A COMPARISON OF INTRATHECAL MORPHINE OR FENTANYL ON THE DURATION OF POSTOPERATIVE ANALGESIA AT NAMIBIAN TEACHING HOSPITALS IN WINDHOEK

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ABSTRACT

Background: Pain management is a cornerstone in the management of femoral fractures. Poorly controlled perioperative pain is associated with detrimental short-term and long-term effects. Addition of intrathecal opioids has been shown to produce a dense block and enhance analgesic effect. The objective of the study was to compare the duration of postoperative analgesia of intrathecal morphine or fentanyl for femur fracture surgery at Namibian Teaching Hospitals in Windhoek.

Methodology: This was a prospective randomised double blinded control study which was done in February – July 2021; in which 60 patients above 18 years scheduled for femur fracture surgeries received standard spinal anaesthesia with 0.5% heavy bupivacaine 12.5 mg plus 100 mcg morphine (ITM group) or 25 mcg fentanyl (ITF group). Data was collected using a form designed for the study and analysed with the statistical package for social sciences **(**SPSS for windows 26.0, SPSS Inc., Chicago, IL, USA).

Results: Participants in the ITM group had a significantly longer time to first request for analgesic (14.5 ± 8.03 hours) versus the ITF group (7.07 ± 3.07 hours), p = 0.0001 and reduced total opioid consumption in 24 hours. The postoperative pain scores (verbal numerical rating scale) at rest and with movement were significantly lower in 2^{nd}, 4^{th} and 6^{th} hour in the ITM group compared to the ITF group ($p < 0.05$). No significant difference was observed between the two groups in terms of pruritus, nausea and vomiting. Respiratory depression was not observed in any participant in the two groups. Patient satisfaction with analgesia was superior in the ITM group (p = 0.0001). No significant association was confirmed between type of femur fracture and the total opioid consumption in 24 hours.

Conclusion: Use of intrathecal morphine significantly increased the duration of postoperative analgesia and reduced the total opioid consumption.

Keywords: intrathecal fentanyl, intrathecal morphine, postoperative analgesia, femur fracture

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LIST OF ABBREVIATIONS AND ACRONYMS

WHO	World health Organisation
DVT	Deep vein thrombosis
ERAS	Enhanced recovery after surgery
IHK	Intermediate Hospital, Katutura
WCH	Windhoek Central Hospital
NSAIDs	Non-steroidal anti-inflammatory drugs
ADH	Antidiuretic hormone
VRS	Verbal rating scale
NRS	Numeric rating scale
VAS	Visual analogue scale
FP	FACES pain scale
VNRS	Verbal numeric rating scale
PONV	Postoperative nausea and vomiting
PCA	Patient-controlled analgesic
ASA	American Society of Anaesthesiologists
SD	Standard deviation
QID	Four times a day
BD	Twice a day
PRN	Per rising need

SPSS	Statistical package for social services
ITM	Intrathecal morphine
ITF	Intrathecal fentanyl
CSF	Cerebrospinal fluid

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DEDICATION

This study is dedicated to my mother Catherine Chadambura and to the memory of my late father, Dr Wonder Chadambura, whose sacrifices directed me to where I am today.

DECLARATION

I Mandiudza Maria Murakwani, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

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CHAPTER 1

INTRODUCTION

1.1 Background of study

Femur fractures are of great concern as they can reduce one's quality of life and cause significant morbidity and mortality, if not treated properly. Appropriate management usually involves a multidisciplinary approach during the perioperative period. The goals of surgical intervention are early mobilisation and weight bearing which reduce the risk of pulmonary complications and thromboembolic events.[1] Orthopaedic procedures are associated with high pain scores on the first postoperative day and procedure-specific pain treatment recommended in the management of postsurgical pain.[2] Pain management is essential in achieving early rehabilitation postoperatively.[1]

Epidemiology: A World Health Organisation (WHO) report ranked Namibia as having one of the highest road traffic accidents in sub-Saharan Africa.[3] Chatukuta and his colleagues highlighted that lower limb fractures resulting from motor vehicle accidents in Namibia come with heavy financial burden on patients during treatment and rehabilitation,[4] therefore effective pain management would engender early mobilisation, early rehabilitation and effectively reduce hospital stay and costs.[4,5,6]

Classification: The classification of femur fractures depends on the site of the fracture: hip, mid shaft and distal femur.[1] Hip fractures are of immense concern in the elderly affecting 18% of the female population and 6% of the male population globally.[7]

Surgery: Surgical intervention in the management of these fractures is through conventional or minimally invasive approaches with resultant tissue damage associated with inflammation which exacerbates the pain experienced in the postoperative period.[1,7] Current literature supports early surgical intervention within

48 hours to stabilise the fractured femur and reduce the risk of complications and further tissue damage.[8,9] Adequate perioperative analgesia is therefore essential to allow the patient to mobilise early, attain optimal functional recovery and reduce the incidence of postoperative mortality and morbidity.[5]

Anaesthesia: The choice of anaesthetic technique for femur fracture surgery is based on its effect on the patient's clinical status as well as its potential for prolonged postoperative analgesia.[10] The common anaesthetic approaches are general anaesthesia or regional anaesthesia or a combination of both.[10] Both techniques can be performed with or without the addition of local infiltration or a single shot or continuous peripheral nerve block such as a femoral or a fascia iliaca block; these blocks play a role in postoperative pain management. Epidural anaesthesia can also be performed as the epidural catheter remains in-situ for postoperative pain management, although it may delay mobilisation due to limb weakness.[10] Non-steroidal anti-inflammatory agents, paracetamol and dexamethasone serve as co-analgesics in multimodal perioperative pain management irrespective of the anaesthetic technique employed.[11]

Spinal anaesthesia is widely performed for femur fracture surgery as it is associated with reduced rates of venous thromboembolism, major blood loss, myocardial infarction, pneumonia as well as reduced hospital stay. The suggested mechanisms include altered coagulation, increased blood flow and improved breathing unimpaired by pain and a decrease in the surgical stress response.[8,12]

Pain Management: Poorly controlled perioperative pain is associated with detrimental short term and long-term effects. Unmitigated pain results in physiological changes in multiple systems such as the cardiovascular system where sympathetic stimulation increases the heart rate and blood pressure thereby increasing the risk of myocardial

ischaemia. Effective pain control contributes to clinically valuable outcomes such as patient mobilisation and quicker recovery, which can result in a reduced risk of deep vein thrombosis (DVT), shortened hospital stay and reduced costs.[13, 14]

The principles of enhanced recovery after surgery (ERAS) include optimising pain relief, reducing the surgical stress response, early mobilisation and empowering the patient to regain independence as quickly as possible post-surgery. These principles are critical in the management of femur fractures post-surgery. Acute pain can result in immobility thereby increasing the risk of DVT.[5, 6] Chronic pain syndromes can complicate poorly managed pain which will incapacitate patients and affect their long-term quality of life.[14]

Spinal anaesthesia can be performed with bupivacaine only but the addition of intrathecal adjuvants has been shown to enhance analgesic effects. The addition of intrathecal adjuvants like ketorolac, magnesium sulphate, ketamine as well as opioids such as morphine and fentanyl have been shown to produce a denser block and enhance analgesic effect. The optimal neuraxial opioid dose is a balance between the conflicting demands of providing adequate analgesia while minimising dose-related adverse effects.[11, 13]

1.2 Statement of the problem

Femur fracture surgery is associated with postoperative pain due to manipulation and damage of tissue. Enhanced recovery after surgery is encouraged allowing early mobilisation of the patient and avoid complications relating to immobility such as deep vein thrombosis, pneumonia, urinary tract infections and prolonged hospital stay.[11] Immobility can be exacerbated by pain.

The current anaesthesia practice at Intermediate Hospital, Katutura (IHK) and Windhoek Central Hospital (WCH) for femur fracture surgery is spinal anaesthesia

with or without fentanyl as well as general anaesthesia with the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and parenteral opioids in the postoperative period. Concerns about delayed respiratory depression preclude the use of intrathecal morphine in our centre.

With the introduction of the anaesthesia speciality training in Namibia in 2018 the registrars are undergoing training to perform epidural anaesthesia and ultrasound guided femoral blocks for the perioperative pain management of femur fractures in the future.

Currently, there is a dearth of publication in Namibia specifically that assessed adequacy of postoperative pain management after femur fracture surgery with respect to the use of intrathecal adjuvants such as morphine and fentanyl, making this study imperative.

There is a need to provide evidence to improve the knowledge and practice of postoperative pain management for patients who have femur fracture surgery. This would allow the setting of evidence-based protocols in the two teaching hospitals.

1.3 Objectives of the study

Overall Objective

To compare the analgesic effect of intrathecal morphine versus fentanyl added to bupivacaine for spinal anaesthesia by assessing the time to first request for analgesic in patients following femur fracture surgery at Intermediate Hospital, Katutura and Windhoek Central Hospital.

Specific Objectives

1) To compare the difference in the duration of analgesia between patients given intrathecal bupivacaine-morphine and bupivacaine-fentanyl for spinal anaesthesia by using time to first analgesic request between the 2 groups following femur fracture surgery
2) To determine total Pethidine consumption between the groups in the first 24 hours after femur fracture surgery
3) To compare postoperative pain scores at rest and during movement at 2 hours, 4 hours, 6 hours, 12 hours, 24 hours between the patients in the 2 groups after femur fracture surgery
4) To evaluate adverse effects of bupivacaine-fentanyl and bupivacaine-morphine for spinal anaesthesia for femur fracture surgery
5) To assess patient satisfaction with analgesia between the 2 groups after femur fracture surgery

1.4 Hypothesis

Null hypothesis

There is no difference in the duration of postoperative analgesia between patients given intrathecal morphine and fentanyl added to spinal anaesthesia for femur fracture surgery.

Alternate hypothesis

There is a difference in the duration of postoperative analgesia between patients given intrathecal morphine and fentanyl added to spinal anaesthesia for femur fracture surgery.

1.5 Significance of study

The safety concern about intrathecal opioids, especially morphine has made its use off-limits among anaesthesia providers in the Windhoek-based Teaching hospitals. It is hoped that this study would provide evidence to improve the knowledge and practice of postoperative pain management for patients who have femur fracture surgery in line with international best practice.

1.6 Limitations of the study

Patients enrolled in the study had their femur fracture surgeries performed by different orthopaedic surgeons who used different surgical approaches. For this reason, only the patients that were operated by the three (3) senior medical officers and three (3) specialist orthopaedic surgeons in the orthopaedics department were enrolled in the study.

Patients enrolled in the study had different types of femur fractures and efforts were geared towards enrolling equal numbers of the different types.

1.7 Delimitations of the study

The patient population was limited to WCH and IHK.
The data was collected over six (6) months from February 2021 to July 2021.

1.8 Summary

This chapter highlights the impact of postoperative pain management as a cornerstone in the management of femoral fractures as well as the current anaesthesia practise at WCH and IHK. The research objectives and hypothesis were also discussed in this chapter. The significance of this study, limitations as well as delimitations were also presented.

