the reasons been patients had less perceived pain, more satisfaction and better quality of analgesia. The doctors noted that

there had been some problems with the intravenous lines required for the management of the PCA pumps as mentioned earlier.

The self application of the PCA pump required patient understanding which is hampered by patients with language barriers or cultural differences. Constant application of analgesia such as an elastomeric pump in these instances could provide better pain analgesia.

5.4 Implications in daily practice

The continuous bupivacaine infusion in the incisional site increases the options for postoperative pain relief. From this study it is noted that participants with the bupivacaine infusion had decreased pain intensities in the first hour post operation. The participants also had a decreased level of dynamic pain intensity in three of the four time periods and lastly decreased worst pain intensity up to six hours post operation. This pain relief option could provide better pain analgesia but not reduce patients' opioid consumption. Faster recovery and earlier discharge from hospital care was not investigated. Pain relief devices that do not employ intravenous access will possibly provide better patient satisfaction as are less cumbersome. However the pain relief of these elastomeric pumps in the incisional wound may only relieve the somatic component of the pain post operation and not the visceral component.

5.5 Implications in future research

Pfannenstiel incisions cover about 2-3 dermatomes, whereas midline incisions cover several dermatomes. It can be postulated that the incisional bupivacaine infusion will benefit patients more who undergo midline incisions. Studies in South Africa have not been carried out in this group of patients.

The VAS score does not correlate with the participant's opioid consumption. This should be further investigated and evaluated. This might be due to the VAS score reflecting somatic and visceral pain components rather than just the somatic component which the bupivacaine infusion was most likely providing analgesia for in the incisional site. Limitations of this pain score for post operation pain should be further elucidated and investigated.

5.6 Conclusion and summary

This chapter reviewed and discussed the statistical analysis of the data collected. It also discussed the logistical and practical issues of the elastomeric pump and PCA pumps in postoperative pain management.

Statistical analysis of the pain intensity scores and opioid consumption in participants who had a bupivacaine infusion in the incisional site shows that these participants had less pain intensity scores of varying types at different observation periods but no difference in opioid consumption between the control group and device group. The study does therefore refute the hypothesis that there is no decreased pain intensity in patients with bupivacaine

infusions into the incisional site post total abdominal hysterectomy, however does support the hypothesis that there is no difference in opioid requirements compared to the control group. Because the data collected was reliable and valid, the findings and hence implications, for the use of a bupivacaine infusion in the incisional site post total abdominal hysterectomy in South Africa is clinically important and relevant.

6 Appendix A: Ethics clearance certificate

Please note that the title was changed and approved by the Postgraduate Committee in September 2009.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Russell

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER MO70701**
PROJECT	Does the use of local anaesthetic infusion into the surgical wound reduce the opioid requirement post total abdominal hysterectomy
INVESTIGATORS	Dr S Russell
DEPARTMENT	Anaesthesia
DATE CONSIDERED	07.07.27
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.12.13 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr E Frohlich

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

7 Appendix B: Approval letter by hospital management

The Management
Coronation Hospital
Johannesburg
14 February 2008

Dear Dr Russell and Dr du Plessis

Approval for the commencement of your clinical study

This letter serves to confirm that together with Dr Murphy we have discussed your intention to implement a clinical study in this hospital.
I am aware of your study protocol and that this study is titled: *Does the use of local anaesthetic infusion into the surgical wound reduce the opioid requirement post total abdominal hysterectomy.*

I give permission for it to be undertaken.

Yours sincerely

Dr Masilela 15/2/08

CC: Matron Jacobs

Appendix C: Patient information Pamphlet

Information leaflet and informed consent

STUDY NUMBER:

STUDY TITLE: Does a bupivacaine infusion into the incisional site reduce opioid requirement post total abdominal hysterectomy.

INVESTIGATOR: DR SAMANTHA RUSSELL

INSTITUTION: CORONATION HOSPITAL – *now know as the Rahima Moosa Mother and Child Hospital*

DATE AND TIME OF FIRST INFORMED CONSENT DISCUSSION

Dd	Mm	yyyy

INTRODUCTION

Good day, my name is Dr Russell; I am a registrar in Anaesthesiology at Helen Joseph and Coronation Hospital. I would like to invite you to be part of a research study entitled; Does a bupivacaine infusion into the incisional site reduce opioid requirement post total abdominal hysterectomy.

1. Before agreeing to participate, it is important that you read and understand the reason for the study, the study procedures, as well as the alternative procedures that are available to you. You have the right to withdraw from the study at any time. This information leaflet is to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study

2. If you have any questions, do not hesitate to ask me.

3. You should not agree to take part unless you are satisfied about all the procedures involved.

4. Please be completely truthful with me regarding your health history.

5. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

PURPOSE OF THE STUDY

You have been booked for an operation to remove your uterus/womb.

I would like you to consider taking part in this study where we use a new pain control device. We want to see if this method will provide better pain relief for you after the operation and whether you will need less morphine to control the pain after the operation.

You will be randomly allocated to one or another group (i.e. like spinning a coin). This procedure helps to ensure that the information gathered during the study is accurate.
The study group will have a tube in the wound and the other group will not. Both groups will have the best treatment available for us at the moment, to control the pain. If you want to stop the trial at any stage you can do so without any harm to yourself

LENGTH OF STUDY AND NUMBER OF PARTICIPANTS:

The study will be performed in Coronation Hospital, Johannesburg. Approximately 40 patients will be involved in this study. The total amount of your time required for this study will be a maximum of 3 days. I will visit you about 6 times during the study.

PROCEDURES:

If you agree to take part in this study, you will first be asked questions and examined to see if you qualify for this study.
At the end of the operation while you are still asleep we will attach a patient controlled pain pump to your drip. Every time you have pain you press a button and a small amount of morphine goes into your bloodstream for pain relief. You can not give yourself too much morphine with this device and you should use it as much as you want.
If you are in the study group the surgeon will insert a tube in the wound site and connect it to another pump. This pump is filled with a pain-killer. You can move around with the pump with no added discomfort. A tiny tube connects to the pump. The flow of

medication into the wound is carefully controlled. There is no need to squeeze or adjust it. As the medicine is released, the pump will get smaller. .

At each visit I will ask you about your pain and whether you have any side effects such as nausea, vomiting and itching. You will also be asked if you are satisfied with the tube.

WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

The pump must not get wet, so while you are washing please keep the pump dry in a plastic bag. The catheter may fall out accidentally.

RISKS OF THE STUDY MEDICINE:

Some participants may experience adverse effects to the medication You need to call your doctor immediately if you experience any of the following:

Redness, warmth where the tube enters your skin

Ringing, buzzing in your ears

Numbness and/or tingling around your mouth, fingers or toes

These occurrences are very rare, but could happen if you are sensitive to the local anaesthetic, get too much of it, or if the catheter has moved out of its correct place.

UNFORSEEN RISKS:

This device has been used for more than ten years overseas (in Scandinavia, Canada and the USA), but this is the first time it has been used in South Africa in government hospitals.

We do not anticipate any side-effects other than those listed above, but should anything untoward occur, please let the ward sister know immediately, and she will contact me at once.

BENEFITS:

The potential benefit from your participation in this study may be:-

Less pain

Continuous pain relief

Faster return to normal activities

Quicker return to normal body function

Clear and groggy-free head

Greater mobility

More comfortable recovery

Less morphine side-effects such as nausea, vomiting, breathing problems, constipation, groggy, 'hangover' feeling

However you may not benefit from this study. Your participation in this study will contribute to medical knowledge that may help other patients that, like you, when they have an operation

ALTERNATIVE TREATMENT:

Alternative treatment is in the form of the usual postoperative pain relief given to patients who have the same operation at this hospital. If you decide not to take part in this study

you will still receive the usual care and treatment given in this hospital by your usual doctor.

BENEFITS AND RISKS OF STANDARD ALTERNATIVE TREATMENT:

The standard treatment is injection, tablets and suppositories.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS STUDY?

You should not participate in this study if you know that you are allergic to Local anaesthetic. (This is a very rare condition.) The catheter and the study medicine will be removed on day 2 and will not restrict your daily activities, however if you take a shower or bath before this time, please make sure that the device and the catheter stay dry.

INTERACTIONS

It is important that you let me know of any medicines (both prescription and over-the-counter medicines), alcohol or other substances that you are currently taking. During this study, you should not take any other pain medicine or alcohol. If you have to, please inform me immediately.

RIGHTS AS A PARTICIPANT IN THIS STUDY:

Voluntary: Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason.

Discontinuation of study treatment: You must inform me if you wish to stop using the pump before the three days are up. I will make sure this is done correctly.

Withdrawal: If you decide to withdraw we will continue to give you the best care possible

NEW FINDINGS

I will provide you with any additional information that becomes available during the study, which may affect your willingness to continue with the study.

FINANCIAL ARRANGEMENTS

There are no additional costs involved for you in this study; all the costs will be borne by the company that is providing the pain pump and the Department of Anaesthesiology, Helen Joseph/Coronation Hospital Complex.

ETHICAL APPROVAL

This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee.

The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

The tubes are supplied by SA Biomedical Services. I do not have any financial or personal interest with this organisation that may bias my actions.

SOURCE OF ADDITIONAL INFORMATION

For the duration of the study, you will be under the care of your gynaecologist, ward nursing staff and me with regards to your postoperative pain management. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact me.

Other doctors from this department who are working on this study are:

Dr E Frohlich; Departmental Head of Anaesthesiology and Pain Specialist

Dr P du Plessis: Consultant Anaesthesiologist

The 24-hour telephone number, which you can reach me is 079 5292505.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2229.

CONFIDENTIALITY

All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

This information will be reviewed by authorised researchers.

The information might also be inspected by the University of the Witwatersrand, Human Research Ethics Committee (HREC), as well as your personal doctor. Therefore, you hereby authorise me to release your medical records to me as well as University of the Witwatersrand, Human Research Ethics Committee (HREC) (if necessary).

These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study. Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but its information will not be disclosed to any third party without your written permission.

9 Appendix D: Consent Form

INFORMED CONSENT

I hereby confirm that I have been informed by the study doctor, Samantha Russell, about the nature, conduct, benefits and risks of this clinical study Does a bupivacaine infusion into the incisional site reduce opioid requirement post total abdominal hysterectomy.
I have also received, read and understood the above written information (Participant Information Leaflet) regarding the clinical study.
I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by me.
I may, at any stage, without prejudice withdraw my consent and participation in the study.
I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT

_____	_____	_____
Printed Name	Signature/Mark or thumbprint	Date and Time

I, Samantha Russell, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

_____	_____	_____
Printed Name	Signature	Date and Time

TRANSLATOR/OTHER PERSON EXPLAINING INFORMED CONSENT (if applicable):

_____	_____	_____
Printed Name	Signature	Date and Time

WITNESS (designation):

_____		
Printed Name	Signature	Date and Time

10 Appendix E: Data Collection Tool

Study number:
A: Age: Previous Caesarean sections:

B: 1 hour post operation
Are you experiencing pain now? YES □ NO □
On this scale, please indicate the worst pain you have had in the past 24 hours

0----------100
No pain Worst pain possible
On this scale, please indicate the pain you experience when you are in bed
0----------100
No pain Worst pain possible

On this scale, please indicate the pain you experience when you cough/move
0----------100
No pain Worst pain possible

Are you experiencing itchiness? YES □ NO □
Have you felt nauseous or vomited in the past 4 hours? YES □ NO □
Amount of IV morphine given:

Satisfaction with catheter? YES □ NO □
Any complications with catheter (dislodgement, signs of infection)
NO □ YES □ Please detail:
Nurses' satisfaction with catheter YES □ NO □
Comments

6 hours postoperative
Are you experiencing pain now? YES □ NO □

On this scale, please indicate the worst pain you have had in the past 24 hours

0----------100
No pain Worst pain possible
On this scale, please indicate the pain you experience when you are in bed
0----------100
No pain Worst pain possible

On this scale, please indicate the pain you experience when you move/cough
0----------100
No pain Worst pain possible

Are you experiencing itchiness? YES □ NO □
Have you felt nauseous or vomited in the past 6 hours? YES □ NO □
Amount of IV morphine given:

Satisfaction with catheter? YES □ NO □

Any complications with catheter (dislodgement, signs of infection)
NO □ YES □ Please detail:
Nurses' satisfaction with catheter YES □ NO □
Comments

