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The use of intrathecal morphine for acute perioperative pain in lower limb arthroplasty surgery: a survey of practice at an academic hospital.

Mpumelelo Bridget Sibanyoni

A research report submitted to the Faculty of Health Science, University of the Witwatersrand, in the Fulfilment of the requirement for the degree Of Masters of Medicine in the branch of Anaesthesiology.

Johannesburg, 2022

Declaration

I, Mpumelelo Bridget Sibanyoni, declare that this research is my own work. It is being submitted for the degree of Masters of Medicine in the branch of Anaesthesiology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or exam at this or any other university.

_____

Signed M.B Sibanyoni

15 May 2022

Abstract

Background and purpose of study

Intrathecal morphine (ITM) provides optimal postoperative analgesia in patients who are scheduled for total knee and hip operation with spinal anaesthesia. However, the ideal dose at which maximal analgesic effect occurs with minimal side effects is not known. This study aimed to describe the use of two doses of ITM, and side effect profile in patients undergoing elective hip and knee arthroplasty.

Methods

This was a prospective, descriptive, and contextual study conducted on patients who had total hip and knee replacement at Chris Hani Baragwanath Academic Hospital from 1 September to 30 November 2020. The sample size consisted of 66 patients who were 18 years and older, American Society of Anaesthesiology (ASA) classification 1-3, patients who had received either 100 mcg or 150 mcg ITM dose under spinal anaesthesia and sent to the ward postoperatively. Visual Analogue Scale (VAS) score was used to assess pain in the first 24 hours, consumption of rescue analgesia and reported side effects were documented.

Results

There was no relationship between age, weight, ASA classification or type of surgery between VAS score classification groups. Patients who received 100 mcg ITM had a higher median VAS pain score 2 (1-5) compared to those who received 150 mcg ITM 1 (0-2), p = 0.01. The need for rescue analgesia between the two groups was marginally less in the 150mcg ITM group (p =0.098). There was no difference in the rate of side effects between the 100 mcg ITM group [12 (41%)] and the 150 mcg ITM group [17 (59%)], p = 0.92. Rescue analgesia was marginally

different between groups, p = 0.09. There were no real differences in the VAS pain scores between the total knee and total hip surgeries. None of the patients experienced clinically significant respiratory depression.

Conclusion

The 150mcg ITM dose provided good analgesic effects with longer duration of action and comparable side effect profile to the 100mcg ITM dose. This dose was not associated with development of respiratory depression and can therefore administered safely to patients who are discharged to the ward postoperatively in a resource constraint environment.

Keywords: Intrathecal morphine, spinal anaesthesia, hip arthroplasty, knee arthroplasty

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Section 1: Literature Review

1.1 Background and historical review

Osteoarthritis is a common musculoskeletal condition that occurs in the elderly due to degenerative changes of wear and tear to the joint. This results in significant pain, and reduced activity of daily living and poor quality of life. Arthroplasty surgery is the treatment of choice for end stage osteoarthritis (1). With the ever-increasing elderly population, there has been a marked increase in demand for total hip and knee replacement surgery. By the year 2030, the demand for total hip and knee arthroplasty is predicted to rise by 174% and 674% respectively so as to maintain quality of life (1).

Hip and knee arthroplasty are painful procedures. Poor pain management augments the stress response which has deleterious effects such as the release of hormones (cortisol, glucagon, and catecholamines) which leads to the increase in oxygen demand in the body that may result in myocardial ischemia after a non-cardiac surgery (2). Poor pain management may also result in suppression of the immune system which predisposes the patient to infection (1). Poor pain control hampers the process of rehabilitation post-surgery, which is one of the corner stone to enhanced recovery post-surgery (3). Immobilisation post-surgery has serious potential complications such as ileus, deep venous thrombosis, pulmonary embolism, and pneumonia (1, 2). Postoperative pain can lead to chronic pain if treated inadequately (1).

Pain in the elderly patients can cause delirium, and anxiety disorder (1, 2). These factors not only delay recovery but also lead to prolonged hospital stay, higher medical costs, and increased burden of work to the healthcare workers (3).

1.2 Multimodal analgesia

The use of multimodal analgesia helps to improve, and accelerate recovery (4). Multimodal analgesia has been advocated as the gold standard for hip and knee arthroplasty (4). It entails the use of different classes of drugs which target different receptors, and different nociceptive pathways (5). It includes patient-controlled analgesia, epidural continuous infusion or patient controlled infusion, peripheral nerve blocks, peri-articular injections, paracetamol, non-steroidal anti-inflammatory drugs, oral opioids, steroids, anticonvulsants, and intrathecal opioids with or without local anaesthetic (5). Intrathecal morphine is a form of analgesic technique that is used by many institutions around the world because it provides excellent analgesia, and decreases opioid requirements postoperatively (6, 7). Intrathecal morphine use has been approved by the United States Food and Drug Administration (FDA) (7), and has been shown to be safe and effective for lower limb arthroplasty (8).

1.3 Pharmokinetic

Morphine may be added to the local anaesthetic bupivacaine for prolonged analgesic and anaesthetic effect. Intrathecal morphine has a longer duration of action due to its hydrophilic

nature, it binds with high affinity to the dorsal horn receptors of the spinal cord, and within the central nervous system, resulting in high concentrations in the CSF (7).

This leads to prolonged presence within the water-soluble CSF, results in a prolonged duration of action (up to 24 hours) after which its concentration gradually declines (7, 9). Morphine is removed from the CSF by the glycoprotein carrier transport system, which is located in the choroid plexus inside the ventricles of the brain (7, 9).

1.4 Mechanism of action

Intrathecal morphine has the same mechanism of action as the other opioids. The opioid receptors (Mu, Delta and Kappa) are all G-protein linked. They activate their signal reducing effects by: decreasing presynaptic calcium entry (inhibiting transmitter release) and increasing postsynaptic efflux of potassium (hyperpolarising cell) and inhibit adenylate cyclase thereby inhibiting transmitter release. These lead to the decreased release of glutamate and substance-p from the pre-synaptic C fibers, which block nociceptive transmission. It also decreases gamma-aminobutyric acid (GABA) and glycine from the dorsal horn of the spinal cord (7).

1.5 Advantages of intrathecal morphine

The advantages of intrathecal morphine are that it is administered at a low dose compared to oral and intravenous doses, has an analgesic effect at rest and on movement without causing lower limb muscle weakness, therefore allows early mobilisation and rehabilitation (1, 7). Intrathecal

morphine is easy to administer, fast and reliable (1, 7). However, it is not without adverse effects. The side effect profile includes pruritus, nausea and vomiting, urinary retention, and delayed respiratory depression (9-12).

1.6 Side effects

Pruritus is the most common side effect and has a reported incidence that varies in rates 0% to 100% across the literature (9, 11). Pruritus is caused by the spread of morphine to the trigeminal nuclease located in the medulla of the brain (9, 12,13). The itch reflex then occurs as morphine interacts with the trigeminal nuclease (9, 12, 13). It is also suggested that pruritus occurs when morphine binds to serotogenic receptors (9, 12, 13). Naloxone, which is a mu antagonist, is the treatment of choice for pruritus, and acts without reversing the analgesic effect of morphine. Ondansetron is a serotogenic antagonist, and nalbuphine a mu antagonist and a kappa agonist, which can also be used to treat pruritus (9, 13).

Nausea and vomiting is a frequently occurring side effect with an incidence of up to 30% (9, 11). Nausea and vomiting is caused by the cephalad spread of morphine in the cerebrospinal fluid. In the brain, the chemoreceptor trigger zone area postrema interacts with opioid receptors (9, 13). Other mechanisms that cause nausea and vomiting are the sensitization of the vestibular system, and delayed gastric emptying (9, 13). Drugs that are used to treat nausea and vomiting are meclizine, promethazine, and metoclopramide (9, 11).

