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Time until first analgesic requirement, post caesarean section under spinal anaesthesia, in HIV-positive patients at Chris Hani Baragwanath Hospital.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesbutg, in partial fulfilment of the requirements for the degree of Masters of Medicine in the branch of Anaesthesia

Johannesburg 2010

DECLARATION

I, Janine Louise Wagner, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesia at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

JL Wagner

Signature

8 th of April, 2011

For those who strive to improve the lives of others.

PRESENTATIONS ARISING FROM THIS STUDY

Presented as a poster at the South Africa Society of Anaesthesiologists (SASA) congress, Bloemfontein, March 2010

PREFACE

During the first year of my training in anaesthesia, I had an impression that many of my HIV- positive patients were requiring greater doses of analgesics intraoperatively. A proportion of my patients were experiencing short durations of analgesia from spinal anaesthetics and were requiring additional analgesia in the recovery room. I had been trained only to perform spinal anaesthetics with 0.5 % heavy bupivacaine and had reservations towards the use of intrathecal opioids, due to fears that my patients would experience postoperative respiratory depression or even apnoea, which would go unnoticed in the extremely busy postoperative recovery wards. With this in mind, I approached the senior Obstetric Anaesthetist, who would later become both my mentor and supervisor, and shared with her my perhaps biased observations. Thus came about the topic for my research project.

I am greatly indebted to Dr Phillipa Penfold for her continuous encouragement, advice, guidance, constructive criticism and support. Not only has she been an integral part of this research project from the development of the topic, but her knowledge and expertise have led to a vast improvement and insight into my own Obstetric Anaesthetic practice.

ABSTRACT

BACKGROUND

Multiple studies have been conducted comparing the efficacy and duration of analgesia obtained from spinal anaesthesia containing local anaesthetics as well as opioids. The literature available has not considered the individual's HIV status as a variable. Postoperative analgesic duration and requirements in this group of patients may differ due to the occurrence of acute and chronic pain syndromes, pain arising from the disease itself, side effects of treatment for HIV infection, or opportunistic infections. Response to opioid analgesia may be altered due to previous opioid exposure, potential increase in nociception, drug interactions and emotional status.

OBJECTIVES

The primary objective of this study was to determine the time to post-operative analgesic request in HIV-positive and negative individuals having caesarean sections under spinal anaesthesia containing bupivacaine or bupivacaine and fentanyl. The secondary objectives of this study were to determine if factors such as height, ethnicity, level of education, CD4 count, and antiretroviral therapy impacted on the duration of analgesia obtained.

METHOD

In consultation with a statistician it was decided that a minimum of 56 HIV-positive and 56 HIV-negative patients would be required to determine if a statistically significant difference in duration of analgesia existed between the HIV-positive and negative individuals. The sample size was calculated assuming that a difference of 20 minutes existed between these patients, with a standard deviation of 35 and a power of 85%, with the significance level set at $p < 0.05$. 30 patients in each of the four subgroups would be required to achieve a power of 100% with standard deviation of 35 and alpha value of 0.05 when analysed by an ANOVA test. The four subgroups studied were: HIV-positive bupivacaine (HPB), HIV-positive bupivacaine and fentanyl (HPBF), HIV-negative bupivacaine (HNB) and HIV-negative bupivacaine and fentanyl (HNBF)

It was thus decided that the study should consist of total sample size of 120 individuals; 60 HIV-positive and 60 HIV-negative. 30 patients in each group would receive 2ml 0,5 % heavy bupivacaine and 0,4ml normal saline and 30 would receive 2ml 0,5 % heavy bupivacaine and 0,4 ml fentanyl (20ug).

Intrathecal drugs were administered in a double-blinded fashion utilising pre-mixed coded syringes and a standardised spinal technique was employed.

Time of administration of anaesthetic was noted and patients were monitored at 30 minute intervals thereafter until analgesia was requested. A visual analogue pain score was utilised to monitor the patient's pain.

Once patients requested analgesia nursing staff were informed and analgesia given according to ward protocol.

RESULTS

The data collected showed that the addition of fentanyl to the intrathecal injection significantly prolongs the duration of analgesia by a range of 25-80 minutes. It was determined that HIV infection, CD 4 count, antiretroviral therapy, height, ethnicity, and level of education did not significantly alter the duration of analgesia obtained from intrathecal injection.

CONCLUSION

Intrathecal anaesthesia provides limited postoperative analgesia. HIV infection itself has no effect on the duration of analgesia obtained. The addition of 20 ug fentanyl to hyperbaric bupivacaine significantly prolongs the duration of analgesia in the post-surgical care unit.

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CHAPTER ONE – INTRODUCTION

1.1 Introduction

Multiple studies have been conducted comparing the efficacy and duration of analgesia obtained from spinal anaesthesia, containing local anaesthetics and opioids. The duration of post-operative pain relief and time to first analgesic request following spinal anaesthesia ranges from 90 to 190 minutes for intrathecal bupivacaine alone and up to 184 (+/- 20) minutes for intrathecal fentanyl and bupivacaine [1-13].

Most of these studies have been conducted in the developed world in populations where the prevalence Human Immunodeficiency Virus (HIV) infection is known to be low [14] .

Between 523 and 706 caesarean sections are performed monthly at Chris Hani Baragwanath Hospital (CHBH) [15]. The prevalence of HIV-infection in these obstetrics patients ranges from 30-35% and voluntary counselling and testing rates in the antenatal clinic are as high as 90%. Intrathecal opioid administration is often avoided or limited to low doses due to the fear of inadequate monitoring for post-operative respiratory depression. The high turnover of patients, overloaded post-caesarean section ward, and limited nursing staff available to nurse patients has led to standardised provision of post-operative analgesia, which may be inadequate for many patients.

Inadequate postoperative pain control can have a severe impact on both the mother and infant, and numerous deleterious effects of post-operative pain in obstetric patients are well described [16].

Estimates of the prevalence of pain in patients with HIV/AIDS range from 40%-93%. Despite the high frequency of pain in these patients, pain relief is often overlooked and there is no literature available concerning duration of postoperative analgesia obtained from intrathecal anaesthesia. Postoperative analgesic duration and requirements in HIV-positive patients may differ as multi-faceted pain as well as acute and chronic pain syndromes are commonly encountered. HIV- positive individuals often have pain arising from multiple aetiologies occurring concurrently due to various aspects of the disease itself, side effects of treatment for HIV infection, opportunistic infections e.g. cytomegalovirus, neuropathies due to nutritional deficiency, critical illness neuropathy, and cytokine-mediated neurotoxic effects [17-23] . Response to opioid analgesia may be altered due to previous opioid exposure, potential increase in nociception, drug interactions and emotional status [17-23]. Although opiate-resistant pain has been described in HIV/AIDS patients, it is not a common finding [23]. It may be possible that HIV infection will alter the duration of postoperative analgesia obtained from intrathecal anaesthesia.

1.2 Problem statement

The duration of analgesia obtained from caesarean sections under spinal anaesthesia in HIV- positive patients is unknown and may differ from that achieved in HIV- negative patients.

1.3 Aim

The aim of the study was to determine if HIV- positive patients having caesarean sections under spinal anaesthesia containing bupivacaine or bupivacaine and fentanyl had differing durations of analgesia to HIV- negative patients.

The null hypothesis of the study is that there is a no difference in the duration of analgesia obtained from spinal anaesthesia, containing bupivacaine or bupivacaine and fentanyl, in HIV-positive patients compared to HIV-negative patients.

The alternative hypothesis is that there is a difference in the duration of analgesia obtained from spinal anaesthesia, containing bupivacaine or bupivacaine and fentanyl, in HIV-positive patients compared to HIV-negative patients.

1.4 Objectives

The primary objective of this study was to determine whether there was a difference in the time to first post-operative analgesic request in HIV- positive and negative patients after having undergone a caesarean section, under spinal anaesthesia, containing bupivacaine or bupivacaine and fentanyl.

The secondary objectives of this study were to determine if factors such as height, ethnicity, level of education, CD4 count, and antiretroviral therapy impacted on the duration of analgesia obtained.

1.5 Research assumptions

1.6 Study design

This study is a prospective, randomised, quantitative double-blinded observational study.

1.7 Ethical considerations

1.7.1 Ethical clearance

The study has been approved by the regional Ethics Committee – the committee for research on Human Subjects (Medical) of the University of the Witwatersrand (Appendix A).

1.7.2 Post-Graduate approval

The study has been approved by the Post-Graduate Committee of the University of the Witwatersrand, Faculty of Health Sciences (Appendix B)

1.7.3 Site approval

Permission to complete this research project, collect data (including HIV status) from patient's files and to interview patients has been granted by the Clinical Director of CHBH. (Appendix C).

1.7.4 Patient consent

Patients were invited to participate in the study. Patients received a printed document (Appendix D) explaining the reason for the study, exactly what their involvement in the study would be, their right to refuse to participate without repercussions to their care, and their right to withdraw from the study at any time. A 24-hour contact number was supplied should they have required further information. The printed information was provided in English. The researcher and a translator provided verbal information in a language that the patient could understand if they could not understand English, or were not able to read the document. Written consent was obtained from all patients agreeing to participate (Appendix E).

1.7.5 Declaration of Helsinki

The research was conducted according to the principles described in the Declaration of Helsinki [25] .

1.8 Summary of methodology

After permission from the relevant authorities was granted, participants were identified in the labour ward or in labour admissions ward. Participants matching the inclusion criteria were approached for inclusion into the study.

Written informed consent was obtained preoperatively from patients without exclusion criteria. The patients were made aware that their participation was voluntary and that their results would be analysed by means of a numerical code system. All information that would link their identity to the trial results would remain separate and confidential.

Use of medically knowledgeable translators was made if a language barrier was encountered or if the patient requested that the information and consent forms be explained to them in a language of their choice. Translation was provided by a team of anaesthetic trained nursing sisters who worked in the obstetric theatres.

In consultation with a statistician it was decided that a minimum of 56 HIV-positive and 56 HIV-negative patients would be required to determine if a statistically significant difference in duration of analgesia existed between the HIV-positive and negative individuals.

The sample size was calculated assuming that a difference of 20 minutes existed between these patients, with a standard deviation of 35 and a power of 85%, with the significance level set at $p < 0.05$. 30 patients in each of the four subgroup: HIV-positive bupivacaine (HPB), HIV-positive bupivacaine and fentanyl (HPBF), HIV-negative bupivacaine (HNB) and HIV-negative bupivacaine and fentanyl (HNBF) would be required to achieve a power of 100% with standard deviation of 35 and alpha value of 0.05 when analysed by an ANOVA 1- way test (assuming a normal distribution).

The study consisted of total sample size of 120 individuals. 30 HIV-positive patients received intrathecal bupivacaine alone (HPB) and a control group of 30 HIV-negative patients received the same treatment (HNB); 30 HIV-positive patients received intrathecal bupivacaine and fentanyl (HPBF) and a control group of 30 HIV-negative patients received the same treatment (HNBF). A schematic representation of the research groups is shown in **Figure 1.1**.

Information was collected from the patient interviews as well as the patients' hospital files and antenatal records. The information collected included height, weight, age, ethnicity, education, HIV status, CD4 count, and whether the patient was receiving antiretroviral therapy.

Intrathecal drugs were administered in a double-blinded fashion utilising pre-mixed coded syringes and a standardised spinal technique was employed. Spinal anaesthetic options included 2ml 0,5 % heavy bupivacaine and 0,4ml normal saline or 2ml 0,5 % heavy bupivacaine and 0,4 ml fentanyl (20ug).

Time of administration of anaesthetic was noted and patients were monitored at 30 minute interval thereafter until analgesia was requested. Visual analogue pain score was utilised to monitor the patients' pain. **Figure 1.2** depicts the visual analogue scales utilised.