24 hours postoperative
Are you experiencing pain now? YES □ NO □
On this scale, please indicate the worst pain you have had in the past 24 hours

0----------100
No pain Worst pain possible
On this scale, please indicate the pain you experience when you are in bed
0----------100
No pain Worst pain possible

On this scale, please indicate the pain you experience when you move/cough
0----------100
No pain Worst pain possible

Are you experiencing itchiness? YES □ NO □
Have you felt nauseous or vomited in the past 18 hours? YES □ NO □
Amount of IV morphine given:

Satisfaction with catheter? YES □ NO □
Any complications with catheter (dislodgement, signs of infection)
NO □ YES □ Please detail:
Nurses' satisfaction with catheter YES □ NO □
Comments

30 hours postoperative
Are you experiencing pain now? YES □ NO □
On this scale, please indicate the worst pain you have had in the past 24 hours

0----------100
No pain Worst pain possible
On this scale, please indicate the pain you experience when you are in bed
0----------100
No pain Worst pain possible

On this scale, please indicate the pain you experience when you get out of bed
0----------100
No pain Worst pain possible
Are you experiencing itchiness? YES □ NO □
Have you felt nauseous or vomited in the past 6 hours? YES □ NO □
Amount of IV morphine given:

Satisfaction with catheter? YES □ NO □
Any complications with catheter (dislodgement, signs of infection)
NO □ YES □ Please detail:
Nurses' satisfaction with catheter YES □ NO □
Comments