The incidence of urinary retention is 42% to 80% (6,9,13). Intrathecal morphine inhibits the sacral plexus (parasympathetic nervous system) in the sacral spinal cord by interacting with mu and delta receptors, resulting in the relaxation of the detrusor muscles which are located within the urinary bladder wall (6, 9, 13). This leads to urinary retention. The treatment of urinary retention is either catheterisation of the urinary bladder, or administration of bethanecol (6, 9).

Delayed respiratory depression is infrequent, but is the most feared side effect which is not well defined (9, 14). Samuel et al. (14) defined delayed respiratory depression as a respiratory rate of less than 10 breaths per minutes, oxygen saturation of less than 90%, arterial carbon dioxide of more than 50mmHg, and sedation. Delayed respiratory depression occurs when morphine in the cerebrospinal fluid reaches the respiratory centre in the ventral medulla of the brain stem (9, 15, 16). Delayed respiratory depression usually occurs 3.5 hours to 12 hours after intrathecal morphine injection with a peak at 6 hours (9, 13, 17).

The incidence of respiratory depression following intrathecal morphine administration is low, and has even been documented not to occur in some studies or cases (14, 15). The dosage of intrathecal morphine which causes a respiratory depression has not been determined, and is therefore unclear (14). However, there is a dose related side effect correlation (16). The incidence of respiratory depression raises a question about whether to monitor patients in an intensive care unit or high care postoperatively (14, 18). Increased monitoring of the patients is a challenge, particularly in hospitals with limited resources (8, 12, 18). The treatment for respiratory depression is naloxone which is a mu antagonist, or nalbuphine which is a mu antagonist and a kappa agonist, together with ventilatory support where indicated (9).

1.7 Conclusion

There is no fixed recommended dose of intrathecal morphine (7). Intrathecal morphine doses range from 0,1 mg to 0,5 mg depending on the type of surgery (7). According to Bujedo (17), intrathecal morphine at low doses, 100 mcg to 200 mcg, combined with a local anaesthetic for regional anaesthesia were used in arthroplasty surgery, and achieved satisfactory postoperative pain control. Higher doses are said not to be necessary, and are important for limiting side effects (12, 17, 19).

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Section 3: Draft article

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The use of intrathecal morphine for acute perioperative pain in lower limb arthroplasty surgery: a survey of practice at an academic hospital.

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Abstract

Background and purpose of the study: Intrathecal morphine (ITM) provides optimal postoperative analgesia in patients who are scheduled for total knee and hip operation with spinal anaesthesia. However, the ideal dose at which maximal analgesic effect occurs with minimal side effects is not known. This study aimed to describe the use of two doses of ITM, and side effect profile in patients undergoing elective hip and knee arthroplasty.

Methods: This was a prospective, descriptive, and contextual study conducted on patients who had total hip and knee replacement at Chris Hani Baragwanath Academic Hospital from 1 September to 30 November 2020. The sample size consisted of 66 patients who were 18 years and older, American Society of Anaesthesiology (ASA) classification 1-3, patients who had received either 100 mcg or 150 mcg ITM dose under spinal anaesthesia and sent to the ward postoperatively. Visual Analogue Scale (VAS) score was used to assess pain in the first 24 hours, consumption of rescue analgesia and reported side effects were documented.

Results: There was no relationship between age, weight, ASA classification or type of surgery and VAS score classification groups. Patients who received 100 mcg ITM had a higher median VAS pain score 2 (1-5) compared to those who received 150 mcg ITM 1 (0-2), $p = 0.01$. The need for rescue analgesia between the two groups was marginally less in the 150mcg ITM group ($p = 0.098$). There was no difference in the rate of side effects between the 100 mcg ITM group [12 (41%)] and the 150 mcg ITM group [17 (59%)], $p = 0.92$. Rescue analgesia was marginally different between groups, $p = 0.09$. There were no real differences in the VAS pain scores between the total knee and total hip surgeries. None of the patients experienced clinically significant respiratory depression.

Conclusion: The 150mcg ITM dose provided good analgesic effects with longer duration of action and comparable side effect profile to the 100mcg ITM dose. This dose was not associated with development of respiratory depression can therefore be administered safely to patients who are discharged to the ward postoperatively in a resource constraint environment.

Keywords: Intrathecal morphine, spinal anaesthesia, hip arthroplasty, knee arthroplasty

Background

In 1979 Wang demonstrated the efficacy of intrathecal morphine (ITM) for postoperative analgesia in patients with genitourinary cancer, since then ITM has become widely used (1). Morphine was the first opioid to be approved by Food and Drug Administration for its use in neuraxial anaesthesia (1, 2). The added benefits of using ITM are that it is simple to administer, it is not associated with increase in blood loss during surgery and has longer duration of action (3). It is cost effective as it leads to early mobilization and decrease hospital stay (2, 4, 5).

Morphine is hydrophilic and its binds high affinity to the central nervous system opioids receptors. This results in its prolonged presence within the water-soluble cerebrospinal fluid resultings in prolonged duration of action up to 24 hours and its cause of delayed respiratory depression (1, 6, 7). Intrathecal morphine also causes other side effects such as postoperative nausea and vomiting, pruritus, and urinary retention (1, 8). Long duration of analgesia has made ITM a suitable option for postoperative analgesia in patients who are scheduled for total knee and hip operation with spinal anaesthesia (3).

The international consensus on anaesthesia-related outcome after surgery group has recommended the use of neuraxial anaesthesia during joint replacement (9). Many studies have endeavoured to define or determine the low dose of ITM with excellent analgesic effects and minimal or no side-effects (8). The dose of 100 mcg – 200 mcg ITM has been shown to provide a good balance between analgesia and side-effects (10, 11). Most patients that are scheduled for

hip and knee arthroplasty are elderly, Intrathecal morphine has the advantage of reducing the stress response and metabolic demand during surgery and anaesthesia in the elderly (12). There is contradicting evidence of where patients should be recovered post-surgery with ITM (1, 10).

We sought to assess the analgesic effect of two doses of ITM, describe the perioperative outcomes ITM related complications/side effects and to assess the safety of managing these patients in a normal ward in a resource constraint environment of arguably the largest hospital on the continent, Chris Hani Baragwanath Academic Hospital (13).

Methods

The study was conducted in the Arthroplasty unit and the Department of Anaesthesiology at Chris Hani Baragwanath Academic Hospital , affiliated with the Faculty of Health Sciences of the University of the Witwatersrand. Approval to conduct the study was obtained from the Human Research Ethics Committee and the University of the Witwatersrand and other relevant authorities. The study followed a prospective, descriptive, and contextual research design. In this study consecutive, convenience sampling method was used. The sample size was calculated based on the incidence of respiratory depression(feared side effect) which is 0.03% using the equation $n = \frac{Z^2 \times p(1-p)}{d^2} = \frac{1.96^2(0.03)(0.97)}{0.05^2} = 44.72 \approx 45\ patients$. The study needed 60 patients sample size to be significant.

This study aimed to describe the use of ITM for perioperative pain in patients undergoing hip and knee arthroplasty who were discharged to the ward postoperatively and the side effect profile associated with ITM injection use.

The study population included patients 18 years and older, American Society of Anaesthesiology (ASA) physical status 1- 3 scheduled for elective knee and hip arthroplasty who received ITM injection and spinal anaesthesia and sent to the ward postoperatively. Written informed consent was obtained from all patients included in the study. Patients were excluded if they were having obstructive sleep apnoea, respiratory diseases, ASA physical status 4 and above, had receive general anaesthetic and intrathecal morphine, and patient records which were illegible. The study period was from 1 September to 30 November 2020.