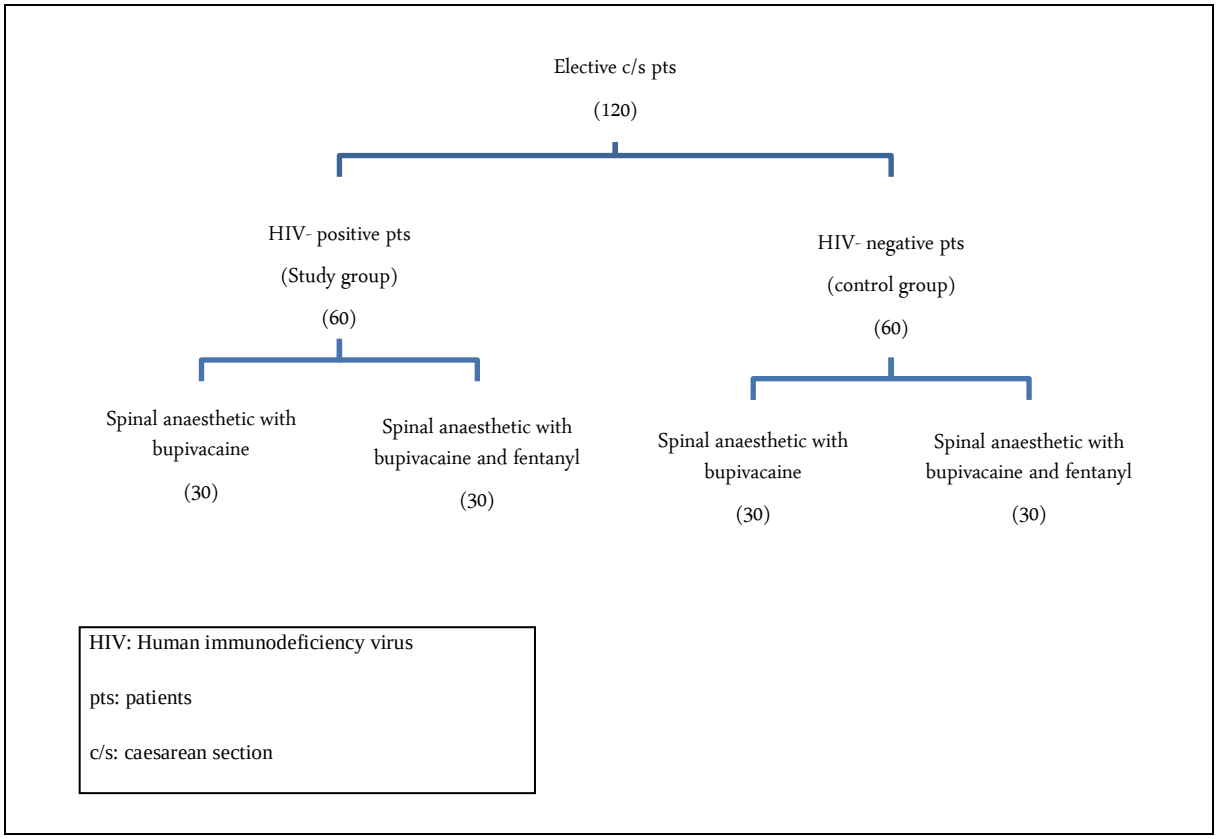

Figure 1.1. Diagram representing research groups

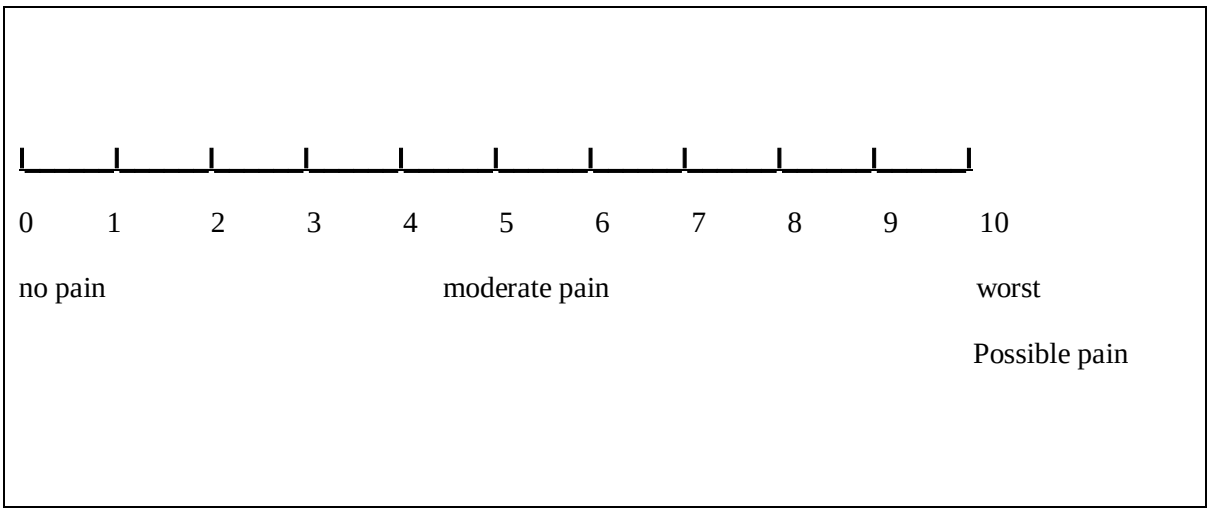

Figure 1.2 Visual analogue scale utilised [22 26].

Postoperative analgesia was prescribed according to the ward protocol which included Omnopon ® (morphine hydrochloride, papaverine hydrochloride, and codeine hydrochloride) and paracetamol. As soon as the patients requested analgesia the ward nursing staff were notified and requested to administer the prescription.

The study ended when there were 30 HIV-positive individuals who have received intrathecal bupivacaine with 30 HIV-negative individuals as a control group and 30 HIV-positive individuals who have received intrathecal bupivacaine and fentanyl with 30 HIV-negative individuals as a control group.

1.9 Significance of the study

The significance of the study will be discussed below.

1.9.1 The results of the study may be able to guide anaesthetists in the possible benefits of varying spinal mixtures.

1.9.2. The study results may provide a rough estimate as to when additional analgesics can be expected to be necessary and thus aid in the better provision of postoperative analgesia to post caesarean section patients at CHBH.

1.9.3 The study may encourage others to pursue the improvement of postoperative pain provision in our hospitals with possible development of postoperative pain teams.

1.9.4 The results of the study may direct further research in the field of providing analgesia in the HIV-positive parturient.

1.9.6 The results of the study might demonstrate that factors such a height, ethnicity, and education may alter the duration of analgesia obtained from spinal anaesthesia.

1.9.7 The results of this study, by defining an expected duration of analgesia, may alert the anaesthetist to early identification of a complicated prolonged block. This may lead to early intervention and possibly a better patient outcome.

1.10 Study limitations

1.10.1 Study period:

The data collection was done over a 6 month period from June to November 2008. The data was collected predominantly in November 2008. The data was collected when it was convenient for the investigator to do so.

This convenient data collection led to a non-continuous selection of patients. This will be mentioned further in the discussion.

1.10.2 Frequent delays and postponement of elective patients:

Only two Obstetric theatres are available at CHBH. Emergency caesarean sections take precedence over elective cases. Patients are frequently repeatedly delayed and postponed. This repeated delay may cause increased patient anxiety which may affect the results obtained. This will be discussed further in chapter 5.

1.10.3 Surgeon variations:

Although caesarean sections are performed using a standardised technique taught at CHBH, the caesarean sections were performed by various different surgeons, with differing levels of experience, differing surgical durations, differing degrees of tissue trauma and blood loss. The impact that this may have will be discussed in chapter 5.

1.10.4 Contextuality:

This study was done in the context of patients presenting for elective caesarean section at CHBH. Generalisation to other populations may be limited.

1.10.5 Retrospective review of data:

Data collected from the antenatal card was collected retrospectively, as with all retrospectively collected data, the quality of the data collected is dependent on the quality of record keeping. In parturients, while antenatal cards are often filled in thoroughly, there are sometimes gaps in the available information.

1.11 Research report outline

This research report will comprise the following chapters:

Chapter One: an introduction to the study, including the aim and objectives of the study, and a brief summary of the methodology used.

Chapter Two: a review of the literature pertinent to topics raised by the study.

Chapter Three: an in-depth description of the methodology used for the study.

Chapter Four: the results of the study

Chapter Five: an interpretation of the results of the study, and a discussion of the issues raised by the results.

Chapter Six: a summary of the study, and conclusions drawn from the study.

CHAPTER 2 – LITERATURE REVIEW

In this chapter we will include a review of the literature pertinent to topics raised by the study. We will discuss the caesarean section, pain arising from the caesarean section, anaesthesia for caesarean sections, the spinal anaesthetic, mechanism of action of local anaesthetics and opiates used in spinal anaesthetics, the definitions of pain, mechanisms of pain in HIV, HIV and AIDS and antiretroviral therapy.

2.1 Introduction

Severe postoperative pain results in unnecessary suffering and potentially severe complications that affect both the mother and infant [16]. Caesarean sections are often associated with severe postoperative pain from the surgical procedure itself, as well as complications of the anaesthetic provided [16 26 27].

In modern anaesthetic practice the prevention of intraoperative pain continues to expand to encompass postoperative care, as well as the treatment and prevention of acute and chronic pain syndromes [28-33]. Postoperative pain continues to be a huge burden in our clinical setting, even though there are numerous simple and cheap methods of monitoring and recording postoperative pain. The high turnover of patients, overloaded post-caesarean section wards, lack of monitoring facilities, and limited nursing staff (who are often the sole providers of postoperative analgesia and pain monitoring) has led to standardised provision of post-operative analgesia, which may be inadequate for many patients.

The knowledge and skills possessed by anaesthetists, to manage postoperative pain continues to be underutilised [26 32].

Pain has been characterized as the most significant disability in people living with HIV/AIDS. Estimates of the prevalence of pain in patients with HIV/AIDS range from 40%-93% [17-20 34.]

Despite the high frequency of pain in these patients, and the increased risk of developing complications and chronic pain syndromes, postoperative pain management is still often inadequate.

Between 523 and 706 caesarean sections are performed monthly at CHBH[15]. Spinal anaesthesia has become the most common and preferred method to provide analgesia during the caesarean section [35-37]. The analgesia obtained from spinal anaesthesia, although ideal for intraoperative pain relief, is often short-lived and inadequate to manage postoperative pain. Multiple studies have been conducted comparing the efficacy and duration of analgesia obtained from various preparations of spinal anaesthetics [1-12 38]. Numerous studies have shown that the addition of fentanyl to spinal anaesthetics prolongs the duration of analgesia and improves the quality of the anaesthetic provided [1-12 38]. Intrathecal opioid administration in our clinical setting is often avoided, or limited to low doses of short acting drugs, due to the fear of inadequate monitoring for post-operative respiratory depression.

It is estimated that more than 42 million people are living with HIV/AIDS, 58% are female, and almost 70% of whom live in sub-Saharan Africa[39-40]. The prevalence of HIV-infection in obstetric patients in sub-Saharan Africa is estimated to range from 25-35% [39 41]. There is currently no literature available that describes the duration of postoperative analgesia obtained from spinal anaesthesia in HIV positive patients.

2.2 The caesarean section

2.2.1 History

The caesarean section is one of the most commonly performed major operations throughout the world [42]. Caesarean section rates as high as 25-50 % of all maternal deliveries are encountered in many countries and vertical transmission rates, in the absence of the use of antiretroviral drugs, as high as 80 % have been reported in some private sector hospitals [43-44].

The caesarean section has been part of human culture since ancient times. Numerous references to the caesarean section appear in ancient Hindu, Egyptian, Grecian, Roman, and other European folklore. The origin of the term "caesarean" has been distorted over time. It is commonly and inaccurately believed to be derived from the surgical birth of Julius Caesar. Ultimately, though, we cannot be sure of where or when the term caesarean was derived [47].

2.2.2. Relevant anatomy and surgical technique

Pain occurring during the performance of a caesarean section comprises both visceral as well as somatic components. Pain originates from the Pfannenstiel / infraumbilical skin incision, stretching of the skin and muscles, intraperitoneal manipulation, incision and traction of visceral and parietal peritoneum, bladder and uterus as well as secondary to diaphragmatic stimulation. The cutaneous nerve supply arises from the anterior rami of the lower thoracic and lumbar spinal roots. The major nerves supplying the anterior abdominal wall are the iliohypogastric nerve (L1), ilioinguinal nerve (L1), subcostal nerves (T12) and intercostals nerves (T7-11). The Pfannenstiel / infraumbilical incision necessitates blockade of T11 to L1 dermatomes [45-46].

Stretching of the skin may require two to four levels higher. The pelvic organs derive their sensory innervations from both sympathetic and parasympathetic nerves. Parasympathetic nerves play a secondary role compared with the sympathetic nerve supply. Most pelvic viscera derive their supply from the coeliac and superior hypogastric plexuses. It is therefore necessary to achieve blockade to a dermatomal level of T6 to ensure adequate intraoperative analgesia [45-46].

2.2.2.1 The Skin Incision

The choice of skin incision is based on surgeon and patient preferences as well as delivery indication and difficulty anticipated. A low transverse incision of approximately 15cm is usually chosen because of its cosmetic appeal and lesser chance of incisional herniation or wound dehiscence. Alternatively, a low vertical incision may be chosen as it allows for quick access to the lower uterine segment, better exposure, less blood loss and easier access to the upper abdomen. The Pfannenstiel transverse skin incision is most commonly used incision. The Joel-Cohen incision is positioned higher, is straight rather than slightly curved and the peritoneum is opened transversely rather than longitudinally. Another alternative is the Maylard incision which requires more dissection and is associated with greater post-operative discomfort. Incisions may be greater than 15cm if a difficult delivery is anticipated [49-50].

2.2.2.2 Separation of the abdominal muscles

Traction is applied by the surgeon and the assistant to separate the rectus abdominal muscles.

2.2.2.3 The Uterine Incision

Having carefully opened the abdomen the surgeon exposes the lower segment of the uterus. The visceral peritoneum is incised and the bladder is pushed down. Approximately 90 percent of all uterine incisions are made in the low transverse rather than vertical direction the uterus is opened slowly and when the bulge of membranes appears it is pricked or torn with a forceps and the amniotic sac is opened fully with a finger from each side [49-50].

2.2.2.4 Delivery of the foetus and placenta

In most circumstances delivery of the foetal head is easy with sufficient fundal pressure.

2.2.2.5 Uterine and Abdominal closure

Uterine and Abdominal closure is completed by continuous running suturing of the uterine, fascial and skin layers to ensure preservation of original blood supply with minimal injury [49-50].

Exteriorization and traction of the uterus is commonly practised at Chris Hani Baragwanath Hospital (CHBH). It is used to decrease blood loss and facilitate suturing but exteriorization has been associated with patients complaining of pain and nausea as well as an increase in the incidence of venous air embolism [49-50].

The visceral and parietal peritoneum is either closed or left open. Non-closure of the peritoneum is the most commonly performed technique performed and is the technique commonly practised by surgeons at CHBH. Non-closure may carry some short-term advantages including lower risk of postoperative infection, shorter operating time and shorter hospital stay. The operating time is slightly shorter (approximately 8 minutes) if the parietal peritoneum is left open and these patients are also known to require fewer doses of postoperative analgesics and to develop fewer adhesions [49-50].

Closure of the fascia is commonly performed in a standard single layer manner using synthetic suture[49-50].

2.2.3 Anaesthesia for caesarean sections

Spinal and epidural anaesthetics are now the most popular choices for elective caesarean sections; spinal anaesthesia is now being used in more than 90% of cases in certain hospitals [36-37] . At CHBH approximately 10-15 % of caesarean sections are performed under general anaesthesia [15].

Regional techniques possibly have several advantages, namely avoiding a potentially difficult airway, decreased risk of gastric aspiration, the avoidance of depressant anaesthetic drugs and neuromuscular blockers, decreased drug delivery to the infant, and allowing the mother to be awake during the delivery. General anaesthesia is associated with an increased risk of gastric aspiration and morbidity associated with an inability to secure the airway [52 53].

The mortality rate with general anaesthesia is 16.7 times greater than that with regional anaesthesia. The newborn's outcome is similar after caesarean section under regional or general anaesthesia [36-37].

The height of the block must extend to at least the T4-T6 dermatome in order to provide adequate intraoperative anaesthesia [52 53].

In elective caesarean sections, the duration of antepartum anaesthesia does not seem to affect neonatal outcome so long as hypotension is treated promptly and protracted aortocaval compression is avoided [54].

Spinal (subarachnoid/ intrathecal) anaesthesia is the most commonly administered anaesthetic due its speed of onset and reliability. The advantages of the technique include a rapid onset, good quality block, with an acceptably low failure rate of approximately 1.3 %. Local anaesthetic overdose or inadvertent intravascular or intrathecal injection of a large dose of local anaesthetic, as can occur with epidural or spinal anaesthesia, can be avoided if spinal anaesthesia is used as small amounts of local anaesthetic are given[52 53 55].The faster onset of the block results in an arguably shorter turn-over time and possible cost savings.