11 Appendix F: Statistical data and tables

```
+-------------------+
| Key               |
|-------------------|
|     frequency     |
| column percentage |
+-------------------+

Enumerating sample-space combinations:
stage 5:  enumerations = 1
stage 4:  enumerations = 2
stage 3:  enumerations = 2
stage 2:  enumerations = 2
stage 1:  enumerations = 0

           |         group
      race |   Control     Device |     Total
-----------+----------------------+----------
   african |        15         12 |        27
           |     68.18      66.67 |     67.50
-----------+----------------------+----------
  coloured |         6          4 |        10
           |     27.27      22.22 |     25.00
-----------+----------------------+----------
    indian |         1          0 |         1
           |      4.55       0.00 |      2.50
-----------+----------------------+----------
     malay |         0          1 |         1
           |      0.00       5.56 |      2.50
-----------+----------------------+----------
     white |         0          1 |         1
           |      0.00       5.56 |      2.50
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(4) =   3.3670   Pr = 0.498
           Fisher's exact =                 0.691

->  tab op group, col chi exact

Enumerating sample-space combinations:
stage 4:  enumerations = 1
stage 3:  enumerations = 2
stage 2:  enumerations = 2
stage 1:  enumerations = 0

           |         group
        op |   Control     Device |     Total
-----------+----------------------+----------
       TAH |        14         10 |        24
           |     63.64      55.56 |     60.00
-----------+----------------------+----------
 TAH & BSO |         7          7 |        14
```

```
           |     31.82      38.89 |     35.00
-----------+----------------------+----------
 TAH & USO |         0          1 |         1
           |      0.00       5.56 |      2.50
-----------+----------------------+----------
myomectomy |         1          0 |         1
           |      4.55       0.00 |      2.50
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(3) =   2.2896   Pr = 0.515
           Fisher's exact =                 0.721

->  tab itchiness1 group, col chi exact

           |         group
itchiness1 |   Control     Device |     Total
-----------+----------------------+----------
        no |        21         15 |        36
           |     95.45      83.33 |     90.00
-----------+----------------------+----------
       yes |         1          3 |         4
           |      4.55      16.67 |     10.00
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(1) =   1.6162   Pr = 0.204
           Fisher's exact =                 0.310
   1-sided Fisher's exact =                 0.230

->  tab n_v_1 group, col chi exact

           |         group
     n_v_1 |   Control     Device |     Total
-----------+----------------------+----------
        no |        18         16 |        34
           |     81.82      88.89 |     85.00
-----------+----------------------+----------
       yes |         4          2 |         6
           |     18.18      11.11 |     15.00
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(1) =   0.3882   Pr = 0.533
           Fisher's exact =                 0.673
   1-sided Fisher's exact =                 0.435

->  tab pain_now6 group, col chi exact

           |         group
 pain_now6 |   Control     Device |     Total
-----------+----------------------+----------
```

```
        no |        13         13 |        26
           |     59.09      72.22 |     65.00
-----------+----------------------+----------
       yes |         9          5 |        14
           |     40.91      27.78 |     35.00
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(1) =   0.7504   Pr = 0.386
           Fisher's exact =                 0.510
   1-sided Fisher's exact =                 0.298

->  tab itchiness6 group, col chi exact

           |         group
itchiness6 |   Control     Device |     Total
-----------+----------------------+----------
        no |        20         13 |        33
           |     90.91      72.22 |     82.50
-----------+----------------------+----------
       yes |         2          5 |         7
           |      9.09      27.78 |     17.50
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(1) =   2.3945   Pr = 0.122
           Fisher's exact =                 0.211
   1-sided Fisher's exact =                 0.130

tab n_v_6 group, col chi exact

           |         group
     n_v_6 |   Control     Device |     Total
-----------+----------------------+----------
        no |        16         12 |        28
           |     72.73      66.67 |     70.00
-----------+----------------------+----------
       yes |         6          6 |        12
           |     27.27      33.33 |     30.00
-----------+----------------------+----------
     Total |        22         18 |        40
           |    100.00     100.00 |    100.00

          Pearson chi2(1) =   0.1732   Pr = 0.677
           Fisher's exact =                 0.738
   1-sided Fisher's exact =                 0.471


->  tab itchiness24 group, col chi exact

itchiness2 |         group
         4 |   Control     Device |     Total
-----------+----------------------+----------
```

```
        no |        11          10 |        21
           |     52.38       55.56 |     53.85
-----------+----------------------+----------
       yes |        10           8 |        18
           |     47.62       44.44 |     46.15
-----------+----------------------+----------
     Total |        21          18 |        39
           |    100.00      100.00 |    100.00

          Pearson chi2(1) =   0.0393   Pr = 0.843
           Fisher's exact =                 1.000
   1-sided Fisher's exact =                 0.549

->  tab n_v_24 group, col chi exact

           |         group
    n_v_24 |   Control     Device |     Total
-----------+----------------------+----------
        no |        13          13 |        26
           |     61.90       72.22 |     66.67
-----------+----------------------+----------
       yes |         8           5 |        13
           |     38.10       27.78 |     33.33
-----------+----------------------+----------
     Total |        21          18 |        39
           |    100.00      100.00 |    100.00

          Pearson chi2(1) =   0.4643   Pr = 0.496
           Fisher's exact =                 0.734
   1-sided Fisher's exact =                 0.368



->  tab itchiness30 group, col chi exact

itchiness3 |         group
         0 |   Control     Device |     Total
-----------+----------------------+----------
        no |        10           8 |        18
           |     47.62       44.44 |     46.15
-----------+----------------------+----------
       yes |        11          10 |        21
           |     52.38       55.56 |     53.85
-----------+----------------------+----------
     Total |        21          18 |        39
           |    100.00      100.00 |    100.00

          Pearson chi2(1) =   0.0393   Pr = 0.843
           Fisher's exact =                 1.000
   1-sided Fisher's exact =                 0.549

->  tab n_v_30 group, col chi exact

           |         group
    n_v_30 |   Control     Device |     Total
```

```
-----------+----------------------+----------
        no |         16         17 |         33
           |      76.19      94.44 |      84.62
-----------+----------------------+----------
       yes |          5          1 |          6
           |      23.81       5.56 |      15.38
-----------+----------------------+----------
     Total |         21         18 |         39
           |     100.00     100.00 |     100.00

          Pearson chi2(1) =   2.4809   Pr = 0.115
           Fisher's exact =                 0.190
   1-sided Fisher's exact =                 0.129

 ->  ttest age, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      22    42.54545    2.083461    9.772299    38.21266
46.87825
  Device |      18    43.61111    1.730425    7.341573    39.96023
47.26199
---------+--------------------------------------------------------------------
combined |      40      43.025    1.371172    8.672052    40.25154
45.79846
---------+--------------------------------------------------------------------
    diff |           -1.065657    2.708354               -6.540855
4.409542
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =  -
0.3935
Ho: diff = 0                              Welch's degrees of freedom =
39.672

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.3480         Pr(|T| > |t|) = 0.6961          Pr(T > t) =
0.6520



->  ranksum age, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
```

```
     Control |       22       398.5         451
      Device |       18       421.5         369
-------------+--------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -7.87
                     ----------
adjusted variance       1345.13

Ho: age(group==Control) = age(group==Device)
             z =  -1.431
    Prob > |z| =   0.1523

->  ttest bmi, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      22    28.79091    1.564707    7.339126    25.53692
32.0449
  Device |      18    31.12222    1.237343      5.2496    28.51166
33.73279
---------+--------------------------------------------------------------------
combined |      40       29.84    1.029506    6.511166    27.75763
31.92237
---------+--------------------------------------------------------------------
    diff |           -2.331313    1.994824               -6.365443
1.702816
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =  -
1.1687
Ho: diff = 0                              Welch's degrees of freedom =
39.2384

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.1248         Pr(|T| > |t|) = 0.2496          Pr(T > t) =
0.8752

->  ranksum bmi, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22       386.5         451
      Device |       18       433.5         369
```

```
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -0.25
                     ----------
adjusted variance       1352.75


Ho: bmi(group==Control) = bmi(group==Device)
             z =  -1.754
    Prob > |z| =   0.0795

->  ttest pain_last1, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      22    72.45455    5.933242    27.82937    60.11569
84.7934
  Device |      18    46.88889    6.978557    29.60751    32.16542
61.61236
---------+--------------------------------------------------------------------
combined |      40       60.95    4.911845    31.06523    51.01486
70.88514
---------+--------------------------------------------------------------------
    diff |            25.56566    9.159892                 7.01253
44.11878
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
2.7910
Ho: diff = 0                             Welch's degrees of freedom =
37.3927

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9959         Pr(|T| > |t|) = 0.0082          Pr(T > t) =
0.0041

->  ttest static1, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
```

```
---------+--------------------------------------------------------------------
-----
 Control |      22       59.25    7.615897    35.72173    43.41187
75.08813
  Device |      18    34.88889    8.352875    35.43825    17.26586
52.51191
---------+--------------------------------------------------------------------
-----
combined |      40     48.2875    5.884679    37.21798    36.38461
60.19039
---------+--------------------------------------------------------------------
-----