CHAPTER 2

LITERATURE REVIEW

Introduction

In this chapter, the literature reviewed are presented. To ensure that the literature was relevant, appropriate and useful, sources used were selected from peer reviewed journal publications, anaesthesia textbooks as well as studies on perioperative pain management.

Pain

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage.[15]

Pain can be classified according to duration (acute or chronic) or pathophysiology (nociceptive or neuropathic). Acute pain is defined as pain of short and limited duration that is associated with well-defined tissue damage. Postoperative pain and trauma related pain are classified under acute pain.[15,16] Acute postoperative pain is typically one that a patient has after a surgical procedure.[15] It is caused by tissue and nerve injuries with associated acute inflammation due to the surgical manipulations.[5,11,12]

There are four complex neurophysiologic processes for experiencing pain: transduction, transmission, modulation and perception. *Transduction* is when a noxious stimulus is converted to an electrical impulse in sensory nerve endings that is then conducted to the central nervous system via a process called *transmission*. The process of altering pain transmission is called *modulation* via inhibitory and

excitatory mechanisms. The thalamus and cortex are thought to be important in pain *perception*.[16]

Tissue damaging stimuli such as surgery or trauma activates nerve endings (transduction) causing pain receptors/nociceptors to be stimulated. Nociceptors are divided into C-polymodal and A-mechanoheat nerve fibres. The stimulus is then transmitted via the afferent nerve fibres through the spinal cord dorsal roots and ascend within the dorsal horn to the brain where the stimulus is analysed to produce a conscious perception of the stimulus as pain. Inflammatory mediators such as substance P, cytokines, prostaglandins, serotonin and kinins are released with the tissue damage which also activates the nociceptors.[17] Physiological, emotional and cognitive states can also have an impact on how pain is perceived hence the complexity and multiple processes in the understanding of the pathophysiology of pain.[18,19] Age, ethnicity, gender and type of surgery have been shown to affect a patient's pain perception.[20,21]

Pain is a common and distressing complication in the postoperative period.[22] The United States Institute of Medicine, reported that 80% of patients had postoperative pain after undergoing surgery. About 88% of these patients reported moderate to extreme pain.[23] It has been observed in other surveys that 70 – 75% of patients have moderate to severe pain after some types of surgery.[24] A prospective study of patients from 179 surgical groups showed that on the first postoperative day, the highest pain scores were after orthopaedic/trauma procedures.[2]

Complications of poor pain management

Postoperative pain should be treated as this facilitates the healing process, rehabilitation, prevention of complications related to poor pain management and

reduced health costs.[25,26] Unrelieved acute pain has adverse physiological and psychological effects in multiple organ systems. These effects are seen in the endocrine system by an increase in the rate of catabolism associated with an increase in catecholamines, adrenocorticotropic hormone and antidiuretic hormone (ADH). An increase in metabolism of carbohydrates, proteins and lipids is a noted adverse effect that causes hyperglycaemia and glucose intolerance which inadvertently affects wound healing. Pain can stimulate the autonomic system affecting the cardiovascular system causing an increased heart rate and blood pressure which increases oxygen demands and the risk of myocardial and coronary ischaemia. An increase in ADH results in oliguria predisposing to acute kidney injury. Poorly managed postoperative pain causes reduced bowel motility predisposing the patient to paralytic ileus, nausea and vomiting. [14,26,27]

Anxiety, helplessness and sleep deprivation related to poor pain control can cause psychological disturbances such as depression as well as increase the risk of developing chronic pain.[14,26,27] Unsatisfactory pain management can affect the patient's immune response delaying wound healing. Mobility is significantly limited in patients with pain which predisposes the patient to thromboembolic events in the postoperative period.[26] Inadequately managed postoperative pain is associated with prolonged opioid use as well as opioid-related side effects. Pain at the surgical site in the first 24 hours of total knee or hip arthroplasty has been described as a significant predictor of persistent opioid use at 6months post-surgery.[28] Respiratory depression, nausea, vomiting, pruritus and constipation are the common adverse effects of opioids that have been associated with a notable burden on quality of life in the postoperative period.[29-31] Opioid-related side effects have been shown to considerably escalate hospital costs and prolong hospital stay.[32] Coley and colleagues performed a

retrospective study of same day surgeries and observed that pain was the main reason for 38% of these patients to return to the facility for care.[32] When postoperative pain is treated successfully it is likely to reduce morbidity and improve patient outcomes.[26]

Pain assessment tools

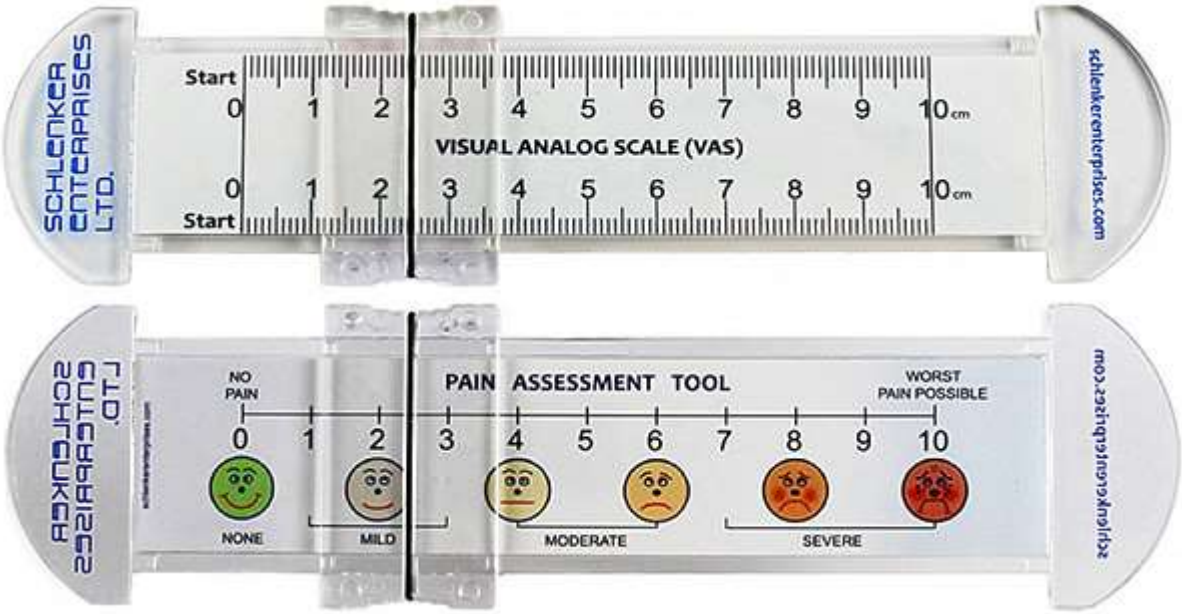
Pain assessment is imperative to ascertain the severity of pain, whether pain management is adequate and if the analgesics administered are effective. Pain assessment tools that are reliable and valid are crucial for effective clinical care of patients and are used to evaluate patients' pain.[33]

Pain is accepted to be a complex subjective multidimensional experience; unidimensional tools are frequently utilised as the main assessment technique in the management of acute pain.[34] Pain is subjective hence the importance of the patient's personal report. Each individual experiences pain in their own unique way even when the stimuli is the same.[16]

The verbal rating scale (VRS), numeric rating scale **(**NRS), visual analogue scale **(**VAS) and FACES pain scale (FP) are the most frequently used pain assessment tools for acute pain.[35,36] Pain can also be assessed and described as mild, moderate or severe using the categorical scale. Hjermstad et al suggested that categorical scales with three response options had limited chances for discrimination and little gain in precision compared to the other scales in assessing and managing pain.[37] Analysis of multiple studies comparing NRS, VRS and VAS in adults done by Hjermstad and his colleagues reported that the elderly and less educated preferred the VRS and the age mixed population favoured the NRS.[37] The intensity of pain is subjective therefore the VAS and NRS function well to accommodate this and are fairly sensitive.[38]

Visual Analogue Scale (VAS)

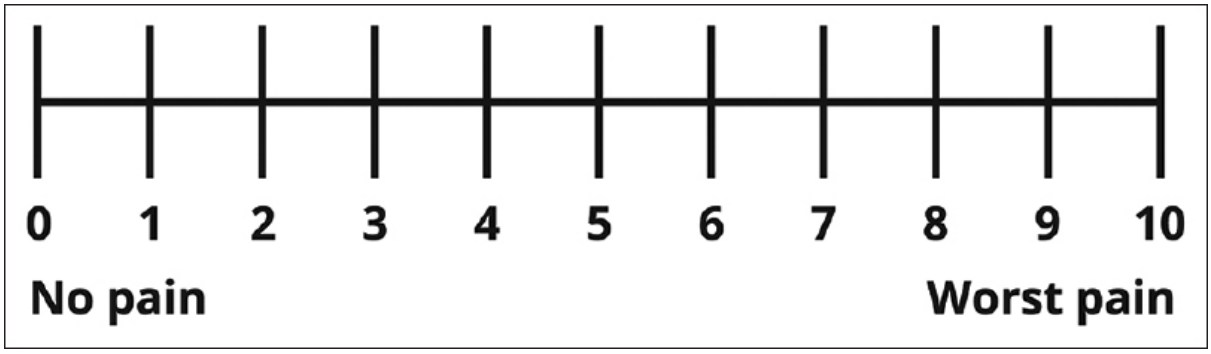
One of the tools used is the VAS where a 0 – 100 mm straight line **(**instrument) is marked at one end ‘no pain’ and the other ‘worst possible pain’. The patient marks a point on the scale that best describes his pain. The assessor has to carry the required instrument around.[14]



Verbal rating scale (VRS)

With the VRS the patient is required to report their pain as none, mild, moderate, severe or very severe. Its effectiveness is limited in a multilingual population.[14]

Numeric rating scale (NRS)



The NRS is another tool that can be used to assess pain that is simple to perform. The scale uses a 0 - 10 scale where a patient is asked to rate their pain with "0" been "no pain" and "10" being the "worst pain imaginable". As a pain assessment tool, it has been shown to be more sensitive than the VRS and VAS.[37,39,40] The verbal numeric rating scale **(**VNRS) is another tool that can be used to assess pain. The scale uses a 0 -10 verbal scale where a patient is asked to rate their pain with "0" been "no pain" and "10" being the "worst pain imaginable".[14] For the paediatric population <5years and adults with cognitive impairment the Wong-Baker FACES pain rating scale can be used as an assessment tool.[14]

The different pain tools are best used to assess acute pain while the patient is at rest and during movement to evaluate comfort, function and the risk of postoperative complications.[38]

Femur fractures

Femur fractures are noted to be the most common cause of mortality and disability in injuries involving the musculoskeletal system.[41] In patients with femur fractures, 46% develop complications; with mortality of about 20 - 54%; as the longest, tubular and the main weight bearing bone. The annual prevalence of femur fractures was approximated to be 9.9 – 10 in every 100 000 people by Salmien, et al.[42-44]