In our clinical setting at CHBH spinal anaesthesia is the technique of choice as onset of anaesthesia is rapid, muscle relaxation is complete, it is technically simple, low local anaesthetic doses are used, a good quality reliable block is achieved with low failure rates of approximately 1.3 %[35 37 59], length of surgery is mostly ranging between thirty and ninety minutes and the patient loads and turnover are extremely high.

Unfortunately the inability to repeat the block and extended postoperative analgesia is a major limiting factor [35 37 59].

2.3 Spinal Anaesthesia

Spinal anaesthesia is a simple technique that entails injection of small doses of local anaesthetic solution into the subarachnoid space [52 55].

2.3.1 History of Spinal Anaesthesia

Spinal anaesthesia was developed over 100 years ago. It has been more than 25 years since neuraxial opioids first underwent rigorous clinical study for use in humans. Spinal anaesthesia was accidentally discovered by J. Leonard Corning of New York in 1885 during experiments with anaesthetic drugs in dogs [53 60 61]

It was first used in human beings in 1898 by Dr August Bier, who employed an assistant to inject cocaine into his own spine. In 1891 Quinke developed the technique of lumbar puncture and the importance of small bore fine needles.

The first described cases of spinal anaesthesia use in the United States were in October 1899 by Taut and Caglieri and December 1899 by Dr Rudolf Matas where spinal anaesthesia was employed for an osteotomy of the tibia and haemorrhoidectomy respectively. In 1907 Barker, in England and Chaput in France worked out the principles of gravity and the technique of 'heavy' injection with 5% glucose.

Spinal analgesia in obstetrics was first used by Kreis, a German, in 1901. It was popularized in the United States by Pitkin in 1928. For years after the first applications of spinal anaesthesia in obstetrics by Kreis, Doloris and Malartic in 1900s, this method of analgesia was condemned due to the high degree of complications, poor results and the lack of understanding of the interaction between the physiologic changes associated with pregnancy and the changes associated with spinal anaesthesia. It wasn't until the 1940's when Adriani and associates established safe, standardised techniques that this method of analgesia became popular in obstetrics [53 60 61]. Since the 1950's it has become a widely used method of analgesia and anaesthesia in obstetrics [62].

2.3.2 History of drugs used in spinal anaesthesia

Originally drugs used in spinal anaesthesia included cocaine, stovaine, strychnine, novocaine and spinocaine. New amino ester local anaesthetics, such as tropocaine, eucaine, benzocaine, and tetracaine, were synthesized between 1891 and 1930 [63].

The amino amide local anaesthetics were prepared between 1898 and 1972 and included procaine, chloroprocaine, cinchocaine, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine and articaine[63].

All these drugs were less toxic than cocaine but they had differing amounts of central nervous system and cardiovascular system toxicity.

Bupivacaine was synthesized in 1957 and has become the most commonly used local anaesthetic agent for spinal anaesthesia in obstetric patients [63]. Its popularity stems from its long duration of action, low cost, reliability, and safety profile.

2.3.3 Mechanism of action of a spinal anaesthetic

The principal site of action for neuraxial blockade is the nerve root. Local anaesthetic is injected into the CSF and bathes the nerve root in the subarachnoid space [52 53 55].

Hogan and Toth have shown that the sizes of the nerve roots of the spinal cord differ between individuals and that this difference may explain the inter-patient differences in neuraxial block quality when an equivalent technique is used. Although dorsal (sensory) roots are larger than anterior (motor) roots, the dorsal roots are often blocked easier. This is explained by the organization of the dorsal roots into component bundles, creating a much larger surface area on which the local anaesthetics act [52 53 55 66].

Direct injection of local anaesthetic into CSF for spinal anaesthesia allows a relatively small dose and volume of local anaesthetic to achieve dense sensory and motor block. Blockade of neural transmission in the posterior nerve fibres interrupts somatic and visceral sensations, whereas blockade of anterior nerve root fibres prevents efferent motor and autonomic outflow. Neuraxial blocks can provide excellent operating conditions by interrupting the transmission of painful stimuli and abolishing skeletal muscle tone below a certain dermatomal level[52 53 55].

The factors which determine and affect this level are discussed later in this chapter. Sensory block interrupts both somatic and visceral pain stimuli below this level, and motor blockade produces skeletal muscle relaxation[53].

2.3.4 Local anaesthetic and opiate use in spinal anaesthesia

There are many choices of drugs available to produce spinal anaesthesia, however local anaesthetics are used most frequently[52 53 55].

When choosing a drug for subarachnoid injection, the duration of the block and analgesia obtained should be taken into account. Commonly used anaesthetic agents include procaine, lidocaine, mepivacaine, tetracaine, ropivacaine, levobupivacaine and bupivacaine [52 53 55].

These drugs provide analgesia which may range between 45-400 minutes. Doses of Bupivacaine usually range between 1.8 and 2.9ml 0.5% hyperbaric bupivacaine to achieve a block below the T4 dermatome [1-13].

The analgesia obtained from spinal anaesthesia has a short duration. This duration may be extended by the addition of opioids and other adjuncts. A systematic review of intraoperative analgesia identified that approximately 24% of patients that receive only hyperbaric bupivacaine experience unacceptable levels of discomfort during spinal anaesthesia for caesarean section. Plain bupivacaine may be associated with intraoperative nausea during manipulation of the uterus at the time of peritoneal closure. This is effect may be decreased by the addition of opioid to the block[52 53].

Neuraxial administration of opioids in conjunction with local anaesthetics improves the quality of intraoperative analgesia, decreases intraoperative discomfort and prolongs the duration of postoperative analgesia [1-13 58 59 73].

However, they also produce several side effects, including pruritis, nausea, vomiting and respiratory depression in a dose-dependent fashion [58 59 73].

A dose of 0.1-0.2 mg morphine added to intrathecally administered local anaesthetics has been demonstrated as the best balance between the improvement of the quality of pain control and minimization of side effects [7]. Morphine, because of its relative hydrophilicity in comparison to other opioids, also has an enlarged potential for rostral migration in the CSF. This may possibly lead to a late respiratory depression [7]. Lipophilic opioids, like fentanyl and sufentanil, have a faster onset of action and lower risk for delayed respiratory depression. Lipophilic opioids are much more frequently used to potentiate nerve block of local anaesthetics. Literature indicates that intrathecal fentanyl is used in more than 40% obstetric anaesthetics. Doses range between 15 to 25 µg [1-13]. Morphine provides good quality long postoperative analgesia but little intraoperative effect because of the slow onset imposed by its relatively poor lipophilicity [52 53 55 67]. Studies have shown antinociceptive synergism between intrathecal opioids and local anaesthetics [1-13].

Fentanyl prolongs the duration of bupivacaine-induced sensory block by 28% [1-13]. The synergism between opioids and local anaesthetics is due to the effect that they exert their antinociceptive effect in the spinal cord by different mechanisms[52 53 67]. The inclusion of fentanyl may provide more than an hour of additional analgesia compared with hyperbaric bupivacaine alone [1-13]. It is important to use the smallest effective opioid dose to minimize potentially adverse maternal and neonatal risks[67]. Beneficial analgesia has to be balanced against known adverse effects, which include respiratory depression, emetogenesis, and pruritis[52 53 67]. Intraoperative respiratory depression and increased sedation occur when doses of more than 40 µg are used[53 67].

Studies indicate that in order to maximize postoperative analgesia, whilst minimizing respiratory depression and pruritis, a dose of approximately 20 µg would be optimal [1-13 53].

Opioids have a dose sparing and synergistic effect with regards to Bupivacaine [1-13]. The lower dose of Bupivacaine needed decreases the risk of side effects and toxicity. The mechanisms by which opiates create a block will be discussed later in this chapter.

Unfortunately pain relief provided by opioids shows inter-individual variability depending on factors such as previous exposure, increase in nociception, drug interactions and emotional status [1-13]; all factors that may be present in patients diagnosed with HIV infection[68].

2.3.5 Mechanism of action of local anaesthetics

The effect of local anaesthetics on nerve fibres varies according to the size of the nerve fibre, whether it is myelinated, and the concentration achieved and the duration of contact. Spinal nerve roots contain varying mixtures of nerve fibres. Smaller and myelinated fibres are generally more easily blocked than larger and unmyelinated ones. Neurons have membrane-bound, voltage-gated sodium and potassium channels that produce membrane depolarization following chemical, mechanical and electrical stimulation. Sodium channels are membrane-bound proteins that are composed of one large alpha subunit through which sodium ions pass and one or two smaller beta subunits. Voltage-gated sodium channels exist in three states- resting, activated (open) and inactivated [52 53 55 67].

If the depolarization exceeds a threshold level of about -55mV, voltage-gated sodium channels are activated, allowing a sudden influx of sodium ions and generating an action potential. Local anaesthetics bind the alpha subunit and block voltage-gated sodium channels from inside the cell [52 53 55 67].

Once the local anaesthetic has blocked the channel, transmission of the impulse is stopped, and hence the action of the nerve is blocked, with resultant clinical effect[52 53 55 67]. With increasing concentrations of anaesthetic neural impulse conduction slows, the rate of rise and magnitude of the action potential decreases, and the threshold for excitation is raised progressively until an action potential can no longer be generated and impulse propagation ceases[67].

Local anaesthetics have a much greater affinity for the channel in the activated and inactivated state than in the resting state. Local anaesthetics may also block calcium and potassium channels and N-methyl-D-aspartate (NMDA) receptors to varying degrees[67].

2.3.6 Mechanism of action of opioid anaesthetics

Administration of opioids into the subarachnoid space may produce a marked and selective inhibition of the small fibres A and C involved in the conduction of pain sensation. Fentanyl is a μ- receptor agonist that exerts its action by opening potassium channels and reducing calcium influx, resulting in inhibition of transmitter release. It also has a direct postsynaptic effect, causing hyperpolarisation and reduction in neuronal activity. Intrathecal fentanyl exerts its effect primarily at the level of the spinal cord but systemic absorption may cause an effect of peripheral receptors[53 67].

Varassi et al. have demonstrated that the subarachnoid administration of 25 μg of fentanyl during spinal anaesthesia in a non-premedicated patient did not alter respiratory rate, end-tidal tension of carbon dioxide, minute ventilation, respiratory drive, respiratory timing or the ventilatory response to carbon dioxide [10].

Side effects of high dose intrathecal opiates include postoperative nausea and vomiting (PONV), in approximately 30% of cases, and pruritis [52 53 67].

These side effects are usually easily managed. PONV can be prevented or treated with cyclizine , and severe pruritis, is ameliorated with intravenous naloxone titrated to achieve an effect without abolishing analgesia[52 53 67].

2.3.7 Factors affecting block height

More than twenty factors may alter spinal block height and therefore time to full regression of block and need for additional analgesia[52 53]. The height of spinal block is thought to be determined by the cephalad spread of local anaesthetic within the cerebrospinal fluid (CSF). **Table 2.1** lists the most important factors associated with block height. Factors include patient specific factors, the technique of injection, characteristics of the spinal fluid and anaesthetic solution[52 53]. Many of these variables have been shown to be of negligible clinical importance. Baricity of the local anaesthetic solution relative to patient position is probably the most important. Baricity is defined as the ratio of the density of the local anaesthetic solution relative to the density of CSF, which averages 1.0003 g/ml-1. Solutions which have the same density as CSF have a baricity of 1.0000g/ml-1 and are termed isobaric. Solutions that are denser than CSF are termed hyperbaric, whereas solutions that are less dense than CSF are termed hypobaric[53 69 70].

Isobaric bupivacaine in saline has a baricity of 0.9983 g/ml-1. Hyperbaric bupivacaine in dextrose has a baricity of approximately 1.0227 g/ml-1. Baricity is an important determinant in the spread of local anaesthetic because gravity causes hyperbaric solutions to flow downward in the CSF to the most dependent regions of the spinal column. Hypobaric solutions tend to rise in the CSF leading to a high block height and possible significant cardiovascular compromise[58 74 75].

The sitting position has a marked influence on the distribution of hypobaric and hyperbaric solutions because this accentuates the effect of gravity. Spinal curvature also affects the movement of injected solutions [58 74 75].

Hyperbaric solutions injected at the height of the lumbar lordosis will tend to flow cephalad to pool in the thoracic kyphosis thus the clinical observation that hyperbaric solutions tend to produce blocks with an average height in the midthoracic region. Temperature may alter the baricity and thus alter the block height. Increasing temperature may decrease baricity[52 71].

Several studies have shown that neither the injected volume nor the drug concentration affect block height when the dose is kept constant [53 72 73].

The site of injection can have an important effect on block height when isobaric solution are administered [53 74]. Injection in the L3-4 interspace led to a block height of T6, whereas injection at the L4-5 interspace reduced the block height to T10 [53 74]. In contrast, Sundnes et al. found no relationship between injection site and block height when hyperbaric solutions are used, presumably because of the overwhelming effect of gravity and position on distribution of local anaesthesia [53 73].

In young adults the most important variable governing block height with hyperbaric local anaesthetic solutions may be lumbosacral CSF volume[53 75]. Higuchi and colleagues performed a detailed examination of the effect of lumbar CSF volume, CSF density, lumbar CSF motion, patient age, weight, height and BMI on spinal block. Multiple linear regressions demonstrated that neither patient age nor height correlated with any clinical characteristics of spinal block. However CSF volume and weight were correlated with peak block height [53 76-82].

Although these variables were statistically significant, the coefficients of determination were small, indicating that these variables account for a relatively small amount of the variability in the block height [53 76-82].

Table 2.1. Factors that alter spinal anaesthetic block height[52 53].

Patient characteristics	Technique of injection	Characteristics of spinal fluid	Characteristics of anaesthetic solution
Volume of cerebrospinal fluid	Site of injection	Volume	Density
Density of cerebrospinal fluid	Direction of needle	Pressure (cough, strain, valsalva)	Amount (mass)
Age	Direction of bevel	Density	Concentration
Height	Rate of injection		Temperature
Weight			Volume
Gender			Vasoconstrictors
Intra-abdominal pressure			
Anatomic configuration of spinal column			
Position			

2.3.8 The post-dural puncture headache and backache post spinal anaesthetic

When properly conducted, spinal anaesthesia can be safely administered [83].

Postdural puncture headaches (PDPH) and backache are common but rarely significant complications of spinal anaesthesia in pregnant woman. PDPH has an incidence as high as 25% in some studies [84]. PDPH is a complication of puncture of the dura mater which typically presents hours after puncture and presents with headache and nausea that typically worsen when the patients assumes an upright posture [53].

It is thought to result from a loss of cerebrospinal fluid through the meningeal needle hole resulting in decreased buoyant support for the brain [53].