    diff |            24.36111    11.30365                1.489048
47.23317
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
2.1552
Ho: diff = 0                              Welch's degrees of freedom =
38.5633

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9813         Pr(|T| > |t|) = 0.0375          Pr(T > t) =
0.0187

->  ranksum static1, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22       523.5         451
      Device |       18       296.5         369
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -4.95
                     ----------
adjusted variance       1348.05

Ho: static1(group==Control) = static1(group==Device)
             z =   1.975
    Prob > |z| =   0.0483

->  ttest dynamic1, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
-----
```

```
 Control |      21    67.16667    6.216849    28.48918    54.19855
80.13479
  Device |      18    39.41667    8.558645    36.31126     21.3595
57.47383
---------+--------------------------------------------------------------
-----
combined |      39    54.35897    5.577994    34.83456    43.06692
65.65103
---------+--------------------------------------------------------------
-----
    diff |               27.75    10.57826                6.246406
49.25359
------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =
2.6233
Ho: diff = 0                              Welch's degrees of freedom =
33.7452

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9935         Pr(|T| > |t|) = 0.0130          Pr(T > t) =
0.0065

->  ranksum dynamic1, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21         502         420
      Device |       18         278         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -4.08
                     ----------
adjusted variance       1255.92

Ho: dynamic1(group==Control) = dynamic1(group==Device)
             z =   2.314
    Prob > |z| =   0.0207

->  ttest morph_given1, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------
-----
 Control |      22    4.890909    .7677174    3.600914    3.294353
6.487465
```

```
  Device |      17    3.352941    .6470588    2.667892    1.981238
4.724645
---------+--------------------------------------------------------------
-----
combined |      39    4.220513    .5252489    3.280178    3.157202
5.283824
---------+--------------------------------------------------------------
-----
    diff |            1.537968    1.004029               -.4930289
3.568965
------------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =
1.5318
Ho: diff = 0                               Welch's degrees of freedom =
38.9068

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9332         Pr(|T| > |t|) = 0.1337          Pr(T > t) =
0.0668

->  ranksum morph_given1, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22         491         440
      Device |       17         289         340
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1246.67
adjustment for ties      -21.83
                     ----------
adjusted variance       1224.84

Ho: morph~n1(group==Control) = morph~n1(group==Device)
             z =   1.457
    Prob > |z| =   0.1451

->  ttest morph_att1, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------
-----
 Control |      22    7.818182    1.897408    8.899633    3.872306
11.76406
  Device |      17    5.470588    2.255903    9.301328    .6882866
10.25289
```

```
---------+--------------------------------------------------------------------
-----
combined |      39    6.794872    1.446378    9.032629    3.866832
9.722912
---------+--------------------------------------------------------------------
-----
    diff |            2.347594    2.947755               -3.632433
8.32762
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
0.7964
Ho: diff = 0                               Welch's degrees of freedom =
35.7071

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.7845         Pr(|T| > |t|) = 0.4311          Pr(T > t) =
0.2155

->  ranksum morph_att1, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22       489.5         440
      Device |       17       290.5         340
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1246.67
adjustment for ties      -28.39
                     ----------
adjusted variance       1218.28

Ho: morph~t1(group==Control) = morph~t1(group==Device)
             z =   1.418
    Prob > |z| =   0.1561

->  ttest pain_last6, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
-----
 Control |      22    60.43182    6.740979    31.61799    46.41319
74.45045
  Device |      18    35.86111    7.830601    33.22243    19.33999
52.38223
---------+--------------------------------------------------------------------
-----
```

```
combined |      40      49.375    5.414479    34.24417    38.42318
60.32682
---------+--------------------------------------------------------------
-----
    diff |            24.57071    10.33243                3.646862
45.49455
------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =
2.3780
Ho: diff = 0                              Welch's degrees of freedom =
37.6203

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9887         Pr(|T| > |t|) = 0.0226          Pr(T > t) =
0.0113

->  ranksum pain_last6, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22       536.5         451
      Device |       18       283.5         369
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -0.76
                       ----------
adjusted variance       1352.24


Ho: pain_l~6(group==Control) = pain_l~6(group==Device)
             z =   2.325
    Prob > |z| =   0.0201

->  ttest static6, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------
-----
 Control |      22    25.79545    3.946155    18.50911    17.58898
34.00193
  Device |      18    26.88889    6.487363    27.52355    13.20175
40.57603
---------+--------------------------------------------------------------
-----
```

```
combined |      40     26.2875    3.588125     22.6933    19.02983
33.54517
---------+--------------------------------------------------------------
-----
    diff |           -1.093434    7.593288               -16.60017
14.4133
------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =  -
0.1440
Ho: diff = 0                              Welch's degrees of freedom =
30.0381

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.4432         Pr(|T| > |t|) = 0.8865          Pr(T > t) =
0.5568

->  ranksum static6, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22       470.5         451
      Device |       18       349.5         369
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -1.27
                     ----------
adjusted variance       1351.73
Ho: static6(group==Control) = static6(group==Device)
             z =   0.530
    Prob > |z| =   0.5958

->  ttest dynamic6, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------
-----
 Control |      22    48.72727    6.491147    30.44618    35.22819
62.22635
  Device |      18    33.97222    7.396174    31.37931    18.36766
49.57678
---------+--------------------------------------------------------------
-----
combined |      40     42.0875    4.958866    31.36262    32.05725
52.11775
```

```
---------+--------------------------------------------------------------
-----
    diff |            14.75505    9.840649               -5.167023
34.67712
------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =
1.4994
Ho: diff = 0                              Welch's degrees of freedom =
37.9581

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9290         Pr(|T| > |t|) = 0.1420          Pr(T > t) =
0.0710

->  ranksum dynamic6, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22         512         451
      Device |       18         308         369
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -1.78
                     ----------
adjusted variance       1351.22
Ho: dynamic6(group==Control) = dynamic6(group==Device)
              z =   1.659
    Prob > |z| =   0.0970

->  ttest morph_given6, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------
-----
 Control |      22    8.227273    1.343466    6.301412    5.433383
11.02116
  Device |      18    10.83333    2.088327    8.860023    6.427348
15.23932
---------+--------------------------------------------------------------
-----
combined |      40         9.4    1.197112      7.5712    6.978613
11.82139
---------+--------------------------------------------------------------
-----
```

```
    diff |           -2.606061    2.483145               -7.668676
2.456555
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =  -
1.0495
Ho: diff = 0                              Welch's degrees of freedom =
31.2732

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.1510         Pr(|T| > |t|) = 0.3020          Pr(T > t) =
0.8490

->  ranksum morph_given6, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22         418         451
      Device |       18         402         369
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -5.97
                     ----------
adjusted variance       1347.03

Ho: morph_~6(group==Control) = morph_~6(group==Device)
             z =  -0.899
    Prob > |z| =   0.3686

->  ttest morphi_att6, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      22    16.59091    4.756704    22.31092    6.698802
26.48302
  Device |      18    33.55556    13.48183    57.19854     5.11139
61.99972
---------+--------------------------------------------------------------------
combined |      40      24.225    6.646812    42.03813    10.78055
37.66945
---------+--------------------------------------------------------------------
    diff |           -16.96465    14.29636               -46.63556
12.70627
```

```
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =  -
1.1866
Ho: diff = 0                              Welch's degrees of freedom =
21.7212

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.1241         Pr(|T| > |t|) = 0.2482          Pr(T > t) =
0.8759

->  ranksum morphi_att6, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       22         425         451
      Device |       18         395         369
-------------+---------------------------------
    combined |       40         820         820

unadjusted variance     1353.00
adjustment for ties       -3.55
                     ----------
adjusted variance       1349.45

Ho: morphi~6(group==Control) = morphi~6(group==Device)
             z =  -0.708
    Prob > |z| =   0.4791

->  ttest pain_last24, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    54.30952    6.266167    28.71519    41.23853
67.38052
  Device |      18    50.52778    7.651036     32.4606     34.3855
66.67005
---------+--------------------------------------------------------------------
combined |      39     52.5641    4.827845    30.14988    42.79064
62.33756
---------+--------------------------------------------------------------------
    diff |            3.781746     9.88955               -16.27143
23.83492
------------------------------------------------------------------------------
```

```
    diff = mean(Control) - mean(Device)                           t =
0.3824
Ho: diff = 0                             Welch's degrees of freedom =
36.1957

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.6478         Pr(|T| > |t|) = 0.7044          Pr(T > t) =
0.3522

->  ranksum pain_last24, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21       439.5         420
      Device |       18       340.5         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -0.77
                     ----------
adjusted variance       1259.23