Fractures of the femur are classified according to the site of the fracture: hip, mid shaft and distal.[1] Most femur fractures are from trauma such as a fall or a motor vehicle accident.[44] Motor vehicle accidents are the most common cause of femur fractures in the young patients.[44] In the elderly osteoporosis plays a significant role in the increased incidence of hip fractures.[7,44] Hip fractures are a common injury in the elderly while mid-shaft and distal femur fractures affect the younger population.[7]

Femur fractures result in tissue damage and nerve injury which stimulates the pain receptors and inflammatory mediators. Contraction of the large muscles around the hip stretch the broken ends of the bone towards each other causing excessive pain. The surgical intervention results in further tissue damage associated with inflammation which exacerbates the pain in the postoperative period.[1,7]

Fracture management usually requires surgery to heal. Initial emergency care includes skin traction to align the fractured bone and alleviate pain. Non-steroidal anti-inflammatory agents, opioids and regional techniques are also used to relieve the pain. Surgical intervention is via insertion of plates, screws, nails or prosthetic implants that cause further tissue and bone damage.[43]

Complications can be life-threatening and include haemorrhage, infection, thromboembolic events and physical disability. Current literature supports early surgical intervention within 24 - 72 hours to avoid these complications by stabilising the fracture and allowing early rehabilitation.[8,45]

Early postoperative rehabilitation of the limb is imperative as it prevents physical disability.[46] Successful rehabilitation is achieved in a patient who has well managed pain. Poorly managed postoperative pain plays a significant role in delayed mobility that affects rehabilitation, prolongs hospital stay and increases the incidence of

thromboembolic events as well as pulmonary complications.[5,6,45] This supports the principles of enhanced recovery after surgery (ERAS) which include optimising pain relief with use of multimodal opioid sparing strategies, reducing the surgical stress response, early mobilisation and empowering the patient to regain independence as quickly as possible post-surgery.[5,6] These principles are crucial in the management of femur fractures post-surgery. Superior outcomes, improved patient satisfaction, reduced hospital stay and reduced costs have been reported by multiple literature.[5,7,11] Orthopaedic surgery has also adopted ERAS protocols for its patients and is well described for total knee arthroplasty.[47]

Spinal Anaesthesia

The anaesthetic technique chosen for patients with femur fractures is based on the planned procedure and patient factors. General or neuraxial anaesthesia (spinal or epidural or combined spinal-epidural) or combined, with the addition of a peripheral nerve block (femoral, sciatic, lateral femoral cutaneous, pericapsular nerve group and obturator nerve blocks) are the various anaesthetic approaches that can be used when femur fractures are repaired.[11]

Studies comparing regional and general anaesthesia for hip fractures have shown a reduction in mortality and pulmonary complications with regional anaesthesia.[48,49] In a 2019 cohort study, spinal anaesthesia was performed for patients undergoing femur fracture surgery there was reduction in rates of pulmonary embolism, major blood loss and reduced hospital stay.[50]

Spinal anaesthesia blocks both sympathetic and parasympathetic autonomic nerves as well as sensory and motor fibres. Hypotension, post dural puncture headache, urinary retention, inadequate or failed block are the common complications of spinal

anaesthesia.[51] Spinal anaesthesia is performed using plain bupivacaine or hyperbaric bupivacaine alone or in combination with an intrathecal adjuvant medication.

Bupivacaine was first discovered in the 1950s and is a long-acting amide local anaesthetic agent.[52] Its mechanism of action is by preventing transmission of nerve impulses along the axonal fibre via blockade of the sodium ion channels at its site of action.[52] It has a duration of action of 1.5 - 5 hours.[53] The routes of administration are subcutaneous, epidural and intrathecal with anaesthesia occurring after injection of bupivacaine via any of the routes at the appropriate concentration. The administration of bupivacaine into the intrathecal space has been shown to reduce postoperative pain and analgesic requirements in patients.[54,55]

Local anaesthetics such as bupivacaine are beneficial in the management of acute pain but their use is limited by their duration of action and their cardiac and central nervous system side effects that are dose dependent.[56] Potent synergistic analgesic effects occur when opioids and local anaesthetics are administered together with no alteration of the sympathetic blockade by the opioids.[51] Use of intrathecal opioids have however been limited by their adverse effects such as respiratory depression, nausea, vomiting and pruritus. Opioids such as tramadol, hydromorphine, buprenorphine, fentanyl, sufentanil and morphine have been used. A study comparing bupivacaine alone and with addition of intrathecal sufentanil and fentanyl for caesarean section reported that the addition of opioid adjuvants prolonged the duration of analgesia.[57]

Other drugs such as alpha 2 adrenoreceptor agonists like clonidine and dexmedetomidine are currently in use. A double-blind study done by Singh and his colleagues highlighted that the use of intrathecal clonidine as an adjuvant compared to

fentanyl and bupivacaine alone provided prolonged analgesia with less adverse effects for transurethral resection of the prostate.[58]

There has been mixed success with the use of dexamethasone, parecoxib, midazolam, neostigmine and magnesium sulphate due to the risk of neurological complications.[56] Dexamethasone used as an intrathecal adjuvant for orthopaedic surgery showed improved duration of spinal anaesthesia.[54] Intrathecal magnesium sulphate was shown to have prolonged postoperative analgesia[59] but isolated studies have highlighted that it has neurotoxic effects.[60]

Intrathecal opioids are very useful agents in acute pain management. Lipophilic opioids like fentanyl have a rapid onset of action but short duration of action while hydrophilic drugs such as morphine have a slower onset but longer duration of action. Intrathecal morphine does pose a greater risk of respiratory depression when large doses are used, concomitant use of additional opioids and age >65 years.[61]

Literature reviewing time to first analgesic request after administration of intrathecal opioids

Karaman and colleagues reported the mean time to first request for analgesics in patients who received intrathecal morphine for caesarean section was 19.5 ± 4.7 hours compared to sufentanil 6.3 ± 5.2 hours.[62] A review of multiple literature showed the average duration of effective analgesia when intrathecal morphine was used was noted to be 18 – 22hours.[63-65]

Khezri et al showed the time to first request of analgesia was 699.38 ± 79.8 minutes when intrathecal fentanyl was added to bupivacaine in patients undergoing lower limb surgery. [66] A study of 80 patients for lower limb surgery who received intrathecal clonidine and fentanyl showed time for first dose of rescue analgesic to be 510.84 ±

24.1 minutes and 434.95 ± 19.16 minutes respectively and which was statistically significant.[67]

Other authors also showed statistically significant difference ($p < 0.001$) in first analgesic requirement time between the intrathecal morphine and fentanyl groups which were 5.9 ± 1.3 hours and 2.6 ± 0.6 hours respectively.[68]

Literature reviewing total opioid consumption in first 24 hours and postoperative scores at rest and during movement after administration of intrathecal opioids

In a prospective observational study done five years ago Kilickaya et al[68] compared the effects of intrathecal fentanyl and morphine on pain in elective total knee replacement surgery. They reported that the patients who received intrathecal morphine had lower pain scores in the 2nd, 6th, 12th and 24th hour as well as needing less analgesics compared to those who received intrathecal fentanyl.[68]

Another prospective randomised double-blind study of 60 parturients compared postoperative analgesia after intrathecal administration of bupivacaine with morphine or fentanyl for elective caesarean section. [69] The authors observed that both intrathecal morphine and fentanyl significantly reduced the intensity of postoperative pain. Intrathecal morphine however increased the duration of postoperative analgesia and reduced the demand for rescue meperidine/pethidine. They reported that between 4 and 20hours postoperatively, the severity of pain was higher in intrathecal fentanyl group.[69]

A randomized controlled trial comparing intrathecal sufentanil or fentanyl for major orthopaedic lower limb surgeries the maximum VAS scores for the intrathecal fentanyl group were reached in 6hours (3.2±1.7) compared to 8hours in the sufentanil

group (2.6 ± 1.6).[70] This trial also reported that during the 24 hour postoperative period the requirement for rescue analgesia was significantly higher in the control group (mean dose 2.67) compared to the sufentanil group (mean dose=1.27) and fentanyl group (mean dose = 1.60).[70]

Literature reviewing adverse effects of intrathecal opioids

The study done by Kilickaya and colleagues also highlighted that there was no significant statistical difference between the patients who received intrathecal fentanyl or morphine for elective total knee replacement in terms of nausea and vomiting.[68] Another study showed similar findings for patients undergoing caesarean section.[69]

However Wiegl et al performed a randomised controlled study four years ago comparing intrathecal morphine and combined fentanyl and morphine for patients undergoing caesarean sections; they reported the incidence of nausea and vomiting in the intrathecal morphine group to be 3.6%, pruritus 35.7% and 0% respiratory depression.[71] Other authors' research also did not observe respiratory depression when 100 – 200mcg of morphine was used intrathecally.[63-65,72] Incidence of respiratory depression and pruritis was 0% when bupivacaine was used alone intrathecally and 5.6 – 45% and 27.8 – 35% respectively with the addition of opioids (fentanyl or sufentanil); this was reported by Ngiam and Chong.[57]

Review of the literature shows that intrathecal morphine is associated with an incidence of 40 – 63% of pruritus.[63-65] and a higher incidence of postoperative nausea and vomiting (PONV).[65] The incidence of pruritus was reported to be 6.66%, respiratory depression 0% and 16.66% for nausea when intrathecal fentanyl was used for patients undergoing lower limb orthopaedic surgery.[66]

Literature reviewing patient satisfaction with analgesia

Sultan and his colleagues demonstrated that doses of 100 - 200 mcg of intrathecal morphine improved patient satisfaction and reduced postoperative patient-controlled analgesia (PCA) usage in patients undergoing total hip replacement.[73] The authors of the randomized controlled trial comparing overall satisfaction in patients who received intrathecal fentanyl with or without morphine for caesarean section also showed that overall satisfaction was higher in the morphine group.[74] Research comparing fentanyl or sufentanil intrathecal pumps reported that patients on sufentanil were significantly satisfied with pain control than patients on fentanyl.[75]

However, Wiegl and colleagues' subjective assessment of patients in terms of anaesthesia, pain management, readiness to undergo such an anaesthesia in future after 24hours of intrathecal morphine and fentanyl administration did not allude to significant differences between the groups.[69]

Summary

In this chapter, postoperative pain was discussed as well the tools to assess it. Femur fractures as well spinal anaesthesia as the anaesthetic approach performed for surgical repair were further discussed and reviewed. The next chapter discusses the research methodology.

CHAPTER 3

RESEARCH METHODOLOGY

Introduction

This chapter provides an outline on how the research was conducted. The chapter presents a narration of both the design and methodology of the research.