A decreased hydrostatic pressure in the subarachnoid space then leads to traction on the meninges with associated symptoms. The incidence of PDPH is less than 1% with small gauge pencil-point spinal needles. The smaller gauge results in less CSF leakage and the pencil-point spreads the collagen fibres of the dura rather than cutting them. The headache is usually mild and resolves with conservative treatment including bed rest, hydration, simple analgesia and caffeine [52 53 84 85].

Backache is a common complaint, but not a true complication, as it occurs with most caesarean sections under spinal and general anaesthesia. It is usually mild and self-limited. The aetiology of backache is not clear but may be related to position during surgery, length of surgery, needle trauma, local anaesthetic irritation and ligamentous strain secondary to muscle relaxation [52 53].

Pregnant women are at a higher risk for the development of postdural puncture headache [52 53]. The occurrence of postdural puncture headache and backache may alter the postoperative analgesic requirements.

The pain from PDPH or backache may be worse than the pain due to the surgery itself. Patients may request analgesia not for the surgical pain but for the back or headache. Factors increasing the incidence of postdural puncture headache are listed in **Table 2.2** [52 53]

Table 2.2 Factors affecting the incidence of postdural puncture headache[52 53].

Age	Younger more frequent
Gender	Females greater than males
Needle gauge	Larger greater than smaller
Needle bevel	Less when needle bevel is placed in the long axis of neuraxis
Pregnancy	Increased when pregnant
Number of Dural punctures	Increased with multiple punctures

2.4 Pain

The word pain was derived from the Latin word Poena which means "punishment"[86].Pain is defined by the International Association for the Study of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [87]. The relief of pain has been one of the primary reasons for the development of health care.

In modern anaesthetic practice the prevention of intraoperative pain continues to expand to encompass postoperative care and treatment and prevention of acute and chronic pain [32]. Despite many advances in the provision of pain services, acute pain after surgery remains a significant cause of morbidity [30 31 33 88]. Patient satisfaction is one of the most important factors in the assessment of surgical outcome [28]. Patient satisfaction is a multidimensional measure with analgesia being one of the most important determining factors [33]. Expectations for an excellent experience are high in healthy obstetric patients [35].

Pain accompanies more than 23 million surgical procedures each year but is managed inadequately in more than half of these patients [33 89]. The provision of adequate postoperative analgesia has become one of the most fundamental aspects of anaesthetic care. Inadequate postoperative pain control can have a negative impact on both the mother and infant [26 55]. Numerous deleterious effects of post-operative pain in obstetric patients have been described [90].

Pain has been experienced to some degree by everyone, regardless of age, status, or economic level. The word can evoke fear. Experience with pain can leave lasting emotional and physical impressions. The experience of pain can therefore be altered by preoperative expectation of a negative event, such as a prior experience of inadequate analgesia [91 92].

2.4.1 Definition and classification of pain

Pain has been introduced as the fifth vital sign by the Joint Commission on Health Care Organization (JCAHO) [93]. Pain is derived from the Latin word Poena which means punishment [86]. Pain is not just a sensory modality but is an experience[86]. The International Association for the Study of Pain defines pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[94]. The relief of pain has been one of the primary reasons for development of health care.

Pain is can be classified into acute, chronic, physiological, pathophysiological (nociceptive or neuropathic) or by aetiology (e.g. postoperative or cancer pain), or by the affected area. Classifications are useful in the selection of treatment modalities and drug therapy[67 95 96.]

Physiological pain describes the situation where a noxious stimulus activates peripheral receptors, which transmit the information until it reaches the brain and is recognized as harmful stimulus. This entity is often referred to as incisional pain [52 67 95 97]. Physiological pain is expected with any surgery, and the magnitude is in keeping with the degree of tissue damage [52 55 67 95].

In pathophysiological pain inflammation or nerve damage gives rise to changes in sensory processing at peripheral and central level with a resultant sensitization [52 53 55]. Stimuli, which normally do not produce pain, are perceived as painful (allodynia) and there is an exaggerated response to painful stimuli (hyperalgesia) once sensitization occurs [52 53 55]. More than 50% of patients continue to have severe pain after surgery and trauma. Evidence shows that inadequate analgesia increases the risk of postoperative complications and may lead to persistent (chronic) pain[98]. Surgery and injuries are considered to contribute to at least 25% of the burden of chronic pain[99].

2.4.2 Factors influencing the experience of pain

The response and interpretation of pain can be highly variable among persons as well as in the same person at different times[100].Physiological, psychological, social, emotional, educational, ethnic, cultural, cellular, molecular, and genetic factors, may all have an impact on the generation and perception of pain [101-103]. According to published literature, females demonstrate a lower pain threshold and lower tolerance of painful stimuli [104].

2.4.3 Acute pain and pain associated with caesarean section

Acute pain can be defined as pain that is caused by noxious stimulation due to injury, a disease process, or the abnormal function of muscle or viscera [52]. It is usually nociceptive. "Nociceptive pain" has been introduced as the term for the usual mode of pain that is generated by an injury that activates nociceptors in peripheral tissue[87]. Nociceptive pain is used to detect, localize, and limit tissue damage. Four physiological processes are involved, namely transduction, transmission, modulation, and perception. This type of pain is usually associated with a neuroendocrine stress that is proportional to intensity [52].

Acute pain includes posttraumatic, postoperative, and obstetric labour pain as well as pain associated with acute medical illness [52]. Excitatory chemical mediators of pain include substance P, calcitonin-gene-related peptide, glutamate, aspartate and adenosine triphosphate as well as other inflammatory mediators such as those listed in **Table 2.3** [52].

Neurotransmitters that inhibit the transmission of pain signals include somatostatin, acetylcholine, enkephalins, beta-endorphins, norepinephrine, adenosine, serotonin, gamma-aminobutyric acid (GABA) and glycine [52].

Table 2.3. List of inflammatory mediators [52].

Hydrogen ions	Histamine	Purines	Leukotrienes
Noradrenaline	Potassium ions	Cytokines	Nerve growth factor
Bradykinin	Prostaglandin	Serotonin	Neuropeptides

Typically acute pain is self-limited or resolves with treatment in a few days or weeks [67 95]. Two types of acute pain exist, somatic and visceral [52]. They are differentiated by origin and characteristic features [52 67 95].

Somatic pain can be further classified as superficial or deep. Superficial somatic pain is due to nociceptive input arising from skin, subcutaneous tissue, and mucous membranes. It is characteristically well localized and described as a sharp, pricking, throbbing, or burning sensation [52 67 95].Deep somatic pain arises from muscle, tendons, joints or bones. In contrast to superficial somatic pain, it usually has a dull, aching quality and is less well-localised. Both the intensity and duration of the stimulus affect the degree of localization [52].

The visceral form of acute pain is due to a disease process or abnormal function of an internal organ or its covering (parietal pleura, pericardium, or peritoneum). Four types are described, namely true localised visceral pain, localized parietal pain, referred visceral pain, and referred parietal pain[95].

Pain is conducted along three neuron pathways that transmit noxious stimuli from the periphery to the central cortex. Primary afferent neurons are located in the dorsal root ganglia, which lie in the vertebral foramina at each spinal cord level [52 67 95] .

Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates and the other into the dorsal horn of the spinal cord. In the dorsal horn, the primary afferent neuron synapses with a second order neuron whose axons cross the midline and ascend in the contralateral spinothalamic tract to reach the thalamus [52 67 95].

Second order neurons synapse in thalamic nuclei with third-order neurons, which in turn send projections through the internal capsule and corona radiata to the post central gyrus of the cerebral cortex [52].

Most nociceptors are free nerve endings that sense heat, mechanical and chemical tissue damage. Cutaneous nociceptors are present in both somatic and visceral tissues. Primary afferent neurons reach tissues by travelling along spinal somatic, sympathetic, or parasympathetic nerves. Somatic nociceptors include those in skin (cutaneous) and deep tissues (muscle, tendons, fascia, and bone). Visceral nociceptors include those in internal organs [52].

Causes of pain from a caesarean section arise from stimuli arising from the skin, subcutaneous tissue, abdominal muscles, visceral and parietal peritoneum, the uterus and bladder [105 106].

Surgery produces a biphasic insult on the human body. First of all, there is trauma to tissue, which produces noxious stimuli and great nociceptive input. Secondly, there is inflammatory process at the site, which is responsible for noxious input. Both of these processes sensitize the pain pathways [52 67 95].

Inadequate postoperative pain control in obstetric patients is postulated to have a severe impact on both the mother and infant. Delayed ambulation, impaired dietary intake, inadequate respiration, thromboembolism, ileus, atelectasis, pneumonia, depression and abnormal development of the infant due to impaired nursing activities are well postulated complications. Poorly controlled postoperative pain is thought to increase the likelihood of chronic pain [16 55 96].

2.4.4 Chronic pain and other complications of acute pain

Chronic pain is defined as pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur [96 99]. This period can vary from one to six months or even longer if the source of pain persists. Chronic pain may be nociceptive, neuropathic, or mixed [99]. Psychological mechanisms or environmental factors frequently play a major role in the development of chronic pain [99 107]. The most common forms of chronic pain include those associated with musculoskeletal disorders, chronic visceral disorders, lesions of peripheral nerves, nerve roots, or dorsal root ganglia, lesions of the central nervous system, and cancer pain [99 107]. Chronic post surgical pain is more common than realised, especially after certain types of surgery e.g. thoracotomy and mastectomy [99].

Predictive factors for developing continuing pain include preoperative pain, repeat surgery, prolonged surgery, severe postoperative pain, surgical approaches with a higher risk of nerve damage, chemotherapy, radiation therapy, and some psychological and depressive symptoms. Chronic pain after caesarean section seems to be a significant problem in at least 5.9% of patients [108].

2.4.5 Managing postoperative pain

Postoperative pain is a major medical and nursing challenge for many hospitals. Inadequate postoperative pain management is an international problem and the need to improve its management is well documented [26 29 31 100 111]. This is especially so in the South African setting, where high patient to staff ratios as well as poorly developed postoperative pain services exist. Fear of uncontrolled post surgical pain is a primary concern in many patients about to undergo surgery [112]. Postoperative pain is a potent trigger of the stress response, it activates the central nervous system, and it is thought to be an indirect cause of adverse effects on various organ systems [113] .

The quality of pain control that can be achieved is more often a function of the time and resources devoted to it, rather than the actual regimens employed [26 29 31 100 111]. A well-coordinated multidisciplinary approach will achieve the best results and 'acute pain control teams' are being established in many hospitals with this aim [26 29 31 100 111]. The use of an acute pain service, including anaesthesiologists together with specially trained nurses and physiotherapists, often has a considerable impact on pain management on the surgical wards [26 29 31 100 111].

Mandatory training programmes in postoperative pain management for all involved staff, including surgeons and ward nurses are advocated. Guidelines and protocols should be made easily accessible [26 29 31 100 111].Regular staff meetings with representatives from the acute pain service team should take place in order to evaluate the effectiveness of the pain service as well as to discuss difficulties encountered [26 29 31 100 111]. Pain management needs to become a greater priority. Shared responsibility, regular and accurate pain assessment and multimodal treatment need to be instituted to ensure improvement [26 29 31 100 111].

2.4.6 Measurement of pain

An important effect of recording of pain assessment scores is that it increases awareness of the need for analgesia which may improve quality of pain control [114-116].

Most commonly adopted methods for measuring pain involve rating scales. These include the Verbal Descriptor Scale / Verbal Rater Scale (VDS/VRS) developed by Keele in 1948 (Figure 2.1), the numeric rating scale (NRS) described by Downie et al. in 1978 (Figure 2.2), and the Visual Analogue Scale (VAS) developed by Clarke and Spear in 1964 (Figure 2.3) [94 114 117 118].

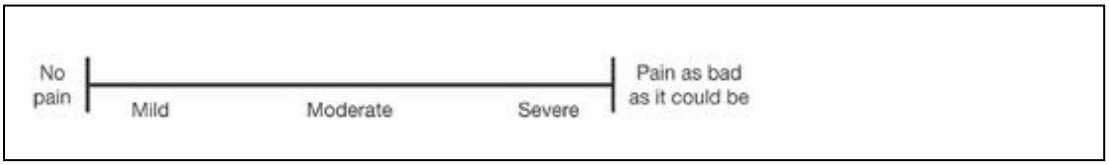

Figure 2.1. A depiction of the verbal descriptor scale[110].

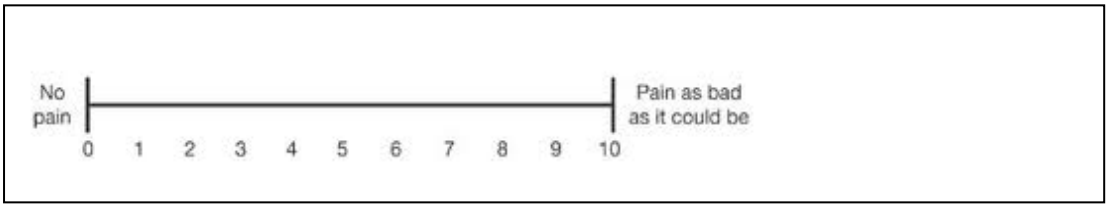

Figure 2.2. A depiction of the numeric rating scale [110].



Figure 2.3 a depiction of the visual analogue faces scale [110].

Keele devised the VDS based on three to five numerically ranked words such as ‘none’, ‘slight’, ‘mild’, ‘moderate’, and ‘severe’, for assessing responses to analgesia over a 24-hour period [114].

Twenty years later, in 1968, Melzack and Casey introduced the Present Pain Intensity (PPI) scale and the McGill Pain Questionnaire (MPQ); this was a five-point scale with an intensity range from ‘no pain’ through to ‘excruciating pain’ [114].

Unfortunately, there exists the potential for ambiguity in some of the words used. ‘Mild’ to one person may mean ‘slight’ pain to another. Severity of pain can also be confused with its frequency. For example, pain may be severe but not experienced very often. Someone may therefore describe this pain as mild [94 114 116 117 119].

Downie et al. described the NRS as either a horizontal or vertical line with ‘0’ indicating no pain, located at the bottom or one extremity and ‘10’, indicating severe pain, at the top or the other. The main advantages of the NRS are its simplicity of administration, scoring, and use, and the fact that it does not involve a need for knowledge of the English language [114].

There is no potential for ambiguity of words, as numbers are used. Its main disadvantage is its unreliability for elderly or very young patients, who may not be able to differentiate between the numbers [113]. Although the NRS does have more categories than the VDS, they are both composed of discrete categories, of which the respondent must choose only one [114].

In adults, postoperative pain is most frequently measured using a linear visual analogue scale (VAS) [115].

