Intrathecal morphine injection practice for acute perioperative pain management at a central hospital: A retrospective review

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

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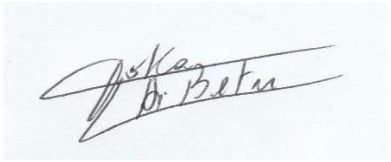
Declaration

I, Di Betu Voka declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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Abstract

Background

Multimodal analgesia has proved to be an effective strategy for managing acute perioperative pain. Neuraxial anaesthesia, including intrathecal morphine injection (ITM), is an important component of multimodal analgesia. This study described the practice of ITM for acute perioperative pain management at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over one year.

Methods

A retrospective, contextual, descriptive research design was followed. The study population consisted of the records of ASA I – III patients 18 years and older who received ITM for postoperative analgesia at CMJAH between 1 January and 31 December 2017. The patients were divided into Group A (received ≤150 mcg ITM) and Group B (received >150 mcg ITM).

Results

In 2017, 131 (2.3%) out of 5 613 general, orthopaedic, vascular and urogynaecology surgery patients received ITM. Group A included 86 (65.6%) and group B 45 (34.4%) records of patients. The mean (SD) dose of ITM was 163.2 (44.1) mcg. ITM was used in combination with bupivacaine in 75 (56.3%) patients with a mean (SD) dose of 8 (3.6) mg in the total sample and 8.2 (3.7) mg for Group A and 7.4 (3.4) mg for Group B. Additional intraoperative analgesia included fentanyl, sufentanil, ketamine, morphine and intravenous paracetamol. Postoperatively, patient-controlled analgesia (PCA) using morphine was used in 12 (9.9%) of patients. The most common non-PCA postoperative pain strategy was a combination of oral tramadol and paracetamol. Of the 121 patients for whom postoperative data were recorded, 30 (24.8%) experienced side effects.

Conclusion

In this study, as a routine practise all patients who received ITM were sent to a high dependency area postoperatively for monitoring. This may have led to the underuse of ITM. The doses of ITM used were within the recommended safe range recommended by the South African Acute Pain Guidelines. The postoperative analgesia side effects experienced by patients were mild and manageable in an appropriately staffed and equipped general ward.

Acknowledgements

I lift my hand to the Most High God who has been my strength and inspiration throughout this amazing journey. Thank you to my wife, family and friends for their support, patience and love! Thank you to all my supervisors for their patience and guidance throughout this long and tortuous journey! Thank you to the statisticians, Dr Gbenga Olorunfemi and Dr Michel Muteba, for your invaluable input to the completion of this work!

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Abbreviations

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CSF	Cerebrospinal fluid
ITM	Intrathecal morphine injection
IV	Intravenous
Non-PCA	Non patient-controlled analgesia
PCA	Patient-controlled analgesia
PO	Per os
SASA	South African Society of Anaesthesiologists

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the author guidelines of the Southern African Journal of Anaesthesia and Analgesia, the journal to which it is intended to be submitted, in order to comply with the university's style guide.

Section 1: Review of the literature

1.1 Introduction

In this section, a review of the literature is presented. A brief background to perioperative pain is given. Multimodal analgesia strategies, neuraxial analgesia and intrathecal opioid injection, are discussed.

1.2 Background to perioperative pain

The perioperative period is an important time. During this time, events occur that have an impact on patients' morbidity and mortality. Perioperative morbidity results in prolonged hospital stay, which increases the burden of health care cost (1). Pain is one of the factors that greatly influence perioperative morbidity, thus requiring optimal management. In the acute perioperative setting, the management of acute pain aims at relieving patients' suffering, achieving early mobilisation, reducing hospital stay and increasing patients' satisfaction (2). Acute perioperative pain management has evolved from a primary opioid-based technique to multimodal analgesia (3). This technique comprises the administration of two or more drugs that act by different mechanisms to provide analgesia (4).

Pain has been redefined by the International Association for the Study of Pain (5) as an "unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage". It is a complex multidimensional symptom resulting from a combination of tissue damage, previous pain experience, personal as well as cultural belief and mood (6). Perioperative pain results from direct damage to nerves and the local inflammatory process due to tissue trauma. The noxious stimuli are perceived by primary afferent pathways and carried to the dorsal horn of the spinal cord and then transmitted to the central nervous system (7).