Study location

The study was carried out at the University of Namibia teaching hospitals: Intermediate Hospital, Katutura and Windhoek Central Hospital which are the tertiary referral hospitals in Namibia. During the course of the study, the Anaesthesia department for the two teaching hospitals had two (2) full time specialist anaesthetists, two (2) part time specialist anaesthetists, nine (9) registrars and fifteen (15) medical officers. There is one orthopaedic ward at WCH with 30 beds while IHK has three wards with 110 beds in total.

Study population

In this study, the target population comprised patients who were 18 years and above scheduled to undergo femur fracture surgery under spinal anaesthesia and had written informed consent.

Inclusion criteria

Patients aged 18 years and above, who were scheduled to undergo femur fracture surgery under spinal anaesthesia, who were American Society of Anaesthesiologists (ASA) physical status I or II and who gave written informed consent.

Exclusion criteria

Patients with kidney disease.

Patients with liver disease.

Patients with polytrauma.

Study Design

This was a prospective randomised controlled double blinded study carried out over a period of six (6) months (February 2021 to July 2021). Patients scheduled for femur fracture surgeries were recruited into one of two groups to receive spinal anaesthesia with 0.5% heavy bupivacaine 12.5mg plus 100 mcg morphine or 25 mcg fentanyl after obtaining written informed consent.

Sampling technique

Consecutive patients who met the eligibility criteria were recruited into one of the two groups using a simple random sampling technique by a computer-generated set of random numbers prepared by an independent individual who was not involved in the study. The numbers were kept in a sealed envelope before the commencement of the study.

Sample size determination

The primary outcome of the study was to compare the analgesic effect of intrathecal morphine versus fentanyl added to bupivacaine for spinal anaesthesia by assessing the time to first request for analgesic in patients following femur fracture surgery at Intermediate Hospital Katutura and Windhoek Central Hospital.

The sample size was calculated based on the assumptions below using a precision based formula for estimating sample sizes as follows: -

Precision based calculation

The following assumptions were made to accommodate the primary objective of the study at

- 95% confidence level - Z_α as significance level
- Z_β 80% power using a pooled standard deviation (SD) of 5.5 hours to first request for analgesia from a previous study by Kilickaya et al[68]
- Difference (D) or margin of error of 3 hours to first request for analgesia between groups
- The sample size per group $N = \frac{SD^2 * (Z_\alpha + Z_\beta)^2}{D^2}$ =27. The total for the two groups is 54
- Adding 10% attrition rate, this will make a sample size of 60 with 30 patients in each group

According to the precision based calculation above the sample size of 60 patients can be used as well to accommodate the other objectives of this study especially the evaluation of the adverse effects.

Data collection procedure and instruments

Data was collected using a structured questionnaire from patients for femur fracture surgery who were given spinal anaesthesia.

Eligible participants were randomly allocated into the two treatment groups based on a computer-generated table of numbers. An independent individual (statiscian) who was not involved in the study performed the computer-generated randomisation before the study. The patient picked a sealed envelope with a computer-generated number which he/she gave to the anaesthetist who mixed heavy bupivacaine with the adjuvant in a syringe as per the treatment in the envelope. Only the anaesthetist knew what was administered to the patient. The questionnaire was only written the computer-generated number on the envelope. The outcome assessor in the ward was not the anaesthetist who gave the spinal anaesthesia. The outcome assessor who took the pain scores and vital signs was not aware of the spinal anaesthesia drugs administered to the patient. The questionnaire the outcome assessor filled in only had the patient details and computer-generated number. The filled in questionnaires were given to the statiscian who then entered the data as he was the only one with access to the computer-generated number, he had created correlating with which drug was administered to the patient.

All participants received a standard spinal anaesthetic in the sitting position with a 22 or 25G quincke or pencil point spinal needle. The intrathecal morphine (ITM) group (n=30) received 12.5 mg (2,5ml) heavy bupivacaine plus 100 mcg (0.5ml) preservative-free morphine, total volume 3 ml. The preservative-free morphine was diluted with sterile water to make a 1mg/ml solution and 1ml = 1mg morphine was mixed in a 5ml syringe with 4ml sterile water to make a 200mcg/ml solution from which 100mcg (0.5ml) of the morphine was taken and added to the heavy bupivacaine. While the intrathecal fentanyl (ITF) group (n=30) received 12.5 mg (2.5 ml) heavy bupivacaine plus 25 mcg fentanyl, total volume 3 ml.

The time of performing the spinal injection was taken as time zero and durations were measured from this time. The patient and the outcome assessor were blinded in terms of the patients' treatment groups.

In the first 24 hours postoperative pain management consisted of: -

- Paracetamol 1g intravenously four times a day (QID)
- Diclofenac 75mg intramuscular twice a day (BD)
- Pethidine 1mg/kg intramuscular per rising need (PRN) as rescue opioid analgesia

The patients were followed up postoperatively after 2 hours, 4 hours, 6 hours, 12 hours and 24 hours to fill in the questionnaire with the assistance of the outcome assessor who was also blinded in terms of the patients' treatment groups.

Postoperatively, all the patients were admitted into the room closest to the nursing station and had their respiratory rate, oxygen saturation, blood pressure and pulse rate monitored once per hour for the first 12 hours. Thereafter, these measurements were taken at least once every 2 hours for the next 12 hours (from 12 to 24 hours). Oxygen, naloxone and resuscitation equipment was readily available in the room the patients are nursed postoperatively. In the event of respiratory depression indicated by a respiratory rate of <10 breaths per minute and/or oxygen saturation of <90% the nursing staff were required to give the patient oxygen via a face mask and naloxone 0.4mg intravenously with continuous monitoring of the respiratory rate, oxygen saturation, blood pressure and pulse rate with the objective to maintain an oxygen saturation of ≥94% and respiratory rate of ≥10breaths per minute. The doctor on call would be immediately informed to review the patient.

Timetable

The study was carried out from February 2021 to July 2021 with collection of data via structured questionnaires.

Structured Questionnaire

The Structured Questionnaire was used for the: -

Assessment of first request to rescue analgesia

Assessment of pain scores using the verbal numeric rating scale

Side effects of the different drugs used for spinal anaesthesia

Assessment of patient satisfaction with the postoperative pain treatment

Data Analysis

The statistical package for social sciences (SPSS version 26 software package) was used to analyse the data. Nominal variables were presented as numbers with percentages. Continuous variables were presented as mean ± SD, or as median and interquartile range, as appropriate. Data was presented in tables and figures. Data distribution was checked with the help of a statistician. For categorical variables, chi-squared tests were performed to analyse the difference between the intrathecal morphine versus fentanyl group.

Patient satisfaction and participants' demographics were summarised using descriptive statistics. Associations of the data was shown by making use of analytical statistics. Subgroup analysis was done for the participants with subtrochanteric, intertrochanteric, mid-shaft, distal and neck of femur fractures. Statistical significance was considered, if the p value was <0.05.

Research ethics

Ethical approval was sought from the institutional Ethics committees of the University of Namibia and Ministry of Health and Social Services (attached Annexure 1.1 and 1.2). Written informed consent was obtained from the patients**.**

Confidentiality of data

The patients' names were not used in the study, rather serial numbers only. All information obtained pertaining to patients was treated with strict confidentiality. In case of publications, no personal identifying information will be used.

Benefits of participation

Participation or withdrawal from the study was on a voluntary basis, with no loss of benefits either tacit or implied to the participants.

Good clinical practice

Both groups of patients had access to analgesia to control their postoperative pain. No patient was disadvantaged in any way from participation in the study. All patients participating in the study were treated in accordance with the ethical guidelines of the Ministry of Health and Social Services and the Health Professions Councils of Namibia.

Dissemination of results

The results of the study will be presented locally to the Anaesthesia and Orthopaedics departments, as well as the hospital management of both IHK and WCH. A

presentation of the findings of this study will be done internationally at scientific meetings and submitted for publication to peer-reviewed biomedical journals.

Summary

This chapter described the research design, methods, study population and sampling methods. The data collection, analysis as well ethical issues were also discussed.

CHAPTER 4

RESULTS OF THE STUDY

Introduction

In this chapter, the data obtained from the study was analysed and the results are presented as texts, tables, pie charts and graphs in line with the objectives of the study.

4.1 Distribution of the groups

A total of 60 participants were recruited for this study and divided into two (2) groups: 30 participants received intrathecal morphine (ITM) and the remaining 30 received intrathecal fentanyl (ITF).

4.2 Demographic characterisation of the subjects

There were slightly more male participants (51.7%) than females. (See Table 1)

Table 1: Gender distribution

Gender	Frequency, n	Percentage %
Male	31	51.7
Female	29	48.3
Total	60	60

The mean (SD) of the study participants was 60 ± 19.3 years, as shown in Table 2.

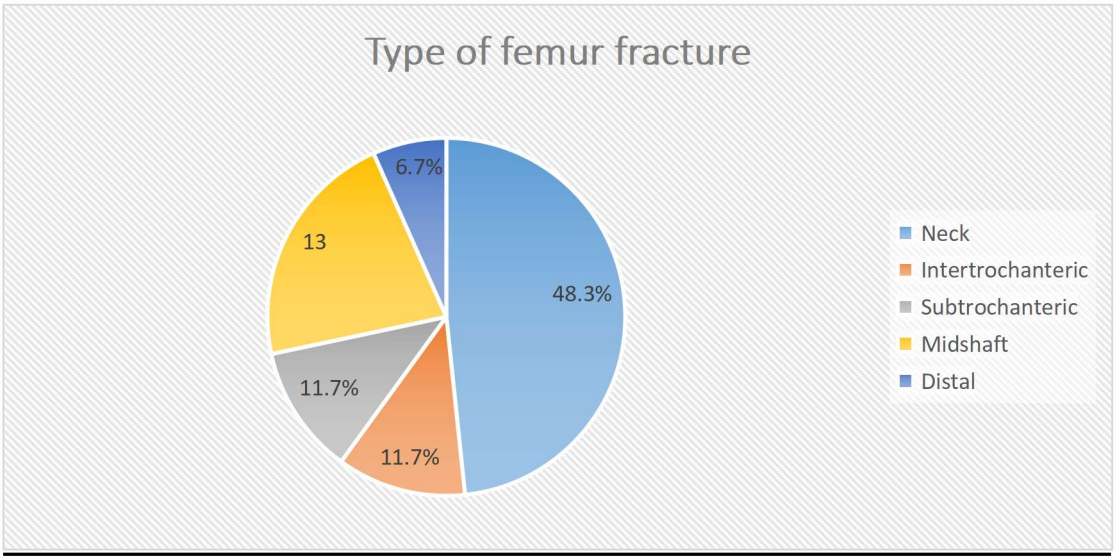
Table 2: Age distribution

Total number	60
Mean age (SD)	60 (19.3)
Median age	64
Minimum Age	18
Maximum age	90

4.3 Type of femur fractures

The most common type of femur fracture was the neck of the femur, according to Figure 1. This was followed by midshaft fractures and the least common site was distal femur. Hip fractures (neck, intertrochanteric and subtrochanteric) accounted for 71.7 % of the femur fractures.