The VAS is a sensitive, simple, efficient, minimally intrusive, reproducible method that correlates well with other reliable methods [114 119 120].The VAS was first developed over 70 years ago by Maxwell and is possibly the most widely used assessment tool in the measurement of pain [92 114]. The scale consists of a line, usually 10cm (100mm) in length. The VAS line indicates extremes of the sensation being measured. The left side represents 'no pain' and the right side represents 'unbearable pain'. The patient is asked to mark a point on the line that indicates their current degree of sensation. Intensity of sensation is scored by measuring the millimetres from the left-hand end of the scale to the mark made by the patient, thereby obtaining a number between 0 and 100 (or 0 and 10) that represents the severity of pain [92 114 115 119 120].

Some authors have claimed that the VAS is confusing. However, it has been reported that only 7% of patients could not use it after a single explanation [114]. The VAS may be difficult to use in the postoperative period because of the effects of the anaesthetic, sedation, nausea or blurred vision. Patients with motor problems might experience difficulty in completing the scale [92 114 115 119 120]. However, this limitation was remedied by Choiniere and Amsel, in 1996, who developed a visual analogue thermometer (VAT) [114].

The later is very similar to the VAS and consists of a plasticized card with a red band which can be moved from left (no pain) to right (unbearable pain) [114].

The reliability of VAS is well documented in the literature. Many authors have feared that the sedative effects of spinal anaesthesia, especially when opioid anaesthetics have been included, may alter the patient's response to the VAS. The VAS has, however, been shown to be sensitive tool despite the sedative and stimulant effects of drugs [92 115 119 120 121].

The "faces" pain scale is another scale described. It is more useful in patients with whom communication may be difficult or when language barriers exist [117 122].

The patient is asked to point to various facial expressions ranging from a smiling face (no pain) to an extremely unhappy one that expresses the worst possible pain [117 122].

2.5 HIV/AIDS

In 2007, there were 33 million people who were living globally with HIV and 2.7 million were newly infected [125]. South African has one of the highest prevalence rates of HIV infection in the world [130]. There are an estimated 5.5 million people infected with HIV in South Africa, many of whom are unaware of their status [130]. The majority of HIV infections occur in individuals of reproductive age, and more than half of these are women [131]. More than 90% of the children infected with HIV globally were as a result of vertical mother-to-child transmission [39 40 129 133]. South African surveys place antenatal prevalence in the range of 15%–40.7%, with a national average of 29.1% [134].

2.5.1 Antiretroviral therapy

Antiretroviral therapy has been described as the greatest advancement in the treatment of HIV infection. The course of HIV disease has been drastically altered by the development of highly active anti-retroviral therapy (HAART). HAART has led to HIV/AIDS becoming more of a chronic disease state rather than a progressive terminal illness [137].

Drugs for treatment of HIV infection are classified into several classes according to the mechanisms of inhibition of viral replication. The four classes most commonly used are reverse transcriptase enzyme inhibitors, protease enzyme inhibitors, integrase inhibitors and entry inhibitors [95 125 137].

Drug interactions commonly occur due to the polypharmacy that exists in the treatment of HIV-positive patients. Drug interactions include effects on the efficacy, toxicity, absorption, distribution, metabolism and elimination of drugs. HAART may also cause renal and hepatic dysfunction [125] [137].

Altered pharmacokinetics is a more complicated interaction, and is mostly mediated through inhibition or induction of hepatic liver enzyme, particularly CYP450 (CYP) 3A4 enzyme. Protease inhibitors (PIs) (e.g. Saquinavir, Ritonavir, Indinavir, and Lopinavir) and NRTI's (e.g. Zidovudine, Lamivudine, and Tenofovir) are the most implicated in drug interactions. It is postulated that these drugs may reduces fentanyl clearance and therefore prolong its clinical effects as well as side-effects [125] [137]. Drug interactions, and altered pharmacodynamics and pharmacokinetics may alter the duration of analgesia obtained from spinal anaesthesia.

2.5.2 HIV/AIDS and the nervous system

The central and peripheral nervous systems are frequently affected by HIV/AIDS [140].

The presence of neurological manifestations, such as overt dementia, may impair the ability of the patient to provide preoperative consent and may increase brain sensitivity to sedative or psychoactive drugs (opioids, benzodiazepines, and neuroleptics).

Opportunistic infections may be associated with increased intracranial pressure. Increased intracranial pressure and central nervous system infections (meningitis, encephalopathy, or myelopathy) are contraindications to neuraxial anaesthesia. 30% of adults and 50% of children suffering from AIDS will develop neurological disorders [141] [142].

Neurologic involvement may be due to the virus itself such as direct infection, inflammation, demyelination or degenerative process [141 142].

The diagnostic approach to patients with HIV infection and neuropathy, myopathy or other neurological deficit consists of taking a comprehensive neurological history and physical examination.

Opportunistic infections and neoplasms of the nervous system, secondary to immune deficiency, also occur. Every structure within the nervous system may be affected, including the meninges, brain, spinal cord, peripheral nerve and muscle [142 144].

In the early stage of infection, headaches, photophobia, meningoencephalitis, depression, irritability, Guillain-Barre-like syndromes, or cranial and peripheral neuropathies can be observed. The latent phase of the disease is associated with demyelinating neuropathy and vertebral fluid pathology [140 142 143].

The late period of HIV infection is associated with meningitis, focal or diffuse encephalopathy, myelopathy, myopathy, and peripheral neuropathy [140 142 143].

HIV-associated neurocognitive impairment (HNCI) is a spectrum of disorders with the most severe impairment considered as AIDS dementia complex or HIV encephalopathy. Autonomic neuropathy has also been described in HIV-infected individuals. New onset of seizures can also occur and can progress to status epilepticus [140 142 143].

A thorough evaluation of the nervous system should be conducted before performing neuraxial blockade. Patients with AIDS may be more sensitive to opioids and benzodiazepines as a result of the neurological involvement [140 142 143].

HIV infection, intracranial masses, or opportunistic infections may cause cerebral oedema, cerebral haemodynamic disturbances, and increased intracranial pressure. Peripheral neuropathy is the most frequent neurological complication in HIV patients. It affects approximately 35% of patients with AIDS and manifests clinically as polyneuropathy and myopathy [144 145 147].

Regional anaesthesia has been shown to be associated with reduced morbidity and mortality in a wide range of patients, including HIV positive parturients having caesarean section under spinal anaesthesia [51]. Regional anaesthesia has the advantage of not interfering with the immune system or with antiretroviral drugs. Relative contraindications to regional anaesthesia in these patients include sepsis and bleeding tendencies. The presence of neuropathy may reduce the appeal of regional anaesthesia but there is no data to contradict its use [51]. Articles concerning the effect of spinal anaesthesia in 45 HIV treated patients under caesarean section showed no perioperative complications or changes in immune function or viral load [51 145].

HIV infection causes autonomic neuropathy which may accentuate haemodynamic instability caused by spinal anaesthesia. This may be a concern in patients with advanced HIV infection [95].

Involvement of neurological system may alter the duration of analgesia obtained from spinal anaesthesia.

2.5.3 HIV/AIDS and pain

Visceral, somatic and neuropathic pain are common and debilitating symptoms of HIV disease and are present in approximately 30-62% of HIV patients [18-20].

Pain in HIV can be classified into pain due to the disease itself, as a side-effect of treatment or, unrelated to the disease or its treatment [19]. People with HIV disease often have pain arising from various stimuli occurring concurrently and the pain has profound affect on their quality of life [18 20 34]. Depression, which is frequently present in HIV-positive individuals, is associated with increased postoperative pain [18].

Pain experienced by HIV- positive patients includes chest pain, oral cavity pain, headache, peripheral neuropathic pain, abdominal pain, anorectal pain, and musculoskeletal pain [18 20]. Pain is associated with significant psychological and functional impairment. Individuals with pain have significantly more depressive symptoms, psychological distress, and feel more hopeless than those without pain [18]. Prolonged insult to the body produces changes in the nervous system which alter the normal physiological response to a noxious stimulus [146]. Peripheral neuropathy is one of the most frequent neurological complications of HIV [147]. Distal symmetrical polyneuropathy (where the most common pathology is distal axonopathy) is the most common form of peripheral neuropathy in patients with AIDS [147].

Several mechanisms have been proposed, including direct infection by HIV, and cytokine or inflammatory-mediated neurotoxic effects. Forms of neuropathy other than distal polyneuropathy are mononeuropathy multiplex, inflammatory demyelinating polyneuropathy, progressive polyradiculopathy, autonomic neuropathy and monoradiculopathy [147].

In chapter 2 we have reviewed the current literature and discussed topics pertinent to this research project. This has included discussions pertaining to caesarean sections, spinal anaesthesia, HIV/AIDS and pain mechanisms and measurement.

CHAPTER 3 – METHODOLOGY

This chapter will provide an in-depth description of the methodology used for the study.

3.1 Study design

This study was a prospective, randomised, double-blinded, quantitative, observational study.

Prospective: The patients were followed forward in time until the required data was collected.

Randomised: individuals at the beginning of the study were randomly allocated to one of two drug treatment groups according to the order in which they were entered on a computer generated list.

Double-blinded: The researcher, as well as the anaesthetist administering the spinal anaesthetic, were unaware of the patients' HIV status or the drug treatment that the patient was given.

Quantitative: The study determined the relationship between one independent variable and another dependent variable.

Observational: The data was collected without any intention of intervening in any aspect of the management of the participants.

This study design was chosen because a double-blinded randomised data collection has been recognised to be a robust method, providing a reliable means with which to conduct scientific research.

The study design chosen would provide an appropriate means to determine the duration of analgesia obtained from spinal anaesthesia, utilising different drug treatments in caesarean section patients at CHBH, and would enable a comparison of durations of analgesia achieved in HIV- positive and HIV- negative individuals.

3.2 Study Site

The study was conducted in the obstetric theatre and post-caesarean section ward in the maternity wing of CHBH, in Soweto, Johannesburg. CHBH is a 2800-bed tertiary public hospital, which services a population in the low-income bracket. There are about 1800-2000 deliveries and approximately 550-650 caesarean sections performed monthly at CHBH[15]. Even though CHBH is a tertiary referral hospital, not all women delivering at CHBH require tertiary-level care.

3.3 Study population

The study population consisted of women aged between 18 and 45 years, presenting for elective caesarean section, who use government-provided health services at CHBH.

Elective caesarean sections at CHBH are usually performed for patients, who have been identified at the antenatal clinic, where either the mother or foetus is at high risk of complications related to vaginal delivery, or augmentation of labour. This includes patients who have undergone previous caesarean sections where trial of labour is not possible, twin pregnancies, abnormal foetal lies, foetal abnormalities and obstructed birth passages e.g. severe vaginal papilloma virus infections. HIV infection is currently not an indication for elective caesarean section.

3.4 Study period

The data collection was done over a period of 6 months from June to December 2008, with the majority of data collected in November 2008.

3.5 Ethical considerations

The study was approved by the regional Ethics Committee – the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand (Appendix A).

The study was approved by the Post-Graduate Committee of the University of the Witwatersrand, Faculty of Health Sciences (Appendix B).

Permission to complete this research project, collect data from patients' files and to interview patients was granted by the Clinical Director of CHBH (Appendix C).

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki [25].

3.6 Definitions

The following definitions were used in this study:

Elective caesarean section: A caesarean section that is performed on a pregnant woman on the basis of an obstetrical/medical indication or the request of the patient. The elective caesarean section is usually a "planned caesarean section" and usually performed prior to labour [132].

HIV- positive patient: A patient that has tested positive for HIV using a rapid HIV test and confirmed using an HIV ELISA test.

Time to analgesic requirement: time (measured in minutes) from administration of spinal anaesthetic until request of subsequent analgesia, to relieve surgically associated pain, postoperatively.

Ethnicity was defined as an affiliation resulting from racial or cultural ties. Patients were presented with four options (Zulu, Sotho, Xhosa or Other) and asked to choose the most applicable option available.

3.7 Sample population and sampling method

In consultation with a statistician, it was decided that a minimum of 56 HIV-positive and 56 HIV-negative patients would be required to determine if a statistically significant difference in duration of analgesia existed between the HIV-positive and negative individuals. The sample size was calculated assuming a true difference of 20 minutes existed between these patients, with a standard deviation of 35 and a power of 85%, with the significance level set at $p < 0.05$. 30 patients in each of the four would be required to achieve a power of 100% with standard deviation of 35 and alpha value of 0.05 when analysed by an ANOVA 1- way test (assuming a normal distribution). Patient study groups are demonstrated below in **Figure 3.1.** and consisted of HIV-positive bupivacaine (HPB), HIV-positive bupivacaine and fentanyl (HPBF), HIV-negative bupivacaine (HNB) and HIV-negative bupivacaine and fentanyl (HNBF)

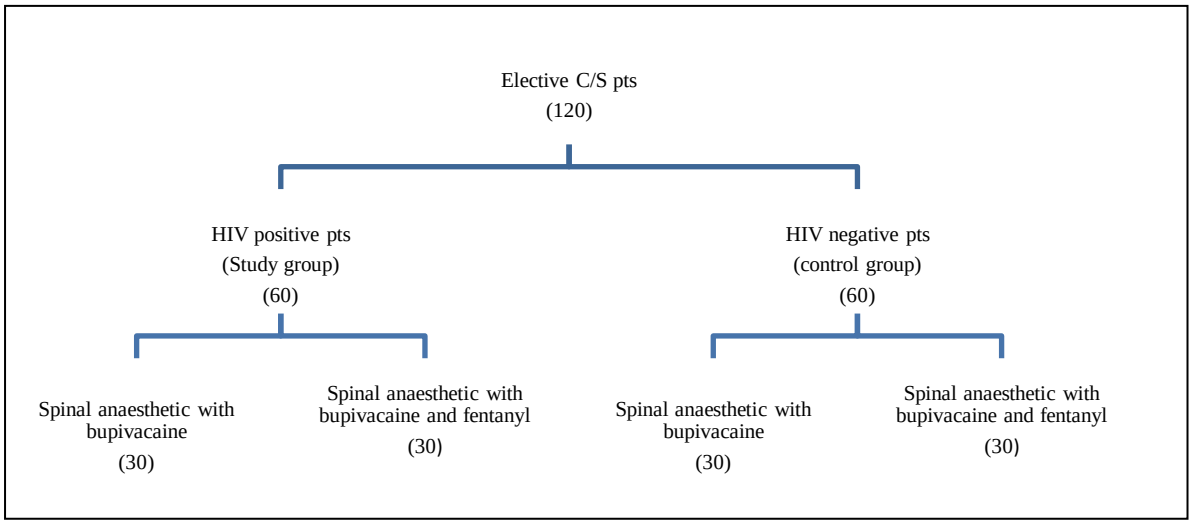

Figure 3.1 Diagram illustrating study groups.