Ho: pain_l~4(group==Control) = pain_l~4(group==Device)
             z =   0.550
    Prob > |z| =   0.5827

->  ttest static24, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    28.69048    6.232545    28.56111    15.68962
41.69134
  Device |      18    22.52778    3.823618    16.22224    14.46065
30.59491
---------+--------------------------------------------------------------------
combined |      39    25.84615    3.778319    23.59559    18.19735
33.49496
---------+--------------------------------------------------------------------
    diff |            6.162698    7.311954               -8.700151
21.02555
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
0.8428
```

```
Ho: diff = 0                              Welch's degrees of freedom =
33.8041

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.7974         Pr(|T| > |t|) = 0.4053          Pr(T > t) =
0.2026

->  ranksum static24, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21       423.5         420
      Device |       18       356.5         360
-------------+---------------------------------
    combined |       39         780         780


unadjusted variance     1260.00
adjustment for ties       -0.89
                     ----------
adjusted variance       1259.11

Ho: static24(group==Control) = static24(group==Device)
             z =   0.099
    Prob > |z| =   0.9214

->  ttest dynamic24, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
-----
 Control |      21    60.88095    5.879029     26.9411    48.61751
73.14439
  Device |      18    39.16667    6.638297    28.16391    25.16108
53.17225
---------+--------------------------------------------------------------------
-----
combined |      39    50.85897     4.68804     29.2768    41.36853
60.34941
---------+--------------------------------------------------------------------
-----
    diff |            21.71429    8.867354                3.755475
39.6731
------------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =
2.4488
```

```
Ho: diff = 0                              Welch's degrees of freedom =
37.5046

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9904         Pr(|T| > |t|) = 0.0191          Pr(T > t) =
0.0096

->  ranksum dynamic24, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21       501.5         420
      Device |       18       278.5         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -0.77
                     ----------
adjusted variance       1259.23

Ho: dynam~24(group==Control) = dynam~24(group==Device)
             z =   2.297
    Prob > |z| =   0.0216

->  ttest morph_given24, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    24.66667    2.117201    9.702233    20.25026
29.08307
  Device |      18    25.11111    3.938986     16.7117    16.80058
33.42165
---------+--------------------------------------------------------------------
combined |      39    24.87179    2.115485     13.2112    20.58922
29.15437
---------+--------------------------------------------------------------------
    diff |           -.4444444    4.471929               -9.613176
8.724288
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =  -
0.0994
Ho: diff = 0                              Welch's degrees of freedom =
27.4419
```

```
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.4608         Pr(|T| > |t|) = 0.9216          Pr(T > t) =
0.5392

->  ranksum morph_given24, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21       441.5         420
      Device |       18       338.5         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -3.06
                     ----------
adjusted variance       1256.94

Ho: morp~n24(group==Control) = morp~n24(group==Device)
             z =   0.606
    Prob > |z| =   0.5442

->  ttest morph_att24, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
-----
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
-----
 Control |      21    36.28571     4.75051    21.76957    26.37632
46.1951
  Device |      18    49.66667    10.42809    44.24265    27.66532
71.66802
---------+--------------------------------------------------------------------
-----
combined |      39    42.46154    5.479054    34.21668    31.36977
53.5533
---------+--------------------------------------------------------------------
-----
    diff |           -13.38095    11.45916               -36.99556
10.23365
------------------------------------------------------------------------------
-----
    diff = mean(Control) - mean(Device)                           t =  -
1.1677
Ho: diff = 0                             Welch's degrees of freedom =
24.7107
```

```
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.1270         Pr(|T| > |t|) = 0.2541          Pr(T > t) =
0.8730

->  ranksum morph_att24, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21         405         420
      Device |       18         375         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -0.89
                     ----------
adjusted variance       1259.11

Ho: morp~t24(group==Control) = morp~t24(group==Device)
             z =  -0.423
    Prob > |z| =   0.6725

->  ttest pain_last30, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    45.90476    7.621134    34.92443    30.00735
61.80217
  Device |      18    41.66667    8.400319    35.63954    23.94354
59.38979
---------+--------------------------------------------------------------------
combined |      39    43.94872    5.581043     34.8536    32.65049
55.24695
---------+--------------------------------------------------------------------
    diff |            4.238095    11.34227               -18.72632
27.20251
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
0.3737
Ho: diff = 0                             Welch's degrees of freedom =
37.8396

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
```

```
 Pr(T < t) = 0.6446         Pr(|T| > |t|) = 0.7107          Pr(T > t) =
0.3554

->  ranksum pain_last30, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21         434         420
      Device |       18         346         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -1.28
                     ----------
adjusted variance       1258.72


Ho: pain_l~0(group==Control) = pain_l~0(group==Device)
             z =   0.395
    Prob > |z| =   0.6931

->  ttest static30, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21     27.2381    5.026077    23.03238    16.75388
37.72231
  Device |      18    20.05556    5.459131    23.16113    8.537797
31.57331
---------+--------------------------------------------------------------------
combined |      39    23.92308    3.694588    23.07269    16.44377
31.40238
---------+--------------------------------------------------------------------
    diff |             7.18254    7.420482               -7.839113
22.20419
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
0.9679
Ho: diff = 0                             Welch's degrees of freedom =
38.0253

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
```

```
 Pr(T < t) = 0.8304         Pr(|T| > |t|) = 0.3392          Pr(T > t) =
0.1696

->  ranksum static30, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21       462.5         420
      Device |       18       317.5         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -0.89
                     ----------
adjusted variance       1259.11

Ho: static30(group==Control) = static30(group==Device)
             z =   1.198
    Prob > |z| =   0.2310

->  ttest dynamic30, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    54.30952    6.825153    31.27678     40.0725
68.54654
  Device |      18    32.55556    6.193488    26.27674    19.48844
45.62267
---------+--------------------------------------------------------------------
combined |      39    44.26923    4.921065    30.73204    34.30705
54.23141
---------+--------------------------------------------------------------------
    diff |            21.75397    9.216399                3.11169
40.39625
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
2.3604
Ho: diff = 0                             Welch's degrees of freedom =
38.977

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9883         Pr(|T| > |t|) = 0.0234          Pr(T > t) =
0.0117
```

```
->  ranksum dynamic30, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21       490.5         420
      Device |       18       289.5         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -0.64
                     ----------
adjusted variance       1259.36

Ho: dynam~30(group==Control) = dynam~30(group==Device)
             z =   1.987
    Prob > |z| =   0.0470

->  ttest morph_given30, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    8.333333    1.033564    4.736384    6.177357
10.48931
  Device |      18    5.777778    1.068123    4.531661    3.524236
8.03132
---------+--------------------------------------------------------------------
combined |      39    7.153846     .762249    4.760244    5.610754
8.696939
---------+--------------------------------------------------------------------
    diff |            2.555556    1.486318               -.4519492
5.56306
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =
1.7194
Ho: diff = 0                              Welch's degrees of freedom =
38.5416
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.9532         Pr(|T| > |t|) = 0.0936          Pr(T > t) =
0.0468

->  ranksum morph_given30, by(group)
```

```
Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
-------------+---------------------------------
     Control |       21         480         420
      Device |       18         300         360
-------------+---------------------------------
    combined |       39         780         780
unadjusted variance     1260.00
adjustment for ties       -7.14
                     ----------
adjusted variance       1252.86

Ho: morp~n30(group==Control) = morp~n30(group==Device)
             z =   1.695
    Prob > |z| =   0.0901

->  ttest morph_att30, by( group) unequal welch

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf.
Interval]
---------+--------------------------------------------------------------------
 Control |      21    12.57143    2.094859    9.599851    8.201629
16.94123
  Device |      18    14.72222    5.894389    25.00778    2.286148
27.1583
---------+--------------------------------------------------------------------
combined |      39     13.5641    2.906504    18.15111    7.680193
19.44801
---------+--------------------------------------------------------------------
    diff |           -2.150794    6.255579               -15.13184
10.83025
------------------------------------------------------------------------------
    diff = mean(Control) - mean(Device)                           t =  -
0.3438
Ho: diff = 0                              Welch's degrees of freedom =
21.7753

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff >
0
 Pr(T < t) = 0.3671         Pr(|T| > |t|) = 0.7343          Pr(T > t) =
0.6329

->  ranksum morph_att30, by(group)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       group |      obs    rank sum    expected
```

```
-------------+---------------------------------
     Control |       21       455.5         420
      Device |       18       324.5         360
-------------+---------------------------------
    combined |       39         780         780

unadjusted variance     1260.00
adjustment for ties       -4.21
                        ----------
adjusted variance       1255.79

Ho: morp~t30(group==Control) = morp~t30(group==Device)
             z =   1.002
    Prob > |z| =   0.3165
```