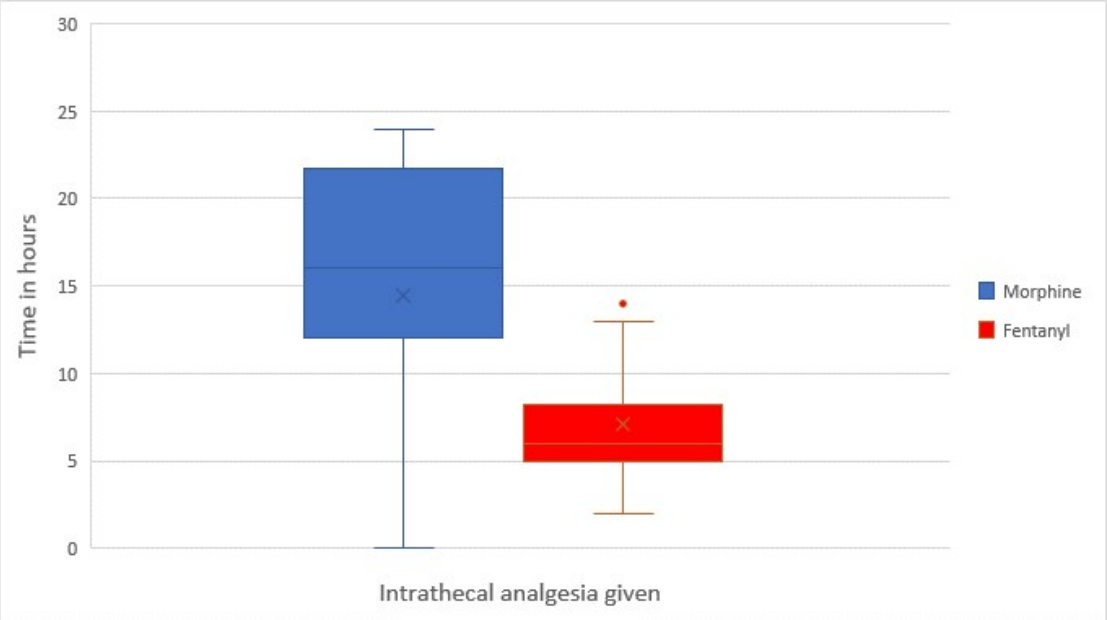
Figure 1: Type of femur fractures



4.4 Time to first request for analgesic

According to Figure 2, the morphine group had a longer time to first request for analgesic compared to the fentanyl group, which was significant (p = 0.0001).

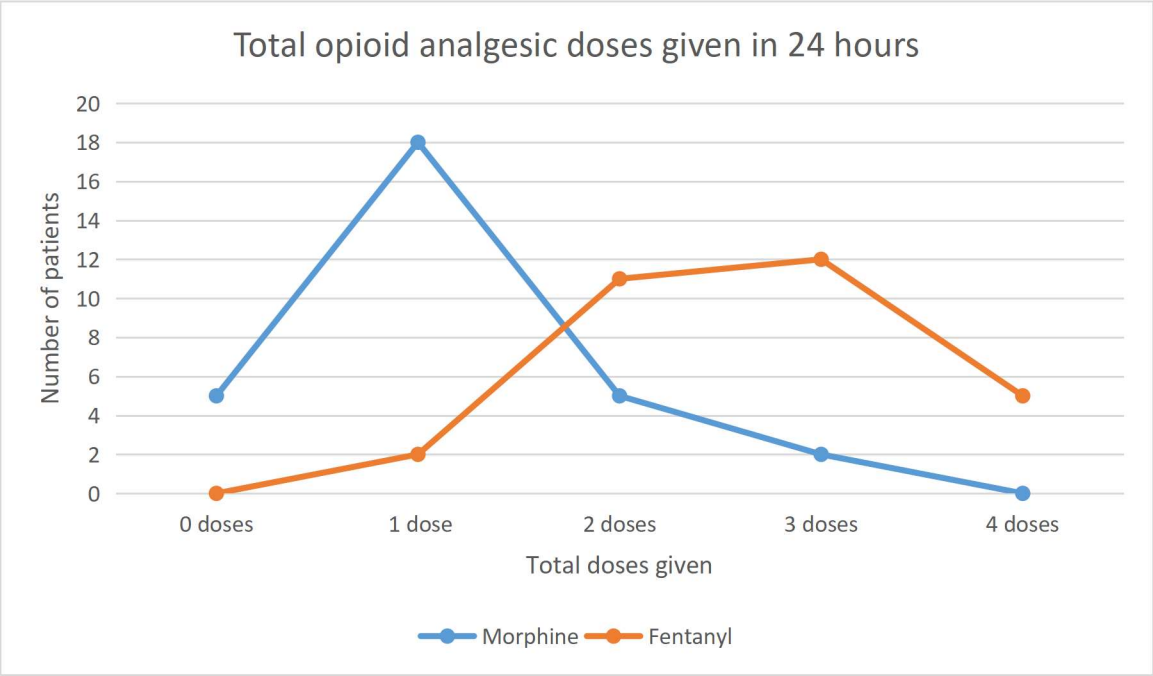
Figure 2: Time to first request for analgesic



4.5 Total opioid analgesic doses given in 24 hours

The mean total opioid doses given were lower in the morphine group (1.1 dose) compared to 2.7 doses in the fentanyl group. The p-value (0.0001) confirmed that there was a significant association between the intrathecal opioid administered and the number of rescue analgesic doses requested within 24 hours.

Figure 3: Total opioid analgesic doses given in 24 hours



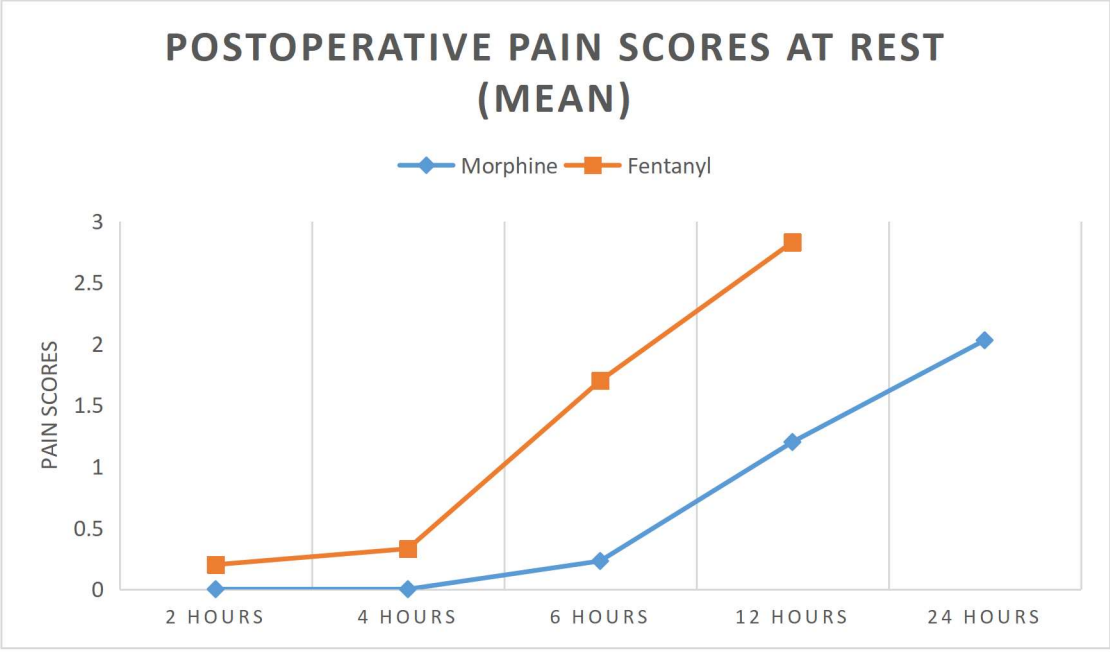
χ^2 - 32.193 p- value = 0.0001

4.6 Postoperative pain scores at rest and with movement

4.6.1 Postoperative pain scores at rest

According to Figure 4, the postoperative pain scores at rest of the participants in the morphine group were significantly lower than the fentanyl group in the 2nd, 4th and 6th hours as indicated by the p values at these three time periods – 0.043, 0.0001 and 0.014 respectively.

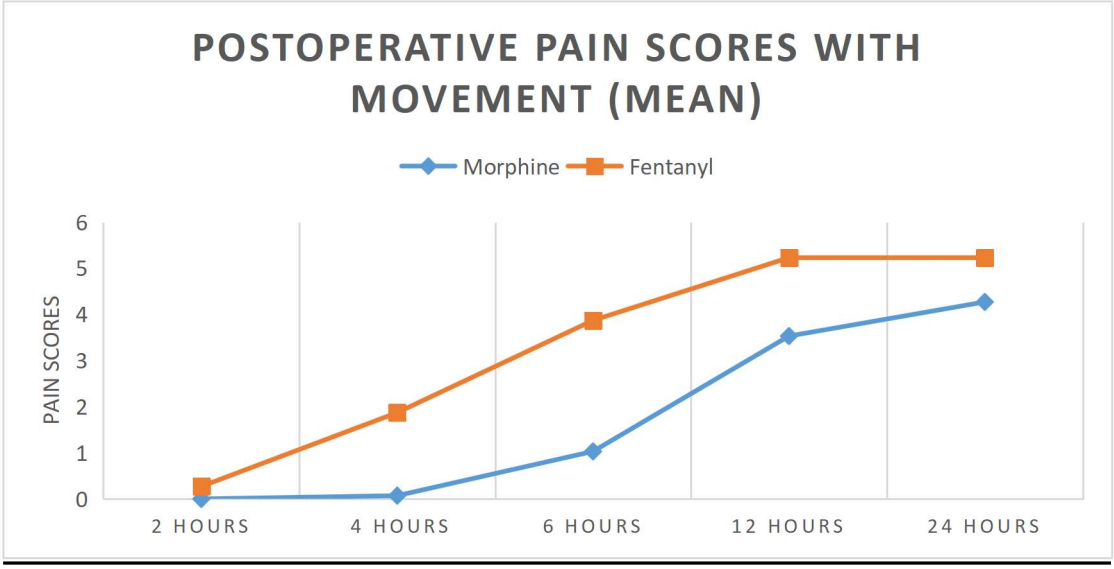
Figure 4: Postoperative pain scores at rest



4.6.2 Postoperative pain scores at rest with movement

The postoperative pain scores with movement of the subjects in the morphine group were significantly lower in the 2nd, 4th and 6th hours compared with the ITF group as indicated by the p values at these three time periods - p = 0.043, 0.0001 and 0.014 respectively, as shown in Figure 5.