Consecutive convenience sampling was used. The hospital runs two obstetric theatres for elective and emergency caesarean sections.

A daily list of all elective caesarean section that were scheduled for surgery was compiled. These patients were approached in the antenatal admissions ward for inclusion in the study. The selection process stopped once 120 patients with 30 patients in each study groups had been recruited.

3.8 Inclusion criteria

ASA I and II elective patients who had been identified as needing elective caesarean sections under spinal anaesthesia for delivery were approached for inclusion in the study.

3.9 Exclusion criteria

The following patients were excluded from the study:

3.9.1 Patients who were deemed to need emergency surgery.

3.9.2 Patients who did not obtain an adequate anaesthetic block for surgery. Patients who required additional analgesia or sedation intra-operatively.

3.9.3 Patients younger than 18 years or otherwise unable to give informed consent

3.9.4 Patients with contraindications pertaining to spinal anaesthesia.

3.9.5 Patients whose HIV status was not available from their records or who had not been tested for HIV during their pregnancy.

3.9.6 ASA III and IV patients. (According to the American Society of Anaesthetists classification ASA III and IV patients are patients with a systemic disease that results in moderate to severe functional impairment or a disease which is an immediate threat to the patient's life) [52 55].

3.10 Data collection

Patients were invited to participate in the study. Patients received a printed document (Appendix D) explaining the reason for the study, exactly what their involvement in the study would be, their right to refuse to participate without repercussions to their care, and their right to withdraw from the study at any time. A 24-hour contact number was supplied should they have required further information. The printed information was provided in English.

The researcher and a translator (anaesthetic nursing assistant) provided verbal information in a language that the patient could understand if they could not understand English, or were not able to read the document. Patients were requested to sign a consent document (Appendix E).

Data was then collected from the patients' antenatal and hospital records and entered onto the data sheet (Appendix D). HIV status, CD4 count and whether the patient was receiving antiretroviral therapy was recorded separately by a research assistant or anaesthetic intern. If no assistant was available this information was collected after completion of the study.

Patients' names and hospital numbers were kept separate to the data collection sheets, and were encoded by a numerical code system. The code was only known to the investigator. All information that would link patient identity to the trial results remained separate and confidential. A list of syringe codes, and patients details were kept locked away for the duration of the study, and remain available only to the researcher.

Patients were allowed to withdraw their participation at any time, and at no time was a patient coerced into participation.

3.10.1 Patient Information:

Data capture was managed by entering values onto a separate page for each patient, as well as onto a spreadsheet. The details of the collected data are as follows:

3.10.1.1 Height

The patients' heights were measured by the researcher using a measuring tape. Patients were asked to stand against a wall with their feet together and measurements were then taken. The patients heights were measured in centimetres and the patients were grouped into three categories:

i. 140-150 cm

ii. 151-160 cm

iii. more than or equal to 161 cm

These categories were chosen as most average female patient's heights at CHBH range between and 140-170 cm. The 10 cm groupings were chosen to simplify the height comparisons.

3.10.1.2 Weight

The patients' weights were measured in kilograms. Weights were taken from the antenatal green card from the most recent antenatal visit.

If no weight was available, or if weights available were taken more than two weeks prior to surgery, patients were weighed by the researcher using a calibrated ward scale.

3.10.1.3 Age

The age of the patient was recorded in years.

3.10.1.4 Ethnicity

Ethnicity was defined as an affiliation resulting from racial or cultural ties. The patients' ethnicities were recorded as one of the four following categories:

3.10.1.4.1 Zulu

3.10.1.4.2 Sotho

3.10.1.4.3 Xhosa

3.10.1.4.4 Other

Patients were presented with the above four options and asked to choose the most applicable option available. These categories were chosen because they represented the most common ethnic groups of patients attending CHBH as reported during the patient interviews.

3.10.1.5 Education

The patients' levels of education were ascertained. These groups were chosen to reflect the educational system as it exists in South Africa. The patients were grouped as:

3.10.1.5.1 Primary (patients completed primary school but not matriculated)

3.10.1.5.2 Secondary (patients who had matriculated)

3.10.1.5.3 Tertiary (patients who had completed a post- matriculation course, diploma or degree)

3.10.1.6 HIV status (positive or negative as confirmed by an ELISA test result)

3.10.1.7 CD 4 count

The CD 4 count result was recorded as the most recently available result in the patients' records. Patients were grouped as those having CD 4 counts of:

3.10.1.7.1 More than and equal to 250 cells/µl

3.10.1.7.2 Less than 250 cells/µl

3.10.1.7.3 None available

Although AIDS is defined as CD 4 count less than 200, these groups were chosen because of the South African HAART initiation guidelines, which start HAART in patients with CD 4 counts of 250 or less [150].

3.10.1.8 Whether the patient was taking antiretroviral therapy (yes or no)

Patients were considered to be taking antiretroviral therapy if they were taking HAART therapy or taking antiretroviral therapy to prevent mother- to- child transmission (PMTCT) but did not include those who had obtained only a single dose of nevirapine preoperatively.

3.10.2 Procedure in the operating theatre

When the patient presented to theatre for surgery intrathecal drugs were be administered in a double-blinded fashion utilising pre-mixed coded syringes and a standardised spinal technique was utilised. Spinal anaesthetics were administered by, or were overseen by the researcher. The content of the syringes was drawn up according to a computer-generated random sequence list. The researcher had no knowledge of the content of the syringe. A separate log book was kept containing information regarding the patient's HIV status, CD 4 count, ARVs and syringe contents.

The spinal anaesthetic was performed with the patient in a seated position at the level of the L4/L5 interspace.

An aseptic technique was utilised. 2ml of 2% lignocaine was infiltrated subcutaneously. A 25-gauge pencil point needle was employed. CSF was freely aspirated and the contents of the syringe injected.

Two spinal anaesthetic options available were:

Option 1:

2ml 0,5% heavy bupivacaine and 0,4ml saline

Option 2:

2ml 0,5% heavy bupivacaine and 0,4 ml fentanyl (20ug)

The starting time of the anaesthetic was measured from the time of injection of the syringe contents. Time of administration of anaesthetic was noted on the patient data collection sheet and patients were monitored, using the visual analogue, at 30-minute intervals from the time of administration of the spinal anaesthetic.

A visual analogue and faces scale, as shown in **Figure 3.2**, was administered by the researcher to determine post-operative pain scores.

Patients were monitored postoperatively in both the recovery room and post-surgical care ward. Analgesia was given to all patients who requested analgesia.

Postoperative analgesia was prescribed according to the specific ward protocol and generally consisted of Omnopon® 20mg intramuscularly and paracetamol 1g orally.

When analgesia was requested by the patients, ward nursing staff were informed by the researcher, who requested that analgesia be given according to ward protocol.

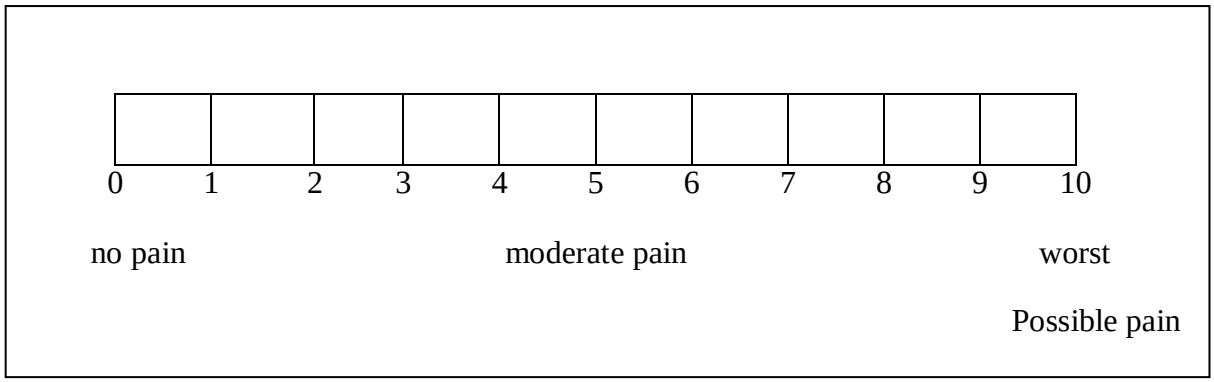

Figure 3.2. Example of the visual analogue scale utilised [22-28].

3.11 Data analysis

The data collected was entered on to a Microsoft Excel ® spreadsheet and submitted for statistical interpretation using the Statistica ® version 8.0 computer programme. The Shapiro Wilk test was used to test for normality of distribution of the data. The data was found to follow a non-normal distribution. We had planned beforehand to analyse the data using student t-test and ANOVA test (assuming a normal distribution), but because the data followed a non-normal distribution we chose to analyse data utilising the Mann Whitney U and/or Kruskal Wallis test, depending on the number of variables to be compared. Median, minimum, and maximum values, standard deviation and 95 % confidence intervals were determined for the study variables.

CHAPTER 4 – RESULTS

In chapter four the results of the study will be discussed.

The data collected was entered on to a Microsoft Excel ® spreadsheet and submitted for statistical interpretation using the Statistica ® version 8.0 computer programme. Median, minimum, maximum values, standard deviation and 95% confidence intervals were determined for the various study variables. The data followed a non-normal distribution as assessed by Shapiro-Wilk test and therefore, the data was analysed using either the Mann-Whitney U-test or Kruskal Wallis test depending on the number of variables compared.

4.1 Sample, patient refusal and exclusion

A total of 134 patients were approached for possible inclusion in the study. Two patients did not give consent because of concerns with confidentiality and fears of victimisation. Eight patients were excluded from participating in the study due to unknown HIV status, inadequate sensory level blockade, conversion to general anaesthesia, or the need for additional intraoperative analgesia or sedation.

The study consisted of a total of 124 patients. Patients were grouped into 1 of 4 groups. The groups were as follows:

- Group 1: HIV-positive bupivacaine (HPB) [30 patients]
- Group 2: HIV-positive bupivacaine and fentanyl (HPBF) [30 patients]
- Group 3: HIV-negative bupivacaine (HNB) [30 patients]
- Group 4: HIV-negative bupivacaine and fentanyl (HNBF) [34 patients]

4.2 Results related to the primary objective

4.2.1 HIV infection and the duration of analgesia

The median duration of analgesia for all HIV- positive patients (HPB + HPBF) was 135 minutes. The median duration of analgesia for all HIV- negative patients (HNB +HNBF) was 138 minutes. These results when analysed utilising a Mann-Whitney U test show no significant difference (p-value 0.75). Median, minimum (Min), and maximum (Max) values as well as standard deviation (SD) and 95% confidence intervals (95% CI) for this data are represented in **Table 4.1** and **Figure 4.1.**

4.2.2 Contents of syringe and duration of analgesia

The duration of analgesia was significantly longer when fentanyl was added to the bupivacaine, (p-value 0.00) however; there were no statistical differences in the duration of analgesia when considering HIV status. (p-value 0.75)

The median duration of analgesia for all patients who received bupivacaine (HNB + HPB) was 120 minutes. The median duration of analgesia for all patients who received bupivacaine and fentanyl (HNBF + HPBF) was 155 minutes.

Median, minimum (Min), and maximum (Max) values as well as standard deviation (SD) and 95% confidence intervals (95% CI) for this data are represented in **Table 4.2** and **Figure 4.2.**

4.3 Results relating to the secondary objectives

Median, minimum (Min), and maximum (Max) values as well as standard deviation (SD) and 95% confidence intervals (95% CI) and p-values for all secondary objectives are represented in **Table 4.3**

It was found that CD 4 count (p-value 0.61), Antiretroviral therapy (p-value 0.29), Height (p-value 0.20), Ethnicity (p-value 0.30) and Education (p-value 0.44) have no significant effect on duration of analgesia.

Table 4.1 Results pertaining to HIV status

Variable	Median (min)	Min(min)	Max (min)	SD	95% CI
HIV-positive	135	55	255	41	35-50
HIV-negative	138	65	280	43	37-52

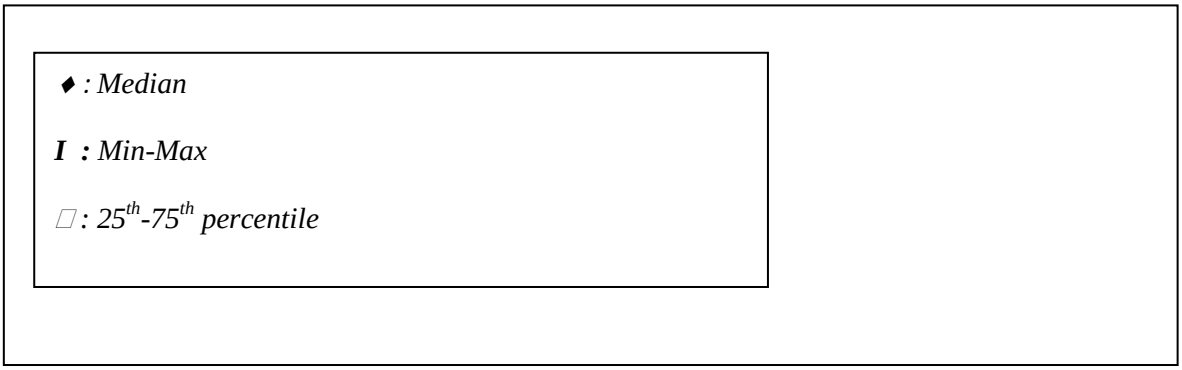

Figure 4.1: Key guide used to describe the box-plot graphs depicted in this chapter.