According to the South African Acute Pain Guidelines (7) endorsed by the South African Society of Anaesthesiologists (SASA), pain causes neurohumoral changes that have the following systemic implications. The stimulation of the sympathetic nervous system may elicit ischaemia in a patient already predisposed to ischaemic

heart disease. A reduction in patients' ability to cough impairs the ability to clear secretions, thus increasing the risk of developing respiratory tract infections. A reduction in functional residual capacity leads to atelectasis. Pain reduces patients' mobility putting them at risk of developing venous thromboembolism. Pain further induces a catabolic state and causes an increase in the adrenocorticotropic hormone, cortisol, antidiuretic hormone, catecholamine, angiotensin II, interleukin 1 and interleukin 6 and tumour necrosis factor levels (7). Uncontrolled acute pain also increases the occurrence of chronic pain due to the wind-up and sensitisation phenomena (3, 7).

1.3 Multimodal analgesia strategy

As stated in Section 1.2, the modern management of pain has evolved from opioid-based analgesia to an opioid-sparing multimodal strategy (3). This evolution from opioid-based analgesia was dictated by the need to reduce the undesirable side-effects associated with the use of opioids in the acute perioperative period (3) and the risk of addiction associated with their prolonged use (8). Rosero and Joshi (3) stated that multimodal analgesia offers an efficient approach to pain management via targeting pain using drugs of two or more different classes given via different methods. This includes:

- opioids given orally, intravenously, intramuscularly, neuraxially or via skin patches
- local anaesthetic administered via infiltration, intraarticular injections, peripheral nerve blocks or neuraxially
- paracetamol given orally, intravenously or per rectum
- non-steroidal anti-inflammatory and cyclooxygenase (COX)-2-specific inhibitors given orally or intravenously
- analgesic adjuncts such as steroids, N-methyl-D-aspartate antagonists, α-2 agonists and anticonvulsants given orally or intravenously (3).

1.4 Neuraxial analgesia

Butterworth et al (9) consider neuraxial analgesia a very important component of multimodal analgesia. It involves giving a spinal, an epidural or a caudal injection

for pain management via a single injection, an intermittent bolus or a continuous infusion. Neuraxial analgesia offers multiple clinical advantages, including reducing postoperative morbidity by reducing the incidence of venous thrombosis and pulmonary embolism, a reduction in cardiac complications in high-risk patients, a reduction in bleeding and transfusion requirements and a decline in the incidence of vascular graft occlusion. In patients undergoing upper abdominal and thoracic surgery, it shows a decline in the incidence of pneumonia and respiratory depression, especially for patients with chronic lung disease. It also allows a reduction in extubation time and decreases the need for mechanical ventilation after major abdominal and thoracic surgery. It also allows earlier return of gastrointestinal function following surgery (9).

The drugs used primarily for neuraxial analgesia are local anaesthetics alone or in combination with opioids such as fentanyl, sufentanil, hydromorphone and morphine (3, 7) or opioids alone (10-12). The combination of local anaesthetics and opioids offers superior analgesia compared to any of these drugs used alone due to the synergistic effects of these drugs (3, 13, 14). Butterworth et al (9) state that the mixture of opioids with local anaesthetic offers an extensive analgesic effect in spinal cord pain transmission. This is facilitated by the direct injection of the mixture at its site of action. Local anaesthetics produce a segmental block by their inhibition of pain transmission in the dorsal root nerves. Local anaesthetics, by binding a specific region of α subunit of the voltage-gated sodium channels, prevent the activation of these receptors and membrane depolarisation, thus preventing the transmission of noxious stimuli (9). This effect, combined with the binding of opioid receptors in the central nervous system, forms the basis of the synergistic effect of local anaesthetics and opioids (15).

1.5 Intrathecal opioid injection

1.5.1 History of intrathecal opioid injection

According to Brill et al (16), the first use of intrathecal opioid injection was by Bier in 1898, when he used cocaine intrathecally. The first published report on intrathecal opioids came from a Romanian surgeon, Racoviceanu-Pitesti, in 1901 (16). Thereafter, research on this technique became dormant until 