After the procedure, patients were monitored in the recovery room then discharged to the ward. In the ward patients were monitored for postoperative pain, pruritus, nausea and vomiting and respiratory depression for the first 24 hours. Respiratory depression was defined as respiratory rate of less than 10 breaths per minutes or oxygen saturation of less than 90%. Patients were treated for the side effects if they experience any.

Pain scores were evaluated using a visual analogue scale from 0 to 10 with 0 indicating no pain and 10 severe pain. Rescue analgesia and time from ITM administration were also documented. The rescue analgesia regimen included paracetamol 1 g, tramadol hydrochloride dose 50 -100 mg, and pethidine 50-100 mg. The pain free hours were divided into 3-hour periods and the median VAS pain scores within the first 24-hours were determined for each group. Patients received either 100 mcg or 150 mcg ITM depending on the anaesthetist who was administering the spinal anaesthesia, automatically patients were divided into two groups according to the dose their received.

Statistical Analysis

Sixty-six patients participated in the study. The categorical variables were described using frequencies and percentages. We used the chi-square test for significance of association between categorical variables and the intrathecal morphine dose (outcome). The Fisher's exact test was used to find the association between categorical variables (age, ASA and type of surgery) and VAS pain scores. Continuous variables were described using median and interquartile ranges since they were not normally distributed according to the Shapiro-Wilk test.

The relationship between continuous variables and intrathecal morphine dose (outcome) was assessed using the Mann-Whitney test. Weight and VAS pain scores association was assessed using the Kruskal Wallis test which is a non-parametric alternative to ANOVA

Results

Sixty-six patients received spinal anaesthesia with ITM injection. Of the 66 patients, 29 (44%) received 100 mcg ITM dose and 37 (56%) received 150 mcg ITM dose. From the 100 mcg ITM dose group, 11 (38%) were male and 18 (62%) were female (Table 1). From the 150 mcg ITM dose group 19 (51%) were male and 18 (49%) were female. Majority of the patients were 50 years old and older. The median (IQR) weight of the patients was 75 (65 – 79) kg in the 100 mcg ITM group and 73 (65 -80) kg in the 150 mcg ITM group (Table 1).

In total, 8 (12.12%) patients were classified as ASA I, 53 (80%) ASA II and 5 (8%) were ASA III. There were 48 (73%) who underwent hip arthroplasty patients compared to 18 (27%) who were underwent knee arthroplasty in the study. Within the hip arthroplasty group 23 (48%) had 100 mcg IT morphine dose while only 6 (33%) of the knee arthroplasty received 100 mcg IT morphine. Twenty-five (52%) patients received 150 mcg IT morphine from the hip arthroplasty group and 12 (67%) patients from the knee arthroplasty group. The overall bupivacaine dose administered was median (IQR) was 14 (13 – 14.5), 13 (12 – 14) in the 100 mcg ITM group and 14 (14 – 15) in the 150 mcg ITM group.

Table 1: Demographic and baseline characteristics

Variable		Overall n = 66	100 mcg ITM n = 29	150 mcg ITM n = 37
Gender	Male	30 (45)	11 (37)	19 (63)
	Female	36 (55)	18 (50)	18 (50)
Age in years	<40	7 (11)	0 (0.0)	7 (100)
	40 – 49	5 (8)	1 (20)	4 (80)
	50 – 59	19 (29)	10 (53)	9 (47)
	60 – 69	23 (31)	9 (39)	14 (61)
	70 +	12 (18)	9 (75)	3 (25)
Weight [Median (IQR)]		74.5 (65 – 80)	75 (65 – 79)	73 (65 – 80)
ASA	I	8 (12)	3 (38)	5 (62)
	II	53 (80)	25 (47)	28 (53)
	III	5 (7.58)	1 (20)	4 (80)
Surgery	THR	48 (73)	23 (48)	25 (52)
	TKR	18 (27)	6 (33)	12 (67)
Bupivacaine	Median (IQR)	14 (13 – 14.5)	13 (12 – 14)	14 (14 – 15)

*Abbreviation: ITM (intrathecal morphine), Abbreviation: ITM intrathecal morphine, THR total hip replacement, TKR total knee replacement, ASA American Society of Anaesthesiology.

There was no relationship between age, weight, ASA classification or type of surgery between VAS score classification groups (Table 2).

A total of 29 (44%) patients did not have side effects in the study. There was no difference in the rate of side effects between the 100 mcg ITM group [12 (41%)] and the 150 mcg ITM group [17 (59%)], p = 0.92 (Table 3). Pruritus was not dose dependant as 11 (50%) patients in each ITM group had pruritus with a total of 22 (33%) overall. The overall number of patients who developed nausea and vomiting was 5 (8%) with 2 (40%) patients in the 100 mcg ITM group and 3 (60%) in the 150 mcg ITM group. Patients who had both pruritus, nausea and vomiting accounted for only 10 (15%) patients of which 4 (40%) were in the 100 mcg ITM group and 6 (60%) in the 150 mcg ITM group. None of the patients experienced clinically significant respiratory depression.

Table 2: Comparison between VAS pain scores and basic characteristics categories

Variable		VAS pain scores n (%)				p-value
		None	Mild 1 – 3	Moderate 4 – 6	Severe >6	
Age in years	<40	3 (43)	2 (29)	1 (14)	1 (14)	0.45
	40 – 49	2 (40)	1 (20)	2 (40)	0 (0)	
	50 – 59	4 (21)	10 (53)	4 (21)	1 (5)	
	60 – 69	4 (17)	14 (61)	1 (4)	4 (18)	
	70 +	2 (17)	6 (50)	2 (17)	2 (17)	
Weight	Median (IQR)	73 (60 – 85)	70 (65 – 80)	73 (69 – 79)	75 (75 – 81)	0.48
ASA	I	1 (12)	5 (63)	1 (12.5)	1 (12.5)	0.61
	II	13 (25)	26 (49)	9 (17)	5 (9)	
	III	1 (20)	2 (40)	0 (0)	2 (40)	
Surgery	THR	11 (23)	24 (50)	9 (19)	4 (8)	0.34
	TKR	4 (22)	9 (50)	1 (6)	4 (22)	

There was a significant difference in median (IQR) VAS pain scores between the 100 mcg ITM and the 150 mcg ITM groups [2 (1 – 5) and 1(0 – 2), respectively], p = 0.01. The need for rescue analgesia between the 100 mcg and 150 mcg ITM groups was marginally different (p = 0.098). Of note is that 19 (29%) patients did not require rescue analgesia. The use of phenylephrine (PEP) and ephedrine was not different between groups.

Table 3: Comparison of post-operative outcomes by ITM dose

Variable		Overall n = 66	100 mcg ITM n = 29	150 mcg ITM n = 37	p-value
Side	None	29 (44)	12 (41)	17 (59)	0.92
Effects	Pruritus	22 (33)	11 (50)	11 (50)	
	Nausea & Vomiting	5 (8)	2 (40)	3 (60)	
	Both	10 (15)	4 (40)	6 (60)	
PEP	Yes	21 (32)	10 (48)	11 (53)	0.68
	No	45 (68)	19 (42)	26 (58)	
Ephedrine	Yes	7 (11)	4 (57)	3 (43)	0.46
	No	59 (89)	25 (42)	34 (58)	
Rescue	Paracetamol	3 (5)	3 (100)	0 (0)	0.098
analgesia	Tramadol hydrochloride	21 (32)	11 (52)	10 (48)	
	Pethidine	15 (23)	5 (33)	10 (67)	
	Paracetamol & Tramadol hydrochloride	6 (9)	4 (45)	2 (33)	
	Paracetamol & Pethidine	2 (3)	1 (50)	1 (50)	
	None	19 (29)	5 (26)	14 (74)	
Pain free time (min) [Median (IQR)]		720 (540 – 1110)	675 (540 – 785)	720 (550 – 1440)	0.31
VAS score Median (IQR)		2 (1 – 4)	2 (1 – 5)	1 (0 – 2)	0.01

*Abbreviation: VAS visual analogue score, PEP phenylephrine, ITM – intrathecal morphine

The patients who had received 100 mcg of ITM had a relatively higher VAS pain score within the first 24 hours when compared to those who received 150 mcg ITM after adjusting for the time it took to start feeling pain (Figure 1).