12 Appendix I: Feedback Form

Questionnaire on the Morphine PCA pumps and ON-Q pain buster catheters

Thank you for taking the time to complete this feedback form.

Did you find that the PCA pumps benefited the patients?

In what why?

Any problems with the PCA pumps?

Were you aware if the wound catheters were used on the trial patients?

If so did you think that the catheters benefited the patients' analgesia?

Any comments?

These comments will be reported in the discussion of the research report

Many thanks for your time, it is very much appreciated

Samantha Russell

26 August 2008

13 References

1. Miller RD, editor. Miller's Anesthesia 6th Ed. Elsevier Churchill Livingstone, 2005

2. Abbott F, Gray-Donald K. The prevalence of pain in hospitalised patients and resolution over 6 months. Pain 1992; 50: 15-28

3. Partridge BL, Stabile BE. The effects of incisional bupivacaine on postoperative narcotic requirements, oxygen saturation and length of stay in the post-anesthesia care unit. Acta Anaesthesiol Scand 1990: 34:486-491

4. Chan VWS. Cost-effectiveness of Ropivicaine and Levobupivacaine in postoperative pain. In: 4th International Conference on Pain Control and Regional Anaesthesia; 2005 Nov 18-22; Cape Town (ZA). 2005:68-73

5. Rawal N. Regional techniques in ambulatory surgery – postoperative pan management at home. In: 4th International Conference on Pain Control and Regional Anaesthesia; 2005 Nov 18-22; Cape Town (ZA). 2005; 154-159

6. Mackey SC. Evaluating outcomes in pain medicine. In: Annual meeting refresher course lectures. American society of Anesthesiologists; 2006 Oct 14-18; Chicago, Illinois. 2006 504:1-4

7. PROSPECT Working Group. Last revision June 2006. http://www.postoppain.org/frameset.htm [Accessed 9 Jan 2009]

8. PROSPECT Working Group. "Abdominable hysterectomy" Last revision June 2006. http://www.postoppain.org/frameset.htm [Accessed 9 Jan 2009]

9. Yentis S, Hirsch N, Smith G. Anaesthesia and Intensive Care A-Z. 2nd ed. Reprint. Butterworth-Heinemann, 2005

10. Gupta A, Perniola A, Axelsson K, Thörn SE, Crafoord K, Rawal N. Postoperative pain after abdominable hysterectomy: A double-blind comparison between placebo and local anesthetic infused intraperitoneally. Anesth Analg 2004; 99: 1173-9

11. Rawal N. Multimodal Analgesia. In: 4th International Conference on Pain Control and Regional Anaesthesia; 2005 Nov 18-22; Cape Town (ZA). 2005:160

12. White PF, Rawal S, Latham P, Markowitz S, Issioui T, Chi L, et al. Use of a continuous local anesthetic infusion for pain management after median sternotomy. Anesthesiology 2003; 99:918-23

13. Nikshat O, Departmental presentation: Pain Survey. n.p., n.pub. 2006.

14. Bassin J, editor. Topics in Obstetrics and Gynaecology, 4th Ed. Julmar Communications, 1998

15. Freyd M. The Graphic Rating Scale. Journal of Educational Psychology 1923; 14:83-102

16. Declaration of Helsinki with World Medical Association amendments (2008). www.wma.net/e/policy/b3.htm (Assessed 2009.06.27)