Figure 5: Postoperative pain scores with movement

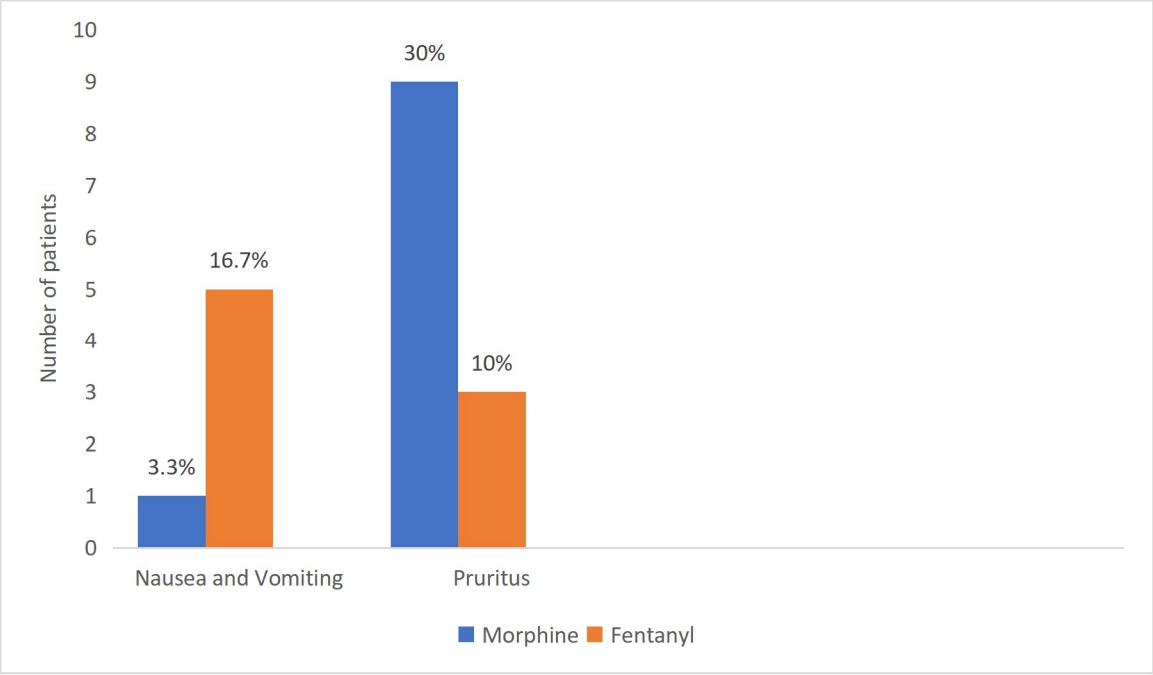


4.7 Side effects of intrathecal morphine and fentanyl

4.7.1 Nausea and vomiting and Pruritus

Nausea and vomiting was more frequent in the fentanyl group (16.7%) compared to the morphine group (3.3%) as shown in Figure 6. Thirty percent (30%) of the patients who received intrathecal morphine had pruritus compared to 10% of those in the fentanyl group. However, there was no significant difference between the two groups in terms of nausea, vomiting and pruritus (p >0.05).

Figure 6: Side effects - Nausea and vomiting and Pruritus



Nausea and vomiting - χ^2 - 2.963 p-value = 0.085

Pruritus - χ^2 - 0.053 p-value = 0.053

4.7.2. Respiratory depression

No respiratory depression or desaturation (SaO_2 < 90%) was observed in participants of the two groups (Table 3).

Table 3: Side effects – Respiratory depression and Desaturation (SaO_2 < 90%)

SIDE EFFECT	**MORPHINE**	**FENTANYL**
Respiratory depression		
Yes, n (%)	0 (0%)	0 (0%)
No, n (%)	30 (100%)	30 (100%)
Saturation (SaO_2) <90%		
Yes, n (%)	0 (0%)	0 (0%)
No, n (%)	30 (100%)	30 (100%)

4.8 Patient satisfaction between groups

Three-quarters of the patients in the ITM group were very satisfied with the treatment while less than 10% of those in the ITF were very satisfied. On the contrary, while none of the patients who had morphine administered were dissatisfied with the treatment, more than 20% of those who had fentanyl were very dissatisfied. The p-value of 0.0001 confirmed a significant association between the intrathecal opioid administered and satisfaction with the treatment by the patient.

Table 4: Patient satisfaction between groups

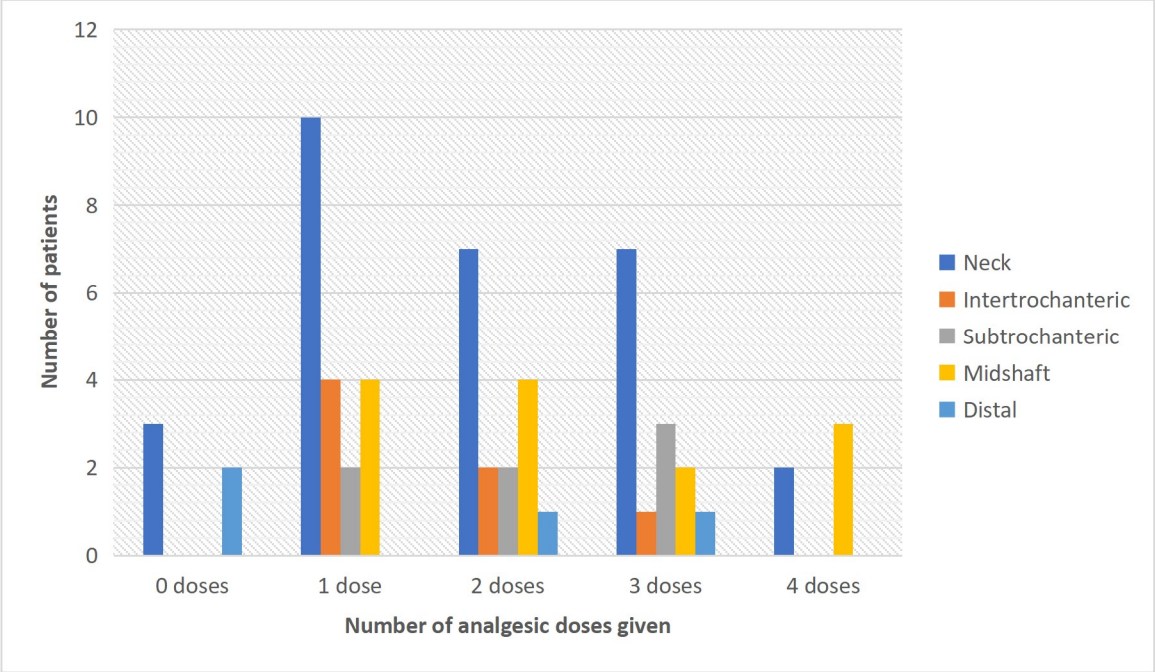
		Morphine	**Fentanyl**
Satisfaction with analgesia	Very satisfied n, (%)	23 (76.7%)	2 (6.7%)
	Satisfied n, (%)	5 (16.7%)	7 (23.3%)
	Somewhat satisfied n, (%)	2 (6.6%)	15 (50%)
	Dissatisfied n, (%)	0 (0%)	6 (20%)

$\chi^2 = 33.92$ p-value = 0.0001

4.9 Subgroup analysis of total opioid analgesic doses given in 24 hours for different types of femur fractures

There was no significant ($p > 0.05$) association between the type of femur fracture and total number of analgesic doses given.

Figure 7: Total opioid analgesic doses given in 24 hours for the different types of femur fracture



p -value = 0.210

Summary

The findings of the study were described in this chapter as per the objectives of the study. The next chapter discusses the relationship between this study and other published studies.

CHAPTER 5

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Introduction

In this chapter, the findings of the study will be interpreted and would be followed by a critique based on studies previously done. The chapter will also draw conclusions in the context of the significance and stated objectives of the study. From these conclusions, recommendations are formulated as well as the limitations of the study are highlighted.

DISCUSSION

Demographics

The results of this research showed that hip fractures were the most common location for femur fractures, which accounted for 71.7%. The mean age of 60 ± 19.3 years, highlighted a high frequency of lower extremity injuries in the elderly population. Wainwright and colleagues also reported that hip fractures were common injuries in the elderly.[7]

Time to first request for analgesic

The current study reported first analgesic request of 14.5 ± 8.03 hours for ITM group twice as long as 7.07 ± 3.07 hours for the ITF group, which was significant p =0.0001. This result demonstrated that intrathecal morphine provided superior and prolonged analgesia compared to intrathecal fentanyl. This finding is congruous with reports from several authors' such as Karaman et al [62], Kilickaya et al [68], Wiegl et al [69] in which morphine was compared with fentanyl or sufentanil as adjuncts during spinal anaesthesia for obstetric or lower limb orthopaedic surgeries.

Opioids administered intrathecally bind to opioid receptors in the spinal cord modulating the pain pathway. Morphine, being hydrophilic when administered intrathecally maintains its concentration in the cerebrospinal fluid (CSF) thereby prolonging the duration of postoperative analgesia and this route has been found to be superior to systemic injections. [13,61] Whereas fentanyl as a lipophilic opioid would be bound rapidly resulting in its CSF concentration reducing quickly, consequently its rapid onset of action is combined with a short duration of analgesic effect.[13,61] Morphine‘s hydrophilicity improves its neuraxial bioavailability as it penetrates the spinal cord slowly and is therefore available in the CSF for a prolonged period with slow clearance from the receptors; in contrast to the more lipophilic fentanyl and the pharmacodynamic implication is prolonged analgesic effect, which explains the findings in this index study.

The current study reported 14.5 ± 8.03 hours, time to first request for analgesia after intrathecal morphine was administered. However, a study done in 2016 showed a shorter time to first request for analgesic after receiving intrathecal morphine for elective total knee replacement 5.9 ± 1.3 hours.[68] Both studies used similar doses of hyperbaric bupivacaine and morphine but there was still a difference in the time to first request for analgesia likely due to that the patients in Kilickaya et al study were undergoing total knee replacement which is one of the most painful orthopaedic procedures.[43]

Total opioid consumption in the first 24 hours

The results from this study highlighted that administration of intrathecal morphine was associated with a lower total opioid consumption (mean dose 1.1) in the first 24 hours compared to intrathecal fentanyl (mean dose 2.7), which was significant p =

0.0001. This finding was in line with a prospective randomised double blinded study by Wiegl and colleagues that reported reduced demand for rescue pethidine when intrathecal morphine was administered for elective caesarean section compared to intrathecal fentanyl.[69] In Turkey, Kilickaya et al also noted similar findings when they compared the effects of intrathecal morphine and fentanyl on pain. Their intrathecal morphine group had reduced total diclofenac consumption compared to the fentanyl group, since diclofenac was the rescue analgesic.[68] The studies agree that total analgesia consumption in the first 24 hours was reduced, irrespective of the class of the rescue analgesic. In this study all the patients received the same basic pain management which was paracetamol and diclofenac, thus the total opioid consumption in terms of doses given reflects the efficacy of the intrathecal opioids. In the case of morphine, the reduced total opioid consumption in the first 24 hours indicated its long postoperative analgesic effect.