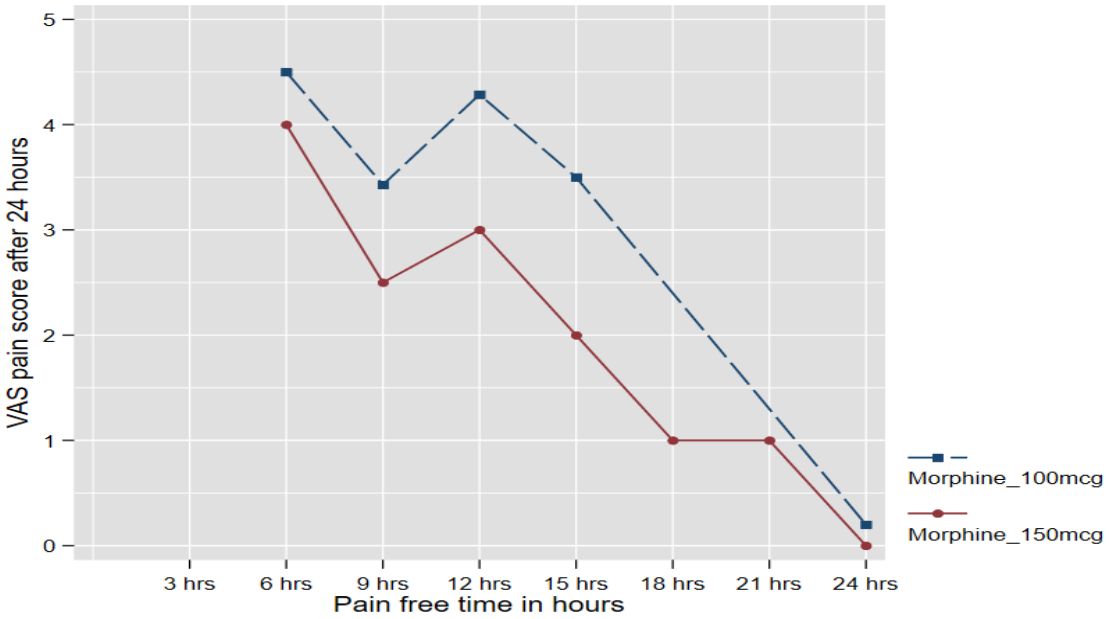

Figure 1: VAS pain scores for patients given 100mcg ITM group and the 150mcg ITM group adjusted for the number of hours it took for the patient to start feeling pain within the first 24 hours.

Although the side effect profile was statistically not different (Figure 2), the percentage of patients who had both pruritus, nausea and vomiting as side effects was high in the 150 mcg ITM group compared to 100 mcg ITM group.

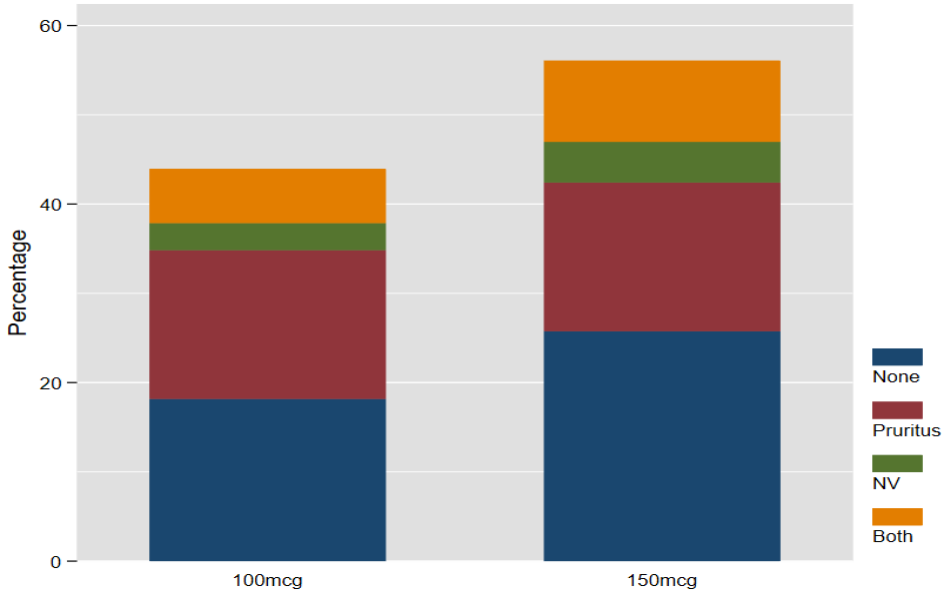

Figure 2: Comparison of side effect profiles between groups

There were no real differences in the VAS pain scores between the two surgeries as observed from the line graphs which cross multiple times in the illustration (Figure 3).

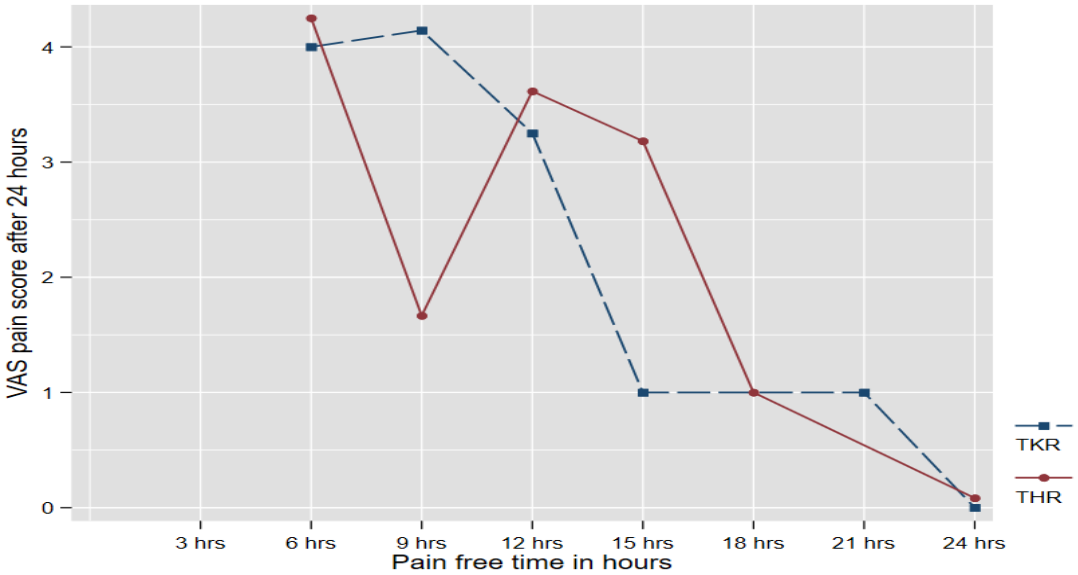

Figure 3: VAS pain score by type of surgery (TKR and THR) adjusted for the pain free hours.