17. Endacott R, Botti M. Clinical research 3: sample selection. Intensive and Critical Care Nursing (2005) 21, 51-55

18. Banks A. Innovations in postoperative pain management: continuous infusion of local anesthetics. AORN Journal 2007, 85(5): 904-914

19. Capdevilla X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of Perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999; 91: 8-15

20. Carr DB, Goudas LC. Acute Pain. Lancet 1999; 353:2051-58

21. Vickers AP. Control of acute pain in postoperative and post-traumatic situations and the role of the acute pain service. Anaesthesia and Intensive Care Medicine 2007(9.1) 16-0

22. Xie W, Strong JA, Meij JTA, Zhang J, Yu L. Neuropathic pain: Early spontaneous afferent activity is the trigger. Pain 2005 116: 243-256

23. American Pain Society Quality of Care Committee: Quality improvement guidelines for the treatment of acute pain and cancer pain. JAMA 1995; 274(23): 1874-1880

24. Liu SS, Richman JM, Thirlby RC et al. 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 2006 203(6): 914-932

25. Wu CC, Fleisher LA. Outcomes research in regional anaesthesia and analgesia. Anest Analg 2000; 91: 1232-42

26. Liu SS, Salinas FV. Continuous plexus and peripheral nerve blocks for postoperative analgesia. Anesth Analg 2003 96:263-272

27. Partridge BL, Stabile BE. The effects of incisional bupivacaine on postoperative narcotic requirements, oxygen saturation and length of stay in the post-anesthesia care unit. Acta Anaesthesiol Scand 1990: 34:486-491

28. Zohar E, Fredman B, Phillipov A, et al. The analgesic efficacy of patient-controlled bupivacaine wound instillation after total abdominal hysterectomy with bilateral salpingo-oophorectomy. Anesth Analg 2001;93:482-7

29. Berde CB. Local Anesthetics: Basic Mechanisms and Clinical implications. In: Annual meeting refresher course lectures. American society of Anesthesiologists; 2006 Oct 14-18; Chicago, Illinois. 2006 141:1-6

30. Rawal N, Axelsson K, Hylander J, Allvin R, Amilon A, Lidegran G, et al. Postoperative Patient-controlled local anaesthetic administration at home. Anesth Analg

31. Goldstein A, Grimault P, Henique A, Keller M, Fortin A, Darai E. Preventing postoperative pain by local anesthetic instillation after laparoscopic gynaecologic surgery: a placebo-controlled comparison of bupivacaine and ropivacaine. Anesth Analg. 2000 Aug; 91(2): 403-407. In PubMed [database online] http://www.ncbi.nlm.nih.gov/PubMed/ [cited 23 April 2007] 998; 86:86-89

32. Moss G, Regal ME, Lichtig L. Reducing postoperative pain, narcotics, and length of hospitalisation. Surgery 1986; 99:206-10

33. McDonnell JG, O'Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The analgesic efficacy of transverses abdominis plane block after abdominal surgery: A Prospective Randomized Controlled Trial. Anesth Analg 2007; 104: 193-197

34. Klein JR, Heaton JP, Thompson JP et al. Infiltration of the abdominal wall with local anaesthetic after total abdominal hysterectomy has no opioid-sparing effect. BJA 2000 84(2): 248-9

35. Chan VWS. Cost-effectiveness of Ropivicaine and Levobupivacaine in postoperative pain. In: 4th International Conference on Pain Control and Regional Anaesthesia; 2005 Nov 18-22; Cape Town (ZA). 2005:68-73

36. Rawal N. Regional techniques in ambulatory surgery – postoperative pan management at home. In: 4th International Conference on Pain Control and Regional Anaesthesia; 2005 Nov 18-22; Cape Town (ZA). 2005; 154-159

37. Rosenberg PH, Veering BT, Urmey WF. Maximum Recommended Doses of Local Anesthetics: A Multifactorial Concept. Regional Anesthesia and Pain Medicine, 2004, 29(6): 564–575

38. Zink W, Bohl J, Hacke W, Sinner B, Martin E, Graf B. Anesthe Analg 2005(101) 548-54

39. Hogan Q, Dotson R, Erickson S, et al. Local anesthetic myotoxiciy: a case and review. Anesthesiolgy 1994;80:942-7

40. Rawal N. Postoperative analgesia and outcome – back to square one? [Abstract]. South African Journal of Regional Anaesthesia 2007; 18-19

41. LeBlanc K, Bellange D, Rhynes VK, Hausmann M. Evaluation of continuous infusion of 0.5% bupivicaine by elastomeric pump for postoperative pain management after open inguinal hernia repair. J Am Coll Surg 2005, 200(2): 198-202

42. Rawal N, Allvin R, Axelsson K, Hallen J, Ekbäck G, Ohlsson T, Amilon A. Patient-controlled regional analgesia (PCRA) at home. Anesthesiology 2002; 96: 1290-6

43. Ranta PO, Ala-Kokko I, Kukkonen JE, Ohtonen PP, Raudaskoski TH, PK Reponen, Rawal N. Incisonal and epidural analgesia after caesarean delivery: a prospective,

placebo-controlled, randomised clinical study. International Journal of Obstretric Anesthesia 2006; 15: 189-194

44. Magnani E, Corosu R, Mancino P, Borgia ML. Postoperative analgesia after cesarean section by continued administration of levobupivacaine with the On-Q Painbuster system over the fascia vs. ketorolac + morphine i.v. Clin Exp Obstet Gynecol.2006; 33(4):223-5 In PubMed [database online] http://www.ncbi.nlm.nih.gov/PubMed/ [cited 23 April 2007]

45. US Food and Drug Administration http://www.fda.gov/cdrh/consumer/problems.html

46. Loeser JD, Butler SH. Bonica's Management of Pain 3rd ed. Lippincott Williams and Wilkins, 2001

47. Stanley G, Appadu B, Mead M, Rowbotham DJ. Dose requirements, efficacy and side-effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery. British Journal of Anaesthesia 1996, 76: 484-486

48. ON-Q® Pain Buster® Post-Op Pain Relief System website http://www.iflo.com/prod_painbuster.php . Copyright 2004-2008 [Assessed 7 April 2009]

13.1 Databases

PubMed. http://www.ncbi.nlm.nih.gov/PubMed/> Bethesda (MD): National Center for Biotechnology and Information, 1966 – Updated daily. (Accessed 2.10.2008)