Motiani and colleagues compared intrathecal sufentanil versus fentanyl for lower limb surgeries and total rescue analgesia consumption in 24 hours mean dose to be 1.60 for the fentanyl group[70] which was less than that found in the current study for the fentanyl group (2.67), however the mean dose required was still higher than the morphine group of our study (1.1). The lower total rescue analgesia consumption could be attributed to the higher dose of hyperbaric bupivacaine used 15mg compared to 12.5mg for this current study as well as the type of surgery. This study assessed patients undergoing femur fracture surgery while the other study's participants had various types of lower limb surgery causing variations in tissue damage from each surgery.

The use of oral and parental opioids in the postoperative period is associated with opioid-related side effects that can escalate hospital costs and prolong hospital stay.[32]

The finding of a lower total opioid consumption in this index study in the ITM group supports the principles of enhanced recovery after surgery which include optimising pain relief with use of multimodal opioid sparing strategies[5,6] as well as reducing opioid-related adverse effects and hospital costs.

Postoperative pain scores at rest and during movement after administration of intrathecal opioids

The result of this study, showed that postoperative pain scores at rest and during movement were significantly lower in the morphine group at the 2nd, 4th and 6th hours compared with the fentanyl group ($p < 0.05$). The differences in this observation are attributable to the properties each of these opioids exhibit. Morphine has been shown to have a higher spinal selectivity compared to fentanyl which facilitates lower pain scores observed with its use.[50,61] Kilickaya et al reported a similar finding of significantly lower pain scores at the 2nd, 6th, 12th and 24th hours in their ITM group.[68] While the observed low pain scores terminated in the 12th hour in this study, theirs extended up to the 24th hour. The different pain assessment tools used in the two studies verbal numeric rating scale (VNRS) versus visual analogue scale (VAS) might account for these differences. Both these assessment tools are unidimensional tools while pain is a complex subjective multidimensional experience.[34] Age and level of education were also reported by Hjermstad and colleagues to affect the preference to a particular assessment tool by patients.[37]

Adverse effects of intrathecal fentanyl and morphine

In this study the incidence of nausea and vomiting was higher in the fentanyl group 16.7% compared to 3.3% in the morphine group although there was no significant difference $p = 0.085$. Other authors also found no significant difference in their

studies for the patients who received intrathecal morphine and fentanyl for elective total knee replacement[68] and for elective caesarean section[69]in terms of nausea and vomiting. The side effects associated with intrathecal opioids are due to the opioids binding to the opioid receptors (Mu, Delta and Kappa) thereby providing the analgesic effect as well as unwanted effects such as respiratory depression, pruritus, nausea and vomiting.[51,61]

Wiegl and colleagues' randomised controlled study comparing intrathecal fentanyl and morphine or morphine alone reported the incidence of nausea and vomiting in their morphine alone group to be 3.6% which was almost similar to this current study 3.3%.[71] Khezri et al who compared intrathecal fentanyl and magnesium in patients undergoing lower limb orthopaedic surgery reported the incidence of nausea and vomiting in the patients that received fentanyl to be 16.66 %[66] , which was comparable with this current study's findings of 16.7 %.

In this study the incidence of pruritus was higher in the morphine group 30% compared to 10% in the fentanyl group. Of note from the current study is that there was no significant difference p-value >0.05. This finding was supported by Wiegl et al who performed a randomised controlled study in 2009 comparing intrathecal fentanyl and morphine for caesarean section and observed that pruritus was higher in the morphine group.[69]

In a 2017 study comparing intrathecal fentanyl and morphine or morphine alone for caesarean section reported the incidence of pruritus in their morphine only group to be 35.7% which was marginally higher than that reported in this current study 30%. The difference could be explained by the use of intravenous pethidine via patient-controlled analgesia by Wiegl and colleagues which would increase bioavailability of

pethidine to 100% increasing the risk of opioid related pruritus combined with the intrathecal morphine administered compared to the current study were pethidine was given intramuscular causing unpredictable concentrations in the systemic circulation depending on absorption at the site of injection.

The current study observed that no patients (0%) in both groups had a respiratory rate < 10 breaths/minute or desaturation <90%. This finding highlighted that intrathecal morphine 100mcg or fentanyl 25mcg was not associated with respiratory depression. This finding was supported by multiple authors who also reported 0% respiratory depression when intrathecal morphine 100 mcg and fentanyl 25mcg were used. (Khezri and colleagues[66], Wiegl and colleagues.[71]) Delayed respiratory depression seen with intrathecal morphine is due to its prolonged duration of action compared to fentanyl where the risk of respiratory depression is early (0 – 1 hour) due to its shorter duration of action. Ngiam and Chong however had 5.6% incidence of respiratory depression in their fentanyl group who received a lower dose of intrathecal fentanyl and hyperbaric bupivacaine for caesarean section compared to this study which could be explained by the level of block that needs to be attained for caesarean section thoracic vertebra 4 - 6 (T4 - 6) compared with this study thoracic vertebrae 10 - 12 (T10 -12) for femur fracture surgery.[57] In this study 100mcg of intrathecal morphine was used with 0% respiratory depression while other authors have observed increased incidence of respiratory depression when doses greater than 200 mcg are administered.[11,13,61]

Patient satisfaction with the analgesia

The results of this study showed that there was a significant association between the intrathecal adjuvant administered and satisfaction with the treatment of postoperative

pain with intrathecal morphine providing higher overall patient satisfaction compared to intrathecal fentanyl. Sultan et al[73] and Sawi et al[74] reported similar findings to support this current study's findings that administration of intrathecal morphine was associated with improved patient satisfaction.

Pain is the most common distressing complication in the postoperative period,[22] if it is managed well the patient will not experience the physiological and psychological adverse effects of pain allowing them to be satisfied with the treatment given. A multimodal approach in terms of postoperative pain management using paracetamol and diclofenac was used in this study for both patient groups in addition to the intrathecal opioid administered. The use of intrathecal morphine in the multimodal treatment of postoperative pain was associated with superior patient satisfaction due to its duration of analgesic effect averaging 18 -22 hours compared to fentanyl that has a shorter duration of analgesic effect.[62-65]

However, Wiegl and colleagues did not find any significant differences between the groups that received intrathecal fentanyl and morphine for elective caesarean section when they had a subjective assessment of the patient's satisfaction after 24 hours.[69] The difference may have been caused by the administration of varying hyperbaric bupivacaine doses 7.5 – 15 mg for the participants in Wiegl et al study compared to a fixed dose of hyperbaric bupivacaine12.5mg used in the current study.

Subgroup analysis of total opioid analgesic doses given in 24 hours for different types of femur fractures

The study showed that there was no significant association between the type of femur fracture and total opioid analgesic doses given in 24 hours ($p > 0.05$). This study compared intrathecal morphine with fentanyl on the duration of postoperative

analgesia for femur fractures. Surgery of different types of femur fractures is associated with varying tissue and nerve injuries as the fracture site and type of surgery is different for each fracture which could impact on severity of postoperative pain and total opioid analgesic doses required.[11,12,15]

CONCLUSION

This study showed that both intrathecal morphine and fentanyl provided postoperative analgesia after femur fracture surgery. Intrathecal morphine had significantly superior and prolonged postoperative analgesia with reduced total opioid consumption as well as higher patient satisfaction with no respiratory depression associated with its use. There was no noted significant difference between the two groups in terms of nausea, vomiting and pruritus. It was also noted that the type of femur fracture was not significantly associated with the total opioid consumption in 24 hours.

RECOMMENDATIONS

1. The use of intrathecal morphine 100mcg for postoperative analgesia for femur fracture surgery. This is based on its prolonged analgesic effect. Its use was precluded by concerns of delayed respiratory depression but this study observed no respiratory depression with the use of this morphine dose.
2. Presentation of the findings of this study to the anaesthesia providers in Namibia highlighting especially findings in terms of safety of intrathecal morphine in terms of respiratory depression. The presentation can be done through the Anaesthesia Society of Namibia's annual congress and continuous professional development meetings done in Windhoek and the regional hospitals.
3. The setup of enhanced recovery of surgery (ERAS) protocols for femur fractures by the orthopaedics and anaesthesia departments with special attention on postoperative pain management incorporating the opioid sparing strategies associated with the use of intrathecal morphine.
4. A further study can be done comparing intrathecal morphine and a combination of intrathecal fentanyl and morphine for postoperative pain management of femur fractures.

LIMITATIONS

1. The participants demographic characteristics could not be extensively analysed that is weight as the patients could not stand to be weighed due to the femur fracture.
2. From the participants enrolled in the study there was no equal distribution in terms of the type of femur fractures.
3. Different surgeons still performed the femur fracture surgeries using different surgical approaches although it was limited to three senior medical officers and three specialist orthopaedic surgeons.
4. The patient population was from the Windhoek Teaching hospitals only.

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ANNEXURES

Annexure 1: Ethical clearances

Annexure 1.1: University of Namibia

FACULTY OF HEALTH SCIENCE

FEEDBACK FROM UPGSC HELD 26/11/2020

FROM: DR L N LUKOLO, HOD, PGS, FACULTY OF HEALTH SCIENCES

Matters arising from previous meeting:

APPROVAL OF SUPERVISOR

6.4.1.1 STUDENT: C MBAPAHA

Dr H. Amukugo were approved to be the supervisor of student C Mbapaha

1. **PROPOSALS FOR NOTING AND APPROVAL OF SUPERVISORS**

Student name and number /Topic	**Recommended Supervisors**
1.Loini Talishi Shivolo, 200505769, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: A Survey On End Of Life Care In The Intensive Care Units In Three Government Teaching Hospitals , Namibia	Recommended supervisor: DR KINGSLEY TOBI Approved
2.Salomon Namupolo, 200111442, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: Paediatric pain assessment with face leg activity cry (FLACC) in post anesthetic care unit (PACU), Windhoek central hospital : an observational, and quality improvement study	**Recommended Supervisors**: Dr JM Mumba Approved

3.Shigwedha, 200404229, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: The Effect Of Oxytocin On Uterine Tone During Elective Caesarean Section At Windhoek state Hospitals	**Recommended supervisor:** DR KINGSLEY TOBI Approved
4. Murakwani 218241564, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: A comparison of intrathecal morphine with fentanyl on the duration of postoperative analgesia at Namibian teaching hospitals in Windhoek	**Recommended supervisor:** Prof Rukewe Approved
5.Shaanika E P , 200110373, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) **Topic:** Prophylactic Phenylephrine Bolus Versus Infusion For Prevention Of Maternal Hypotension During Spinal Anaesthesia For Caesarean Section At Windhoek-Based Teaching Hospitals, Namibia	**Recommended supervisor:** Prof Rukewe Approved

1. **MARKS FOR DISCUSSION AND RECOMMENDATION TO AEC FOR APPROVAL**

1.1 Julia Amunime, MPH, 200410733, (recommended to AEC for approval)
1.2 O Ikeakanam, Doctor of Nursing science (recommended to AEC for approval)
1.3 Harriet Kagoya, PhD in Public Health (recommended to AEC for approval)
1.4 Roswitha Mahalie, PhD, Public Health (recommended to AEC for approval)
1.5 Adenuga B Aderemi, PhD in Pharmacy (recommended to AEC for approval

Annexure 1.2 Ministry of Health and Social Services

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
Windhoek
Namibia

Ministerial Building
Harvey Street
Windhoek

Tel: 061 – 203 2507
Fax: 061 – 222558
E-mail: itashipu87@gmail.com

OFFICE OF THE EXECUTIVE DIRECTOR

Ref: 17/3/3 MMM
Enquiries: Mr. A. Shipanga

Date: 04 February 2021

Dr. Mandiudza M. Murakwani
PO Box 8249
Bachbrecht
Windhoek

Dear Dr. Murakwani

Re: A comparison of intrathecal morphine with fentanyl on the duration of postoperative analgesia at Namibia Teaching hospitals in Windhoek.