Discussion

Median (IQR) VAS pain scores were lower in the 150 mcg ITM group [1(0 – 2)] compared to the 100 mcg ITM group [2 (1 – 5)], p = 0.01. Many studies have been done to find the suitable dose of intrathecal morphine or defining the dose of intrathecal morphine in patients undergoing hip and knee arthroplasty which provide good analgesia and less side effects (3, 5, 7, 8, 10, 11, 14-16) In our setting, the importance is in finding a suitable dose with analgesic effects, and fewer side effects to allow for our patients to be cared for in a normal ward. Dose–response studies demonstrated that ITM have an analgesic efficacy ceiling and the optimal dose of ITM is 0.075 - 0.15 mg (2).

Although there was no significant difference in pain free time between the two groups, there was a marginal difference in need for rescue analgesia with those in the 150 mcg ITM needing less. Importantly no cases of respiratory depression were reported, not only making the 150 mcg ITM superior in pain relief but equivalent statistically in side effect profile.

The 150 mcg ITM group had a high percentage of patients who had nausea and vomiting compared to the 100 mcg ITM group. However, the percentage of patients who had both pruritis, nausea and vomiting as side effects was higher in the 150 mcg ITM group compared to 100mcg ITM group. Previous studies have demonstrated that higher doses of ITM were associated with higher incidences of nausea and vomiting (5, 8, 9, 16). The incidence and severity of nausea and

vomiting is a major concern following the use of ITM particularly as orthopaedic surgery on it own is an independent risk factor of nausea and vomiting (3, 5, 10, 17).

Hassett et.al demonstrated that patients who received 100 mcg ITM had poor pain management compared to the patients who received 200 mcg ITM and 300 mcg ITM (7). The median time to request first rescue analgesia was lower in 100 mcg IT morphine which was 442 minutes compare to 200 mcg IT morphine 607 minutes and 300 mcg IT morphine 857 minutes. In our study we reported median time to rescue of 675 min in the 100 mcg ITM group compared to 720 min in the 150 mcg ITM group.

In this study we found no real differences in the VAS pain scores between the total hip and total knee replacement, $p = 0.34$. A previous study had reported differences in pain scores between these groups (18). The requirement for rescue analgesia (intravenous morphine) was similarly found to be reduced in patients who have total hip replacement compare to total knee replacement (14).

In this study, there were no cases that were reported to have experienced respiratory depression. Some studies use intravenous opioids or patient – controlled analgesia with opioids as rescue analgesia which can also cause respiratory depression (2, 19, 20). The incidence of respiratory depression has been found to be as low as 3% using a doses 0.2 mg to 0.8 mg ITM in one study (21). We postulate that this may be the contributing factor. Delayed respiratory depression occurs at 6 -12 hours and may persist up to 24 hours (22-24).

The median bupivacaine was 13 mg in the 100 mcg ITM and 14 mg in the 150 mcg ITM group respectively and use of phenylephrine and ephedrine were not significantly different, $p = 0.68$ and $p = 0.46$ respectively. Majority of patients were ≥50 years old with no differences in baseline characteristics. More had total hip replacement than total knee replacement.

Limitations

The study is contextual with a small sample size. The results cannot therefore be generalized. It however presents good data for use in similar circumstances such as low to medium income countries with constraint resources.

Conclusion

A 150mcg ITM dose can be used with good postoperative analgesic effects, with longer duration of analgesia and reduced postoperative requirement of rescue analgesia compared to 100mcg in patients scheduled for total hip and knee arthroplasty. Although nausea and vomiting, pruritis were reported at this dose, they were not significantly different and were successfully treated. Most importantly, at this dose, the most dreadful side effect of delayed respiratory depression was not reported. Thus, patients who received 150mcg ITM were safe in a non-high dependency area such as a normal ward postoperatively provided anticipated side effects can be monitored and managed timeously.

Abbreviations

ITM : Intrathecal morphine ; VAS : Visual analogue scale; PEP : Phenylephrine ; ASA American society of anaesthesiology; THR : Total hip replacement ; TKR : Total knee replacement ; NV : Nausea and vomiting

Ethics approval and consent to participate

This study was approved by the Human Research Ethics committee (medical) of the University of the Witwatersrand with the approval number M200670. The patient provided written consent. All methods were carried out in accordance with Declaration of Helsinki and South African Good Clinical Practice Guideline.

Consent for publication

Not applicable

Availability of data and materials

The data is available from the corresponding author on request.

Competing interest

No competing interest.

Funding

No funds were needed in the study.

Authors contributions

MS, NB and NM design, analysed the data and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgement

Not applicable.

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Section 4: Appendices

Appendix 1: Human Research Ethics Committee (Medical) approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr MB Sibanyoni

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200670

NAME: (Principal Investigator)	Dr MB Sibanyoni
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesia Medical School University
PROJECT TITLE:	The use of intrathecal morphine for acute perioparative pain in the lower limb arthroplasty surgery: a survey of practice at an academic hospital
DATE CONSIDERED:	2020/06/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr N Biyase
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/09/07

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore reports and re-certification will be due early in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

Appendix 2: Postgraduate approval

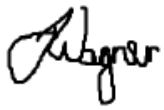
09-06-2010

To whom it may concern

RE: Postgraduate Committee recommended corrections for MMED research proposal for Mpumelelo Bridget Sibanyoni (student number 0604718N). The use of intrathecal morphine for acute perioperative pain in lower limb arthroplasty surgery: a survey of practice at an academic hospital.

Please be advised that I have reviewed the corrections recommended by the Postgraduate Research Committee and find that the student has satisfactorily addressed the committee's concerns.

Kind regards



Dr Janine Wagner

Meeting Chair

Section 5: Proposal

The use of intrathecal morphine for acute perioperative pain in lower limb arthroplasty surgery: a survey of practice at an academic hospital.

Mpumelelo Bridget Sibanyoni

0604718N

Supervisor: Ntombiyethu Biyase

Department of Anaesthesiology

Co-Supervisor: Nolwazi Mokitimi

Department of Anaesthesiology

5.1 Introduction and background

Osteoarthritis is a common musculoskeletal condition that occurs in the elderly due to degenerative changes of wear and tear to the joint. This results in significant pain, and reduced activity of daily living and poor quality of life. Arthroplasty surgery is the treatment of choice for end stage osteoarthritis (1). With the ever-increasing elderly population, there has been a marked increase in demand for total hip and knee replacement surgery. By the year 2030, the demand for total hip and knee arthroplasty is predicted to rise by 174% and 674% respectively so as to maintain quality of life (1).

Hip and knee arthroplasty are painful procedures. Poor pain management augments the stress response which has deleterious effects such as the release of hormones (cortisol, glucagon, and catecholamines) which leads to the increase in oxygen demand in the body that may result in myocardial ischemia after a non-cardiac surgery (2). Poor pain management may also result in suppression of the immune system which predisposes the patient to infection (1). Poor pain control hampers the process of rehabilitation post-surgery, which is one of the corner stone to enhanced recovery post-surgery (3). Immobilization post-surgery has serious potential complications such as ileus, deep venous thrombosis, pulmonary embolism, and pneumonia (1, 2). Postoperative pain can lead to chronic pain if treated inadequately (1). Pain in the elderly patients can cause delirium, and anxiety disorder (1, 2). These factors not only delay recovery but also lead to prolonged hospital stay, higher medical costs, and increased burden of work to the healthcare workers (3).

The use of multimodal analgesia helps to improve, and accelerate recovery (4). Multimodal analgesia has been advocated as the gold standard for hip and knee arthroplasty (4). It entails the

use of different classes of drugs which target different receptors, and different nociceptive pathways (5). It includes patient-controlled analgesia, epidural continuous infusion or patient controlled infusion, peripheral nerve blocks, peri-articular injections, paracetamol, non-steroidal anti-inflammatory drugs, oral opioids, steroids, anticonvulsants, and intrathecal opioids with or without local anaesthetic (5).