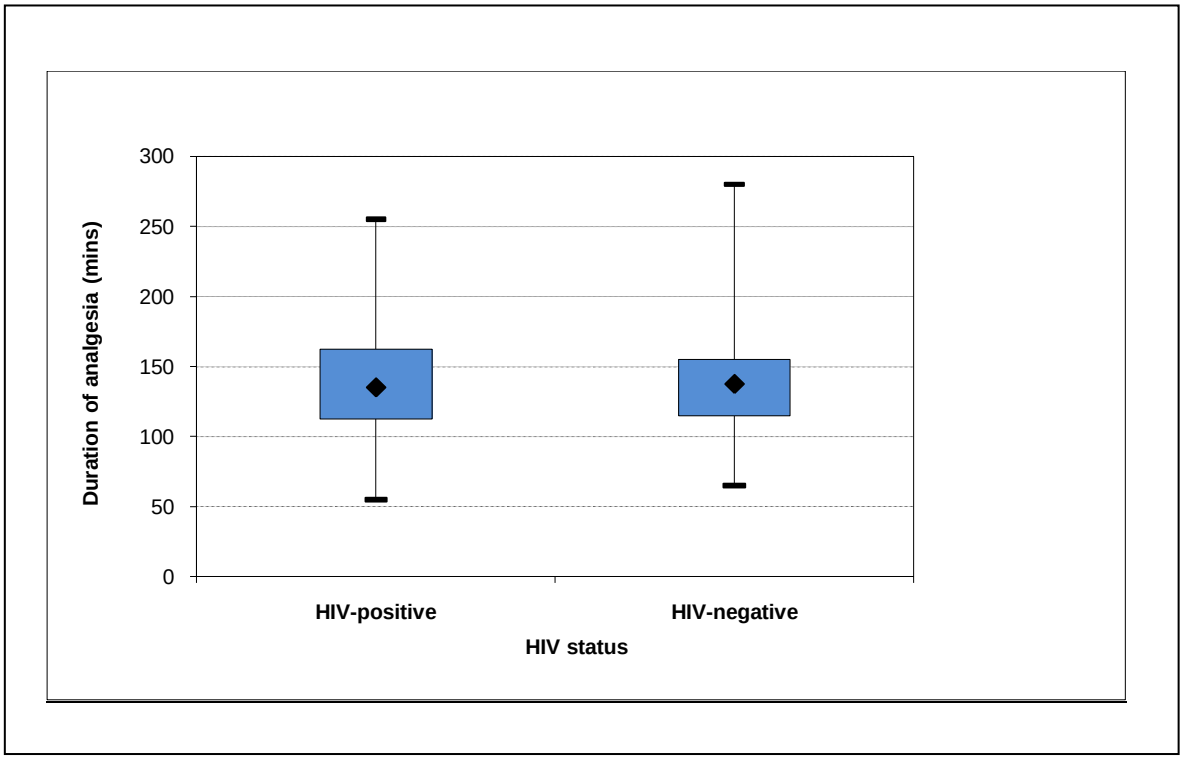

Figure 4.2. Boxplot graph depicting the duration of analgesia in HIV- positive and negative patients

Table 4.2. The duration of analgesia in patients who received bupivacaine and fentanyl comparing HIV status

Variable	Median (min)	Min (min)	Max (min)	SD	95% CI
HPB	118	55	200	26	21-35
HPBF	160	80	255	37	29-49
HNB	120	65	140	20	16-27
HNBF	155	105	280	43	35-56

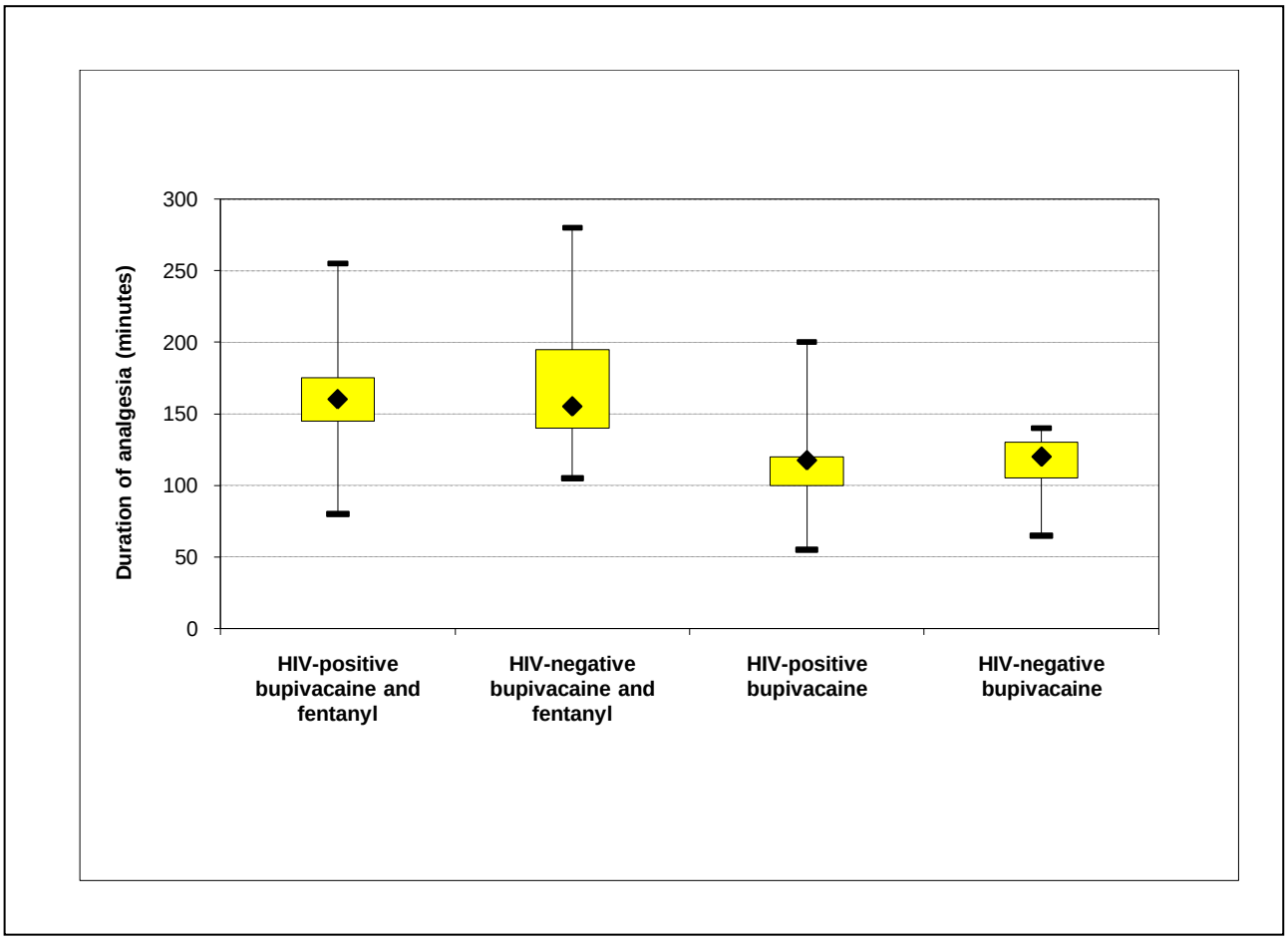

Figure 4.3. Boxplot graph depicting the duration of analgesia in HIV- positive and negative patients according to syringe content

Table 4.3 Table representing the result for secondary objectives studied

Variable	Subgroup	Median (min)	Min (min)	Max (min)	SD	95% CI
CD 4 count	>250	145	75	255	45	36-60
	<250	130	55	220	39	30-57
ARV	yes	145	55	255	45	36-61
	no	120	80	225	38	31-51
Height	140-150	210	150	255	50	28-185
	151-160	140	65	235	40	34-48
	>160	130	55	280	41	34-52
Education	Primary	130	65	280	44	37-53
	Secondary	140	55	260	42	35-53
	Tertiary	138	90	235	39	28-62
Ethnicity	Zulu	130	75	280	45	38-58
	Xhosa	125	80	230	37	27-57
	Sotho	150	55	260	48	38-65
	Other	140	65	235	34	27-44

4.4 Summary of results

In this chapter the results of the study were discussed. The primary objective (HIV status) had no significant effect on duration of analgesia. The addition of fentanyl to the intrathecal injection did cause significant prolongation of the duration of analgesia. The secondary objectives (CD4 count, antiretroviral therapy, height, and ethnicity) had no significant effect on the duration of analgesia obtained from intrathecal injection.

CHAPTER 5 – DISCUSSION

Chapter five will include a discussion of the study in terms of potential limitations of the study, implications for clinical practice and further research. Chapter five will also include an interpretation of the results of the study, and a discussion of the issues raised by the results. In the previous chapter the results of the study were discussed. The null hypothesis was accepted as HIV status was found to have no significant effect on duration of analgesia. The addition of fentanyl to the intrathecal injection did cause significant prolongation of the duration of analgesia. The secondary objectives (CD4 count, antiretroviral therapy, height, and ethnicity) had no significant effect on the duration of analgesia obtained from intrathecal injection

5.1 Discussion of results pertaining to the primary outcome

Current literature states that the addition of fentanyl prolongs the duration of analgesia obtained from intrathecal injection. In the literature the duration of analgesia, obtained from intrathecal injection, is estimated to be 90 to 190 minutes for intrathecal bupivacaine alone and up to 184 (+/- 20) minutes for intrathecal fentanyl and bupivacaine [1-13].

The data collected from this study reflected what has already been described in the literature.

The data collected did not follow a normal distribution curve. This may have been due to an inadequate sample size. The non-normal distribution seen may also be a reflection of the many factors that impact upon interpretation of pain and individual need for analgesia. These factors could not be controlled for.

The results of the study showed that HIV infection did not cause a significant alteration in duration of analgesia, which may be due to an incorrect sample size, or because of incorrect patient selection. The study was designed to determine whether HIV infection altered the duration of analgesia obtained from spinal anaesthesia, assuming a 20 minute true difference existed between HIV-positive and HIV-negative patients.. It was thought that these patients were likely to have neuropathies, pain syndromes or alterations in drug metabolism due to drug interactions. It is possible that a study focussing on patients with known premorbid neurological pathology would have yielded different results. For the purposes of this study, the group of HIV-positive patients were heterogeneous. Investigation into different subgroups within the HIV-positive groups may yield more information in the future.

5.2 Discussion of results pertaining to the secondary outcomes

The sample size was calculated to determine statistical significance with only the primary objective in mind. We did not take secondary objectives into account and therefore the study is not powered to be able to make any definitive statements regarding the secondary objectives and their effect on the duration of analgesia.

5.2.1 Antiretroviral therapy

The study was not designed sufficiently so that syringe contents would be randomised in patients on HAART .Two-thirds of patients taking antiretrovirals received bupivacaine and fentanyl and thus results could be confounded by the addition of fentanyl.

Patients categorised as receiving anti-retroviral drugs included those receiving HAART therapy as well as those that had received antiretroviral therapy as part of therapy to prevention-of-mother-to-child-transmission (PMTCT).

This was an error and in the future studies it would be necessary to separate out the PMTCT group from the long-term HAART patients. The study should have specified which drug regimens patients were on and which specific agents they were receiving as it is predominantly the protease inhibitors and NRTI's that interfere with the clearance of fentanyl and the NNRTI's that have been implicated in the development of neuropathies [55]. Further study is needed in order to determine the effect of HAART therapy on the duration of analgesia.

5.2.2 CD4 count

Majority of patients who had CD4 counts less than 250 were taking antiretroviral therapy. It is difficult to discern if the trend observed was due to low CD 4 counts or due to confounders such as HAART, drug interaction, presence of opportunistic infections or accelerated metabolism of bupivacaine and fentanyl. Further study is needed to define whether or not AIDS and/or HAART shorten the duration of analgesia obtained from intrathecal injection.

The study was not originally designed to specifically test the effect of CD 4 count on the duration of analgesia. Forty six percent of patients in the study, who tested positive, did not have CD 4 counts available. This led to difficulties in assessing the effect of low CD4 counts on duration of analgesia. Although not related to the study, this indicates failure, and a missed opportunity, to follow up and refer positive HIV patients at antenatal clinics to specialised HIV clinic.

It would have been interesting to have collected data pertaining to whether these patients who tested positive were attending peripheral antenatal clinics or were patients attending the CHBH antenatal clinic; and also when these patients presented for the first time to antenatal clinic and whether or not they presented late and if that was the reason for the missed opportunity.

A large number of patients in the CD 4 group greater than 250 cells/µl received fentanyl and thus the longer durations of analgesia may be a reflection of the effect of fentanyl in prolonging the duration of analgesia rather than the effect of the CD4 count.

5.2.3 Height

Current literature states that height affects the level of spinal anaesthesia achieved. It is surmised that shorter people who received the same volume as taller patients would obtain higher levels. With a higher level one would expect a longer duration of analgesia due to time taken for block regression. All of the patients in this study were assessed to have a sensory block height of T4-T6.

The results obtained from our study are interesting in that there is no statistically significant difference between our three height groups even though the data would at first glance appear to be different.

This may be due to an inadequate sample size but may be also be due to incorrect categorisation of heights or the results may have been confounded by an unequal number of patients who received fentanyl in the three groups. There may also be a number of other confounding variables which we are not aware of and have not taken into account. Further study is necessary to determine if height has a statistically significant effect on the duration of analgesia.

5.2.4 Ethnicity and education

This study was not adequately powered to determine whether ethnicity and education do in fact have no significant effect on the duration of analgesia achieved with spinal anaesthesia. The results reflect that perhaps the role of culture in the assessment of pain is not as significant as it is thought to be but further study with a larger sample size is needed to definitively prove or disprove this.

It is possible that the different South African ethnic groups may have similar influences on their experience of pain, being that they are from similar geographical areas, and that it may be interesting to repeat the study looking at more culturally diverse groups.

5.3. Potential limitations of the study

5.3.1. Study period

Data was collected by convenience sampling. Practically the majority of data was collected consecutively throughout November, but the first few cases were accessed more sporadically. This method of sampling is not as robust as other methods, which necessarily introduces a potential for selection bias.

5.3.2 Frequent delays of elective patients

There are two Obstetric theatres available at CHBH. Emergency caesarean sections take precedence over elective cases. Patients are frequently repeatedly delayed and postponed. These patients also experience prolonged episodes of unnecessary starvation preoperatively. Anxiety is thought to decrease pain sensitivity, decrease discriminability between sensation and pain and increase the response in reporting pain [84]

This repeated cancellation and delay may have led to increased patient anxiety, which may affect the results obtained. However, this should have affected both groups equally but may have been a confounding variable, as we did not record or take into account how long patients waited before coming to theatre, the number of times that the patients were cancelled or postponed and for how many hours the patients where needlessly starved preoperatively.

5.3.3 Accuracy of anatomical landmarks

Spinal anaesthetics were given at what was clinically assessed to be the L4/L5 interspace. The level of injection may have varied between patients due to errors in clinical examination, anatomical and physical variations amongst patients. This is a worldwide, recognised inaccuracy. Kooger et al. have postulated that a higher level of injection may lead to a shorter duration of anaesthesia due to increased elimination of local anaesthesia from the subarachnoid space due to an increased surface area available for diffusion and vascular absorption of the drugs [148].