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

3.4 A quarterly report to be submitted to the Ministry's Research Unit;

3.5 Preliminary findings to be submitted upon completion of the study;

3.6 Final report to be submitted upon completion of the study;

3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

BEN NANGOMBE
EXECUTIVE DIRECTOR

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

"Health for All"

Annexure 2: Research permission letters

Annexure 2.1: Intermediate Hospital, Katutura

Republic of Namibia

Ministry of Health and Social Services

Private Bag 13215
WINDHOEK
Namibia

Intermediate Hospital Katutura
Independence Avenue
WINDHOEK

Telephone (061) 203 4004/5
Telefax (061) 222706

Enquiries: Dr. F. M. Shiweda

Date 31 May 2021

OFFICE OF THE CHIEF MEDICAL OFFICER

Dr. Manduidza M. Murakwani
P. O. Box 8249
Bachbrecht
Windhoek

Dr. M. M. Murakwani

RE: **A COMPARISON OF INTRATHECAL MORPHINE WITH FENTANYL ON THE DURATION OF POSTOPERATIVE ANALGESIA AT NAMIBIA TEACHING HOSPITAL IN WINDHOEK.**

The above mentioned subject refers:

This office hereby grants you permission to do a research on a comparison of intrathecal morphine with fentanyl on the duration of postoperative analgesia at Katutura Hospital, Khomas Region, MoHSS.

Please provide this office with a copy of your findings.

Thank you

Yours in health,

1/6/2021

DR. F. M. SHIWEDA
CHIEF MEDICAL OFFICER

MINISTRY OF HEALTH
AND SOCIAL SERVICES
P/BAG 13215
WINDHOEK NAMIBIA
31 -05- 2021
INTERMEDIATE HOSPITAL KATUTURA

Annexure 2.1: Windhoek Central Hospital

9-0/0001

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13215
Windhoek
Namibia

Harvey Street
Windhoek

Tel. No: (061) 203 3024
Fax No: (061) 222886

Enquiries: Mrs. S. Iipinge | Ref. 17/3/3MMM | Date: 01 June 2021

OFFICE OF THE CHIEF MEDICAL SUPERINTENDENT
WINDHOEK CENTRAL HOSPITAL

Dr Mandiudza M. Murakwani
PO Box 8249
Bach Brecht
Windhoek
0818379254/081459692

Dear Dr. Murakwami

SUBJECT: PERMISSION TO CONDUCT A RESEARCH STUDY ON THE COMPARISON OF INTRATHECAL MORPHINE WITH FENTANYL ON THE DURATION OF POSTOPERATIVE ANALGESIA AT WINDHOEK CENTRAL HOSPITAL.

1. Reference is made to your application to conduct the above-mentioned study.

2. This letter serves to inform you that permission has been granted for you to conduct a study at Windhoek Central Hospital, on the above mentioned subject as you have requested and does not include any remuneration.

3. Patient/Client's information should be kept confidential at all times.

4. Preliminary findings to be submitted to Customer care office, Windhoek Central Hospital upon completion of the study.

Thank you for ~~your kind~~ gesture.

Yours sincerely

MINISTRY OF HEALTH AND SOCIAL SERVICES
Private Bag 13215
02-06-2021
Windhoek Namibia
WINDHOEK CENTRAL HOSPITAL

Dr. D.I.UIRAB
CHIEF MEDICAL SUPERINTENDENT

"Your Health, Our Concern"

Annexure 3: Informed Consent

INFORMED CONSENT

A comparison of intrathecal morphine and fentanyl on the duration of postoperative analgesia at Namibian Teaching Hospitals in Windhoek

Title:	Dr.		Initials: M.M
Surname	Murakwani		
Name/s:	Mandiudza Maria		
Academic or equivalent Institutions to which affiliated		Past: University of Zimbabwe	Present: University of Namibia
Present Academic Rank		Anaesthesia Registrar	
Work and employment experiences		Past: Parirenyatwa Hospital, Zimbabwe	Present: Windhoek central and Katutura Intermediate Hospitals
Physical Contact Details {Courier Delivery }:		Erf 1594/1, Specht street, Hochland Park, Windhoek	
Telephone numbers1:		Office: 061 203 3100	Cell: 081 837 9254 / 081 451 9692
Email address:		chadamburamm@yahoo.com	
Academic qualifications and Year obtained/institution		MBChB 2006 University of Zimbabwe DA 2011 Colleges of Medicine of South Africa	
Area/s of Expertise/Specialisation		Primary Anaesthesia	Secondary

Record of publications in the last 10 years

ARTICLES IN PEERED REVIEWED JOURNALS/PROCEEDINGS

Co-author of the case report on Emergence delirium in a schizophrenic patient who underwent craniotomy for elevation of depressed skull fracture under general anaesthesia – Published in the International Journal for case reports, 20 August 2018.

NATIONAL AND INTERNATIONAL CONFERENCES

NONE

CONTRIBUTION IN BOOKS, CHAPTERS IN BOOKS ECT

NONE	NONE

List of **key research projects** undertaken or coordinated for the last 10 years, starting with the most recent:

NONE

Record of **postgraduate student supervision** for the last 10 years, starting with the most recent:

NONE

Principal investigator: Dr. Mandiudza M. Murakwani

Phone numbers: 0814519692 / 0818379254

Sponsor of the Research: None

Research approval number: 17/3/3 MMM

Purpose of the research:

The study will compare the duration of postoperative analgesia of intrathecal fentanyl, morphine for femur fracture surgery as well as the total opioid consumption during the first 24hours.

Procedure of the research:

You are being selected to participate in the study because you meet the following inclusion criteria: you are 18 years and above and you are scheduled for femur fracture surgery under spinal anaesthesia. If you agree to take part in this study, you will be asked questions about the level of pain you have at rest and during movement after spinal anaesthesia. If you agree to participate after reading this consent form, on the day of the operation you will receive spinal anaesthesia and you will assessed 2h, 4h, 6h, 12h, and 24h after the spinal anaesthesia. The verbal numeric rating scale (VNRS) will be used from 0 = no pain to 10 = most severe pain imaginable, which you would self-report to the investigator. The femur fracture operation and spinal anaesthesia would be performed according to the standard operating protocols. Standard monitoring and care during and after the surgery will be given to you. Clinical parameters such as your blood pressure, pulse rate and oxygen saturation will be measured at regular intervals throughout surgery and postoperatively.

Potential risks:

The potential risks are those for every surgery done under spinal anaesthesia such as a fall in blood pressure, slowing or increasing of the heart rate, failure of the spinal block to provide adequate anaesthesia as well as nausea and vomiting. However, these effects are treatable if they do occur.

Potential benefits:

The goal of this study is to improve knowledge and practice of postoperative pain management for patients who have femur fracture surgery.

Financial implication for joining the research:

Participation in this research will not cost you anything except the usual hospital charges for medical services rendered. There will be no waiver of prescribed hospital fees. There will be no payment for participating in this research.

Confidentiality:

To ensure confidentiality a number will be assigned to you and your name will not be written on the questionnaire. The principal investigator will store the data obtained in a computer system with a password only known by her.

Voluntariness:

Participation in this survey is entirely voluntary. We will greatly appreciate your help in taking part in this survey. You are free to decline participation in the survey.

Alternatives to participation:

Your treatment in the hospital will not be affected by your refusal to participate in this research. You have a right to withdraw from the research at any given time, if you choose to.

Consequences of participants' decision to withdraw from the research and procedure for orderly termination of participation:

As a participant you are free to withdraw from the research at any point in time. You must note that information gathered about you before this withdrawal may have been analysed and used in reports and publications. These cannot be withdrawn anymore. However, we promise to comply with your wishes as much as possible.

What happens to participants at the termination of the research?

The outcome of this research will be made available to the University of Namibia as well as the Ministry of Health and Social Security. As a participant of this research, you will be notified if any further information is required or any further participation.

AUTHORIZATION

I GIVE CONSENT TO BE PART OF THIS STUDY THAT HAS CLEARLY BEING OUTLINED TO ME. MY SIGNATURE INDICATES THAT I HAVE READ AND UNDERSTOOD THE INFORMATION PROVIDED ABOVE. I HAVE HAD ALL MY QUESTIONS ANSWERED AND HAVE DECIDED TO VOLUNTARILY PARTICIPATE.

RESEARCH PARTICIPANT:

Signature: _____

Date: _____

STAFF OBTAINING CONSENT:

Signature: _____

Date: _____

A COPY OF THIS CONSENT FORM WILL BE PROVIDED TO YOU.

Annexure 4: Questionnaire

QUESTIONNAIRE

A comparison of intrathecal morphine and fentanyl on the duration of postoperative analgesia at Namibian Teaching Hospitals in Windhoek

1. Serial number_____
2. Diagnosis_____
3. Date of procedure_____
4. Name of procedure_____
5. Sex: M/F (circle)
6. Age_____
7. Time spinal anaesthesia was performed (time zero)- H
8. Postoperative pain assessment – Verbal numeric rating scale

a) 2 hours /10 at rest /10 with movement

b) 4 hours /10 at rest /10 with movement

c) 6 hours /10 at rest /10 with movement

d) 12 hours /10 at rest /10 with movement

e) 24 hours /10 at rest /10 with movement

9. Postoperative time to first request for rescue opioid analgesia - hours
10. Total opioid analgesic doses given in 24 hours - doses
11. Side effects

a) Nausea and vomiting Yes No

b) Pruritus Yes No

c) Respiratory rate <10breaths/minute Yes No

d) Saturation (SaO2) <90% Yes No

e) Other ……... Yes No

12. Patient satisfaction with the effect of the treatment of postoperative pain

a) Very satisfied 0

b) Satisfied 1

c) Somewhat satisfied 2

d) Dissatisfied 3