Intrathecal morphine is a form of analgesic technique that is used by many institutions around the world because it provides excellent analgesia, and decreases opioid requirements postoperatively (6, 7). Intrathecal morphine use has been approved by the United States Food and Drug Administration (FDA) (7), and has been shown to be safe and effective for lower limb arthroplasty (8).

Morphine may be added to the local anaesthetic bupivacaine for prolonged analgesic and anaesthetic effect. Intrathecal morphine has a longer duration of action due to its hydrophilic nature, it binds with high affinity to the dorsal horn receptors of the spinal cord, and within the central nervous system, resulting in high concentrations in the CSF (7). This leads to prolonged presence within the water-soluble CSF, results in a prolonged duration of action (up to 24 hours) after which its concentration gradually declines (7, 9). Morphine is removed from the CSF by the glycoprotein carrier transport system, which is located in the choroid plexus inside the ventricles of the brain (7, 9).

Intrathecal morphine has the same mechanism of action as the other opioids. The opioid receptors (Mu, Delta and Kappa) are all G-protein linked. They activate their signal reducing

effects by: decreasing presynaptic calcium entry (inhibiting transmitter release) and increasing postsynaptic efflux of potassium (hyperpolarising cell) and inhibit adenylate cyclase thereby inhibiting transmitter release. These lead to the decreased release of glutamate and substance-p from the pre-synaptic C fibers, which block nociceptive transmission. It also decreases gamma-aminobutyric acid (GABA) and glycine from the dorsal horn of the spinal cord (7).

The advantages of intrathecal morphine are that it is administered at a low dose compared to oral and intravenous doses, has an analgesic effect at rest and on movement without causing lower limb muscle weakness, therefore allows early mobilisation and rehabilitation (7). Intrathecal morphine is easy to administer, fast and reliable (1, 7). However, it is not without adverse effects. The side effect profile includes pruritus, nausea and vomiting, urinary retention, and delayed respiratory depression (9-12).

Pruritus is the most common side effect and has a reported incidence that varies in rates 0% to 100% across the literature (9, 11). Pruritus is caused by the spread of morphine to the trigeminal nuclease located in the medulla of the brain (9, 12, 13). The itch reflex then occurs as morphine interacts with the trigeminal nuclease (9, 12, 13). It is also suggested that pruritus occurs when morphine binds to serotogenic receptors (9, 12, 13). Naloxone, which is a mu antagonist, is the treatment of choice for pruritus, and acts without reversing the analgesic effect of morphine. Ondansetron is a serotogenic antagonist, and nalbuphine a mu antagonist and a kappa agonist, which can also be used to treat pruritus (9, 13).

Nausea and vomiting is a frequently occurring side effect with an incidence of up to 30% (9, 11). Nausea and vomiting is caused by the cephalad spread of morphine in the cerebrospinal fluid. In the brain, the chemoreceptor trigger zone area postrema interacts with opioid receptors (9, 13). Other mechanisms that cause nausea and vomiting are the sensitization of the vestibular system, and delayed gastric emptying (9, 13). Drugs that are used to treat nausea and vomiting are meclizine, promethazine, and metoclopramide (9, 11).

The incidence of urinary retention is 42% to 80% (6,9,13). Intrathecal morphine inhibits the sacral plexus (parasympathetic nervous system) in the sacral spinal cord by interacting with mu and delta receptors, resulting in the relaxation of the detrusor muscles which are located within the urinary bladder wall (6, 9, 13). This leads to urinary retention. The treatment of urinary retention is either catheterisation of the urinary bladder, or administration of bethanecol (6, 9).

Delayed respiratory depression is infrequent, but is the most feared side effect which is not well defined (9, 14). Samuel et al. (14) defined delayed respiratory depression as a respiratory rate of less than 10 breaths per minutes, oxygen saturation of less than 90%, arterial carbon dioxide of more than 50mmHg, and sedation. Delayed respiratory depression occurs when morphine in the cerebrospinal fluid reaches the respiratory centre in the ventral medulla of the brain stem (9, 15, 16). Delayed respiratory depression usually occurs 3.5 hours to 12 hours after intrathecal morphine injection with a peak at 6 hours (9, 13, 17).

The incidence of respiratory depression following intrathecal morphine administration is low, and has even been documented not to occur in some studies or cases (14, 15). The dosage of intrathecal morphine which causes a respiratory depression has not been determined, and is therefore unclear (14). However, there is a dose related side effect correlation (16). The incidence of respiratory depression raises a question about whether to monitor patients in an intensive care unit or high care postoperatively (14, 18). Increased monitoring of the patients is a challenge, particularly in hospitals with limited resources (8, 12, 18) . The treatment for respiratory depression is naloxone which is a mu antagonist, or nalbuphine which is a mu antagonist and a kappa agonist, together with ventilatory support where indicated (9).

There is no fixed recommended dose of intrathecal morphine (7). Intrathecal morphine doses range from 0,1 mg to 0,5 mg depending on the type of surgery (7). According to Bujedo (17), intrathecal morphine at low doses, 100 mcg to 200 mcg, combined with a local anaesthetic for regional anaesthesia were used in arthroplasty surgery, and achieved satisfactory postoperative pain control. Higher doses are said not to be necessary, and are important for limiting side effects (12, 17, 19).

At Chris Hani Baragwanath Academic Hospital (CHBAH), patients who are scheduled for elective total hip and knee arthroplasty surgery, and have received intrathecal morphine, are commonly sent to the orthopaedic ward. This practice is centre dependent. In some centres patients that receive intrathecal morphine are sent to high dependency areas for postoperative monitoring irrespective of their risk profile. The aim of this study is to describe the use of

intrathecal morphine for perioperative pain in patients undergoing hip and knee arthroplasty surgery who are discharged to the ward postoperatively. Patient profile, risk profile, and outcomes will also be examined.

5.2 Aim

To describe the management and outcome/ side effect profile of intrathecal morphine use for acute perioperative pain management in patients undergoing elective lower limb arthroplasty surgery at CHBAH.

5.3 Objectives

Primary objectives:

- To determine the number of intrathecal morphine injections performed at CHBAH
- To describe the dose of intrathecal morphine and local anaesthetic used
- To describe the type, and dose, of additional analgesics given intraoperatively and within the first 24 hours postoperatively.
- To describe the side effects of patients who have received intrathecal morphine injection occurring in the first 24 hours.

Secondary objectives:

- To determine if there is an association between the intrathecal morphine doses and side effects.

5.4 Research assumptions

Intrathecal: route of administration of a drug into the spinal canal so that it can get into the cerebrospinal fluid.

Morphine: a preservative free drug that acts on opioids receptors.

Side effect: nausea and vomiting, pruritus, urinary retention (absence of spontaneous micturition at 7 hours' postoperative and more than 400mL of urine at catheterization), and respiratory depression (respiratory rate of 10 breaths per minutes, oxygen saturation less than 90 %, arterial blood gas showing acidosis and hypercapnia and sedation).

Obstructive sleep apnoea: obstruction in the upper airway fulfilling the criteria of snoring, tiredness, observed apnoea, blood pressure, body mass index, age, neck circumference, and gender (stop bang) criteria.

Respiratory disease: any disease that changes the normal physiology of the respiratory system.

ASA I: Normal healthy patient.

ASA II: Patient with mild systemic disease, and no functional limitations.

ASA III: Patient with severe systemic disease, and some functional limitations.