Karim et al. have however shown that injection at L2/L3, L3/L4 or L4/L5 did not significantly alter the overall analgesia achieved, but resulted in a significantly faster onset of analgesia [149]. An attempt was made to minimise this effect by having the researcher witness or perform each spinal injection.

5.3.4 Surgeon variations

caesarean sections were performed using a standardised lower segment uterine incision via Pfannenstiel skin incision, but were performed by a multitude of different surgeons with differing levels of experience, which resulted in different surgical durations, different techniques involving exteriorisation of the uterus and differing amounts of blood loss.

By limiting the duration of data collection to a single obstetric specialist trainee rotation, we were able to limit the number of surgeons who performed the caesarean sections.

5.3.5 Contextuality

This study was done in the context of patients presenting for elective caesarean section at (CHBH). CHBH is a tertiary institute that serves the Soweto area but is also a referral hospital for hospitals in the North West province as well as hospitals in the greater Johannesburg and Alberton areas.

Many difficulties are experienced with the referral system from other level 1 and 2 institutes and patients, sometimes even from other provinces, may present to the hospital without appropriate referral. Elective patients are, however, carefully selected and usually followed up at the hospital's antenatal clinic which may limit this influence. Generalisation to other populations may be limited.

5.3.6 Accuracy of data collected

A large amount of data was collected from the patients' antenatal cards and files. There are inherent problems with the retrospective nature of data collection. The accuracy of data entered in these records often relies on the individual completing the records. Weights and CD4 counts recorded were those most recently entered in the records and may not have accurately reflected the actual weights and CD4 counts at the time of caesarean section.

5.4 Discussion with regards to the power of this study

The sample size was originally calculated assuming that a difference of 20 minutes existed between these patients, with a standard deviation of 35 and a power of 85%, with the significance level set at $p < 0.05$. Once the study was completed it was found that only a 3 minute difference existed between these groups and that this difference was found to be statistically insignificant. The power of the study was recalculated assuming a 3 minute difference and was determined to be only 6.74 %. Repeated calculations were done and it was determined that to be able to prove that a statistically significant difference in duration of analgesia between HIV positive and HIV negative patients exists (assuming a difference of 3 minutes with a 80% power and standard deviation of 42) we would have needed 3078 patients. However, if such a larger sample size is needed then perhaps HIV status may not have an effect. Therefore, if the difference of 3 minutes had been a clinically relevant time period, this study would have been underpowered. This study was adequately powered to determine whether a difference of 20 minutes existed, which is a much more useful and clinically relevant time period.

5.5 Discussion with regards to the distribution and statistical tests used to analyse the data

The data collected was analysed by a Shapiro Wilk test and was found to have a non-normal distribution. It was therefore decided to analyse the data utilising non-parametric test, namely the Kruskal Wallis test and Mann Whitney U test depending on the number of variables to be compared.

5.5.1 Discussion with regards to non-normality of data

There are six frequently quoted reasons for non-normality of data which may pertain to the data collection for this research[151]:

5.5.1.1 Extreme Values

Too many extreme values in a data set will result in a skewed distribution. Normality of data can be achieved by cleaning the data. This involves determining measurement errors, data-entry errors and outliers, and removing them from the data for valid reasons[151]. The severity of pain need for analgesia is such a subjective individual concept that this may have resulted in outliers which if removed may have resulted in a normal distribution.

5.5.1.2 Overlap of Two or More Processes

Data may not be normally distributed because it actually comes from more than one process, operator or shift, or from a process that frequently shifts[151]. This may have occurred during our study due to the convenience sampling.

5.5.1.3 Insufficient Data Discrimination

Round-off errors or measurement devices with poor resolution can make truly continuous and normally distributed data look discrete and not normal[151]. This may have occurred due to inherent problems with the visual analogue scale but also because patients were not continuously monitored postoperatively but were followed up 5 to 15 minute intervals.

5.5.1.4 Values Close to Zero or a Natural Limit

If a process has many values close to zero or a natural limit, the data distribution will skew to the right or left[151].

This may be the case in our research project as the drugs used in spinal anaesthetics have specified durations of onset, effect, and half-lives even those these values may be affected by individual physiological parameters such as drug sensitivity, number of receptors available, metabolism and excretion.

5.5.1.5 Data Follows a Different Distribution

There are many data types that follow a non-normal distribution by nature. Examples include log-normal distribution, found with length data such as heights. The data that was collected for this study was of this nature.

5.5.2 Discussion pertaining to the tests used.

The Mann-Whitney U test is the alternative test to the t-test. The Mann-Whitney U test is a non-parametric test that is used to compare two population means that come from the same population. Mann-Whitney U test is also used to test whether two population means are equal or not. [152-156]. The Mann-Whitney U test is a non parametric test; hence it does not assume any assumptions related to the distribution. There are, however, some assumptions that are assumed in Mann-Whitney U test [152-156].

The following are the assumptions for Mann-Whitney U Test[152-156]:

1. Mann-Whitney U test assumes that the sample drawn from the population is random.
2. In Mann-Whitney U test, Independence within the samples and mutual independence is assumed.
3. Ordinal measurement scale is assumed in Mann-Whitney U test.

The Kruskal-Wallis one-way analysis of variance by ranks is a non-parametric method for testing equality of population medians among groups. Intuitively, it is identical to a one-way analysis of variance with the data replaced by their ranks. It is an extension of the Mann-Whitney U test utilised to analyses data from 3 or more groups[152-155 157].

The sample sizes in the Kruskal-Wallis test should be as equal as possible, but some differences are allowed. The Kruskal-Wallis test also has one limitation. If the researcher does not find a significant difference in his data while conducting the Kruskal-Wallis test, then he cannot say that the samples are the same[152-155 157].

Nonparametric test have both advantages and disadvantages.

Advantages of nonparametric procedures are:

(1) Nonparametric test make less stringent demands of the data. For standard parametric procedures to be valid, certain underlying conditions or assumptions must be met, particularly for smaller sample sizes [152-155].

(2) Nonparametric procedures can sometimes be used to get a quick answer with little calculation[152-155].

(3) Nonparametric methods provide an air of objectivity when there is no reliable (universally recognized) underlying scale for the original data and there is some concern that the results of standard parametric techniques would be criticized for their dependence on an artificial metric. For example, patients might be asked whether they feel extremely uncomfortable / uncomfortable / neutral / comfortable / very comfortable [152-155].

(4) Sometimes the data does not constitute a random sample from a larger population. Standard parametric techniques based on sampling from larger populations are no longer appropriate. Because there are no larger populations, there are no population parameters to estimate. Nevertheless, certain kinds of nonparametric procedures can be applied to such data by using randomization models[152-155].

Disadvantages of nonparametric procedures are:

The major disadvantage of nonparametric techniques is that there are no parameters to describe and it becomes more difficult to make quantitative statements about the actual difference between populations. (For example, when the sign test says two treatments are different, there is no confidence interval and the test doesn't say by how much the treatments differ.) However, it is sometimes possible with the right software to compute estimates (and even confidence intervals) for medians, differences between medians. However, the calculations are often tedious and a computer and specialised statistical software is required[152-155].

The second disadvantage is that nonparametric procedures discard information. Ranks preserve information about the order of the data but discard the actual values. Because information is discarded, nonparametric procedures can never be as powerful (able to detect existing differences) or robust as their parametric counterparts when parametric tests can be used[152-155].

5.6 Further research

This research project serves to highlight numerous areas where further research may occur with regards to postoperative pain management and HIV. This project also highlights the need for further research into the adequacy of referral of HIV-positive parturients from antenatal clinics to specialised antenatal HIV clinics at CHBH.

The fact that this study highlights the limited post-operative analgesia achieved from spinal anaesthesia, may prompt others into studying the adequacy of post-operative analgesia and patient satisfaction at CHBH, as well as prompting studies into the improvement of these services.

The difficulties encountered during data collection, and the observation that elective cases are frequently repeatedly postponed, may prompt further research to examine the actual frequency of postponement and delay of elective caesarean sections, the cost of such delay, the possible complications of such deferments and assessment of patient satisfaction and anxiety scores in these patients pre-operatively.

In Chapter five we have discussed the results of the study as pertaining to primary and secondary objectives. Chapter five has also included a discussion of the study in terms of potential limitations of the study, implications for clinical practice and further research. The discussion has included an interpretation of the results of the study, and the issues raised by the results and tests utilised to analyse the research data.

CHAPTER 6 – SUMMARY AND CONCLUSIONS

Chapter six will include a summary of the study, and conclusions drawn from the study.

6.1 Summary

In the previous chapters the results of the study were discussed. The null hypothesis was accepted, as HIV status was found to have no significant effect on duration of analgesia. The addition of fentanyl to the intrathecal injection was shown to cause significant prolongation of the duration of analgesia. The secondary objectives (CD4 count, antiretroviral therapy, height, level of education and ethnicity) were found to have no significant effect on the duration of analgesia obtained from intrathecal injection. It was deemed that the power of the study was actually insufficient and that this study should perhaps be viewed as a pilot study, and that further study with a much larger sample is necessary to definitively prove the effect of HIV on the duration of analgesia.

6.2 Conclusions

The addition of 20 ug fentanyl to hyperbaric bupivacaine significantly prolongs the duration of analgesia obtained from intrathecal injection but provides a limited duration of postoperative analgesia and thus plays a limited part in post-operative pain management.

Spinal anaesthesia containing bupivacaine and fentanyl should preferentially be used to in our hospital setting as provision of postoperative analgesia is often delayed and there is a large population at risk for the development of chronic pain syndromes.

HIV infection itself has no effect on the duration of analgesia obtained from intrathecal injection of bupivacaine alone or in combination with fentanyl and therefore spinal anaesthesia may be the most appropriate method of administering analgesia intraoperatively to HIV positive patients who do not meet other exclusionary criteria.

Interesting questions have been raised by this project, and the potential for further research into these areas has been discussed

The results of this study have provided useful information which can be directly applied in the clinical setting, hopefully improving the care given to parturients presenting for caesarean section at CHBH in the future.

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APPENDICES

Appendix A	Ethics approval certificate
Appendix B	Post-Graduate Committee approval
Appendix C	Permission from Hospital Clinical Director
Appendix D	Patient information sheet
Appendix E	Informed consent form
Appendix F	Data collection sheet

Appendix A Ethics approval certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Wagner

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070902**
PROJECT	Time Until First Analgesic Requirements Po Caesarean Section Under Spinal Anaesthesia
Positive	Patients at CH Baragwana th Hospital
INVESTIGATORS	JL Dr Wagner
DEPARTMENT	Department of Anaesthesia
DATE CONSIDERED	07.09.28
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

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

DATE 07.11.19 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M V
C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : PR Penfold

DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B Post-Graduate Committee approval

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2745

Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
13 March 2008
Person No: 9900734W
PAG

Dr JL Wagner
P O Box 325
Olivedale
2158
South Africa

Dear Dr Wagner

Master of Medicine (in the specialty Anaesthesia): Approval of Title

We have pleasure in advising that your proposal entitled "*Time until first analgesic requirements post caesarian section under spinal anesthesia in HIV positive patients at Chris Hani Baragwanath Hospital*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix C Permission from Hospital Clinical Director

CHRIS HANI BARAGWANATH HOSPITAL

Dr M. R. BILLA
CLINICAL DIRECTOR
PO BERTSHAM
2013
Tel (011) 933 9608
Fax (011) 938 1005
raymondbi@gpg.gov.za

TO: Dr. J. Wagner
Registrar: Anesthetic
Chris Hani-Baragwanath Hospital

Dear Dr. Wagner

MMED Research Project

Your letter dated 17.08.2007 refers.

Permission is hereby granted to do a research project at the hospital provided that all the necessary processes and requirements are fulfilled to undertake this study.

Yours sincerely

Dr. M. R. Billa
Director: Clinical Services
21.08.2007

Appendix D Patient information sheet

Good morning, my name is Dr Janine Wagner. I am a doctor in the Department of Anaesthesia in this hospital. I am conducting a study and would like to include you in it.

You have been identified by your obstetric doctor as needing a caesarean section under spinal anaesthesia to deliver your baby. We want to make sure that you are pain free during your operation and afterwards.

In South Africa many people are HIV-positive. These patients may suffer from chronic pain, have changes in their nerves and they may take medication that may interfere with the medicine we use in the spinal injection. There are many safe medicines to use for spinal anaesthesia we want to look at two routinely used combinations and see if the pain relief that they give is the same for all patients.

If you agree to participate, we will collect some information from you file and antenatal green card including your HIV status. This will all be kept confidential.

We will inject one of two combinations of drugs used for spinal anaesthesia and see how much time passes before you need another pain relief medication. Both combinations are safe and effective and are often used for patients having caesarean sections.

We will need to visit you every 30 minutes until the effects of the medicine have worn off.

If at any time you have pain we will provide you with medication to stop the pain

Your name and hospital number will not be part of the information collected. There will be no way for anyone not involved in the study to know that you have participated or hat information we have collected. All information will be stored according to a secret code system. Keeping your information confidential is of utmost importance to us and your participation in this study will not influence the care you will receive while you are in hospital or afterwards.

Participating in this study is entirely voluntary. If you decide to participate in the study, but change your mind at a later stage, we will remove all your information from the study and this will not change the care you receive.

Before you decide whether you will participate or not, do you have any questions?

If you want to contact me at a later stage about anything you are not sure of regarding the study, I am available at any time at 082 933 7194.

Thank You

Appendix E Informed consent form

I, _____, agree to participate in the study that Dr Wagner has explained to me.

I understand that some information about me will be collected from my file and antenatal card (HIV status, age, weight, parity, gravidity, surgical and anaesthetic history, history of drugs administered prior to, during theatre time and thereafter and duration of pain relief).

I understand that all my information will be given a special code so that no one will be able to trace it back to me.

I understand that my name and hospital number will be kept separate from my information, and will be locked away.

I understand that my participation is entirely voluntary and that I can withdraw from the study at any time.

Signed at _____ on _____

Signature

Appendix F Data collection sheet

Patient Information:

Patient study number	
Age	
Weight	
Height	

Labouring: Yes/No

Duration of labour: _____

HIV status: positive/negative

CD 4 count: _____

Anaesthetic Information:

Time of administration of spinal anaesthetic	
Syringe code	

Post operative monitoring:

Results table:

Time	0h30	1h00	1h30	2h00	2h30	3h00
VAS Score						
Analgesic requested (Y/N)						

Time	3h30	4h00	4h30	5h00	5h30	6h00
VAS Score						
Analgesic requested (Y/N)						

Time at which analgesic given: _____