5.5 Demarcation of the study field

The study will be conducted in Department of Anaesthesiology, affiliated to the Faculty of Health Sciences of the University of the Witwatersrand. CHBAH has 2888 beds, 25 theatres, and 65 000 cases are done annually. There are 3 elective orthopaedics theatres, and the hospital has 7 high care beds for postoperative monitoring.

5.6 Ethical considerations

Approval to conduct the study will be obtained from Human Research Ethics Committee (medical), and the Graduate Studies Committee of the University of the Witwatersrand. Permission has been granted by the Head of Department of Anaesthesia, and the hospital Medical Advisory Committee. Patient consent will be obtained for the study. An information letter (appendix 3) will be distributed to patients participating in the study following which they will be requested to sign the consent form (appendix 3). Life threatening side effects of intrathecal morphine will be addressed during interview if they are present. Supervisor and I will have access to the data. The data will be stored securely for six years after completion of the study. The study will be conducted by adhering to good clinical research practice as per South African Good Clinical Practice Guideline (20), and The Declaration of Helsinki (21).

5.7 Research Methodology

5.7.1 Research design

Burn and Grove describe research design as a "blueprint for conducting a study as it allows maximal control over factors that could interfere with the validity of the findings of the study" (22). Polit describes the research design as a method which allows for investigating in a logical and systemic way (23).

A prospective, contextual, and descriptive design will be used in this study.

Burns and Grove describe a prospective study as a longitudinal cohort study that follows over time a group of similar individuals who differ with respect to certain factors under study, to determine how these factors affect rates of certain outcome (22).

The researcher will examine the anaesthetic charts, and the ward files of the patients who had lower limb arthroplasty. The intrathecal morphine analgesic effects, the doses that the patients received, and the side effects of intrathecal morphine will be noted. Patients will also be interviewed postoperatively.

"Contextual" is described as the small scale world which include, hospital wards, and clinics (22). This study is contextual because it examines or follow up the patients in the hospital who have already received intrathecal morphine.

Burn and Grove state that descriptive design helps to identify the problems in the current practice with a view to improve outcome (22). The aim of descriptive research is to explore and describe real life situations, and to give information of the element as they occur. The ideal dosage of intrathecal morphine has not been identified. The aim is to survey practice and patient outcome

with the view of improving patient outcome, and also poor use of intrathecal morphine can be identified, educate anaesthetists, and improved patients outcome.

5.7.2 Study population

Population is defined as the entire group of people or objects that is of interest to the research, which meet the criteria of the study (22). The study population is the patients who present for elective arthroplasty of the lower limb who meet the inclusion criteria, and who are sent to the ward after receiving intrathecal morphine injection.

5.7.3 Study sample

5.7.3.1 Sampling method

In this study consecutive, convenience sampling will be used.

In convenience (accidental) sampling subjects are included in the study because they happened to be in a right place at a right time (22).

The study will use the available patients because intrathecal morphine is not often given. In this study the patients who received intrathecal morphine for the lower limb surgery who meet the inclusion criteria will be included.

5.7.3.2 Sample size

Convenience sampling of patients who receive intrathecal morphine for hip and knee arthroplasty done during the study period (1st September to 30 November 2020) will be performed. The sample size was calculated based on the incidence of respiratory depression (feared side effect) which is 0.03% using the equation $n = \frac{Z^2 \times p(1-p)}{d^2} = \frac{1.96^2(0.03)(0.97)}{0.05^2} = 44.72 \approx 45\ patients$ The study needed 60 patients sample size to be significant. A total of 60 patients will be sampled.

This was determined in consultation with a biostatistician, and was calculated based on the number of cases performed per month at CHBAH. A p-value of 0.05 will be accepted as significant.

5.7.4 Inclusion and Exclusion criteria

Inclusion criteria:

- patients older than 18 years
- patients presenting for the elective lower limb arthroplasty who have received intrathecal morphine
- patients who are sent to the ward post intrathecal morphine
- ASA I, II, and III patients

Exclusion criteria:

- patients with obstructive sleep apnoea

- patients with respiratory disease
- records that are illegible
- patients who are classified as ASA IV and above
- patients who received a general anaesthetic and intrathecal morphine.

5.7.5 Data collection

A data collection tool is attached (Appendix 1). Patients demographics, intraoperative information, regarding side effects, time to rescue analgesia, and the rescue analgesia administered will be collected.

5.8 Data analysis

Data will be analysed with the assistance of a biostatistician. Continuous numerical data will be presented as mean and standard deviation if normally distributed, and median interquartile range if not normally distributed. Categorical data will be presented as frequency and percentages and will be analysed using the chi-square test. For study, the p-value of 0.05 will be accepted as significant. Linear regression analysis will be done to assess factors associated with morphine doses.

5.9 Significance of the study

This study, by analysing the data on intrathecal morphine injections, will give a better understanding of this practice at CHBAH.

It will describe the incidence of the side effects of intrathecal morphine injection, and may influence clinicians to allow more patients to receive intrathecal morphine injections without requiring high care or intensive care unit admission.

5.10 Validity and reliability of the study

According to Botma (24) validity is “the degree to which a measurement represents a true value”. Reliability represent the consistency the measure achieves for example if a valid instrument is used across the board, it should give the same results” (24).

Validity and reliability of this study will be ensured by the following:

- Use of an appropriate study design
- Use of appropriate data collection methods
- Use of standardized data collection spreadsheet.
- Having a single researcher collect data.

5.11 Potential limitations of the study

This will be a contextual study and therefore the results may not be generalizable to patients receiving intrathecal morphine in other settings. Convenience sampling is a poor type of sampling because it does not control bias. Records may be poorly completed or incomplete for example poorly written anaesthetic charts.

5.12 Project outline

Activity	May 2020	June 2020	July 2020	Aug 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021
Proposal preparation										
Literature review										
Proposal submission										
Ethics approval										
Postgraduate approval										
Data collection										
Data analysis										

Draft article										
Submission										

5.13 Financial plan

The Department of Anaesthesiology will incur the cost of paper and printing.

Item	**Price per page**	**Number of page**	**Copies**	**Total**
Proposal	1	15	10	R 150
Ethics	1	10	25	R 250
Postgraduate application	1	2	6	R 12
Complete report	1	100	4	R 400
Grand total				**R 812**

5.14 References

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5.15 Appendix

Appendix 1: Data collection sheet

1. **Demographics:**

Age			
Gender:	Female	Male	
Weight(kg):			
ASA:	I	II	III
Ward:	48	49	

2. **Intraoperative parameters**

Time of spinal anaesthesia:

Surgery:	Hip replacement	Knee replacement
Dose of spinal mixture:	Intrathecal morphine- mcg	Spinal bupivacaine - mg
Vasopressor total dose:	Phenylephrine- mcg	Ephedrine- mg

3. Postoperative parameters

Side effects and intervention:

Side effect	**Yes**	**No**	**Intervention**
Pruritus			
Nausea and vomiting			
Urinary retention			
Respiratory depression			

Poor outcome:

All 4

3 of 4

2 of 4

1 of 4

Average VAS score in first 24 hours (25)

0	1	2	3	4	5	6	7	8	9	10

0 – no pain

1-3 mild pain

4-6 moderate pain

7-10 severe pain

Rescue analgesia	**Type**	**Dose**	**Time**

Appendix 2: Letters requesting permission

Chris Hani Baragwanath Academic Hospital

26 Chris Hani Road

Johannesburg

1864

Dr M.B. Sibanyoni

2560 Sigegede street
Standerton

2430

16 April 2020

Dear Dr Palesa Mogane

Permission letter to collect data for the study: the use of intrathecal morphine for acute perioperative pain control in total hip and knee joint replacement (arthroplasty) surgery: a survey of practice at a tertiary Academic Hospital

I am conducting research as a part of my Masters of Medicine in Anaesthesiology.

The aim of the study is to determine the number of intrathecal morphine injections performed for lower limb arthroplasty surgery at CHBAH. To describe the dose of intrathecal morphine and local anaesthetic used; the type and dose, of additional analgesics given intraoperatively and within the first 24 hours postoperatively. As well as to describe the side effects of patients who have received intrathecal morphine injection occurring in the first 24 hours, and

to determine if there is an association between the intrathecal morphine doses and side effects.

I am requesting permission from the records gatekeeper to access the records (anaesthetic charts) until the target number of participants is reached as well as to interview patients postoperatively to assess pain scores. No extra cost will be incurred by the hospital.

There will be no harm to the patients, as the study involves interviewing the patients who have received intrathecal morphine for hip and knee arthroplasty, review of an anaesthetic charts, and no patient care will be affected. Only my supervisor and I will have access to the results thus ensuring confidentiality.

Yours sincerely

DR M. B Sibanyoni

073 156 3420

Sibanyonimpume6@gmail. com

Chris Hani Baragwanath Academic Hospital

26 Chris Hani Road

Johannesburg

1864

Dr M.B Sibanyoni

2560 Sigegede street

Standerton

2430

16 April 2020

Dear the hospital research committee

Permission letter to collect data for the study: the use of intrathecal morphine for acute perioperative pain control in total hip and knee joint replacement (arthroplasty) surgery: a survey of practice at a tertiary Academic Hospital

I am conducting research as a part of my Masters of Medicine in Anaesthesiology.

The aim of the study is to determine the number of intrathecal morphine injections performed for lower limb arthroplasty surgery at CHBAH. To describe the dose of intrathecal morphine and local anaesthetic used; the type and dose, of additional analgesics given intraoperatively and within the first 24 hours postoperatively. As well as to describe the side effects of patients who have received intrathecal morphine injection occurring in the first 24 hours, and to determine if there is an association between the intrathecal morphine doses and side effects.

I am requesting permission from the records gatekeeper to access the records (anaesthetic charts) until the target number of participants is reached as well as to interview patients postoperatively to assess pain scores. No extra cost will be incurred by the hospital.

There will be no harm to the patients, as the study involves interviewing the patients who have received intrathecal morphine for hip and knee arthroplasty, review of an anaesthetic charts, and no patient care will be affected. Only my supervisor and I will have access to the results thus ensuring confidentiality.

Yours sincerely

DR M. B Sibanyoni

073 156 3420

Sibanyonimpume6@gmail.com

Appendix 3: Consent form and information sheet

Information Sheet

Study title: The use of intrathecal morphine for acute perioperative pain in lower limb arthroplasty surgery: a survey of practice at a tertiary academic hospital.

Introduction

Good day. I am Dr Mpumelelo Sibanyoni. I am studying for a Masters in Medicine anaesthesia degree at Wits University. I am required to carry out a research project, amongst other things, to get this degree. Research is a process used in seeking new knowledge. I am inviting patients who were given intrathecal morphine after their operation to take part in my research project. The morphine is given to reduce the pain patients feel after the operation. However, it is known to have side effects. I want to find out what side effects the patients felt after being given the morphine. This may help us to find out more about how much morphine to give and for how long and perhaps even whether alternative pain killers should be considered.

Voluntary participation

You do not have to agree to take part in my study. You will receive the same hospital care whether or not you take part. You may change your mind and withdraw at any time, without any penalty.

Study procedure

I would like to do three things with those patients who are willing to participate, as follows:

1. Get information from your hospital file
2. Get information from your anaesthetic chart; this tells me more about what anaesthetic you were given, in what dosage etc
3. I would like to hold an interview with you, to learn how you experienced side effects like nausea and vomiting, itchiness, difficulty passing urine, and difficulty breathing and how much pain you generally experienced. This interview would take place in the ward within the 24 hours after operation and would last about 30 minutes.

Cost

There is neither cost nor payment to you for taking part in this study.

Benefits

There is no direct benefit to you in taking part. It may be that as a result of the study, in future the doctors will be better able to manage the pain that patients experience after operations.

Risks

There are no known risks in taking part.

Confidentiality

I will not be keeping a record of your name and in any report I write up after the study, no individual patients will be identified.

Further Information

If you do not understand anything said in this Information Sheet or have any other question about the study, you may ask me or my supervisor at any time. Our contact details are:

Dr Mpumelelo Sibanyoni: Tel No. 073 156 3420; E-Mail: Sibanyonimpumi6@gmail.com

Dr Ntombiyethu Biyase (Supervisor): Tel No. 082 304 7627; E-Mail: Nana.Biyase@yahoo.com

If you would like to know what is learned from the study, I will be pleased to provide you with a summary on request.

If you agree to take part, I will ask you to sign a Consent Sheet. You will be given a copy of the Consent Sheet and this Information Sheet to keep.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Dr Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

August 2020

Certificate of Consent

Study title: The use of intrathecal morphine for acute perioperative pain in lower limb arthroplasty surgery: a survey of practice at a tertiary academic hospital.

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study. I am free to speak to any of these contacts

Dr Mpumelelo Sibanyoni (Principal Investigator): Tel No. 073 156 3420; E-Mail: Sibanyonimpumi6@gmail.com

Dr Ntombiyethu Biyase (Supervisor): Tel No. 082 304 7627; E-Mail: Nana.Biyase@yahoo.com

Dr Clement Penny, Chairperson of the Human Ethics (Medical) Research Committee: Tel No. 011 717 2301; E-mail: Clement.Penny@wits.ac.za

Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, Tel nos.: 011 717 2700 or 1234; e-mail: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____

Date: _____

Place: _____

Signature or mark _____

Witnessed by:

Name of Witness: _____

Signature: _____

Date: _____

Signature or mark _____

(if possible, this person should be selected by the participant and should have no connection to the study team).

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability to make sure that the participant understands that the following will be done:

1. An interview will be conducted postoperative within the first 24 hours.

2. Obtaining information from anaesthetic chart.

3. Obtaining information from ward file.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntary.

Name of Person taking consent: _____

Signature: _____

Date: _____

Signature or mark _____

Appendix 4: Letter of Approval from Head of Department



CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

DIRECTORATE - ANAESTHESIA

Enquiries: Dr P. Mogane

Tel. number: (011) 933-9334

Email: Palesa.Mogane@wits.ac.za

Department of Anaesthesiology

Chris Hani Baragwanath Academic Hospital

PO Bertsham

2013

21th April 2020

To whom it may concern

RE: PERMISSION TO CONDUCT RESEARCH

This serves to confirm that I grant permission for Dr Sibanyoni to conduct research involving the Department of Anaesthesia at the Chris Hani Baragwanath Academic Hospital. The research topic is titled: The use of intrathecal morphine for acute perioperative pain control in total hip and knee joint replacement (arthroplasty) surgery: a survey of practice at a tertiary academic hospital.

I'd like to wish her luck in this endeavor and I am happy to support her wherever possible.

Kind regards.

Dr Palesa Mogane

Chief specialist and Head of Department

Department of Anaesthesiology

Chris Hani Baragwanath Academic Hospital

University of Witwatersrand

Email: Palesa.Mogane@wits.ac.za

Appendix 5: Letter of Approval from Medical Advisory Committee

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 20th May 2020

TITLE OF PROJECT:

The use of intrathecal morphine for acute perioperative pain in lower limb arthoroplasty surgery: a survey of practice at an academic hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Mpumelelo Sibanyoni

Department: Anaesthesiology

Supervisor : N Biyase

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 20/05/2020

Approved/~~Not Approved~~
Hospital Management
Date: 22/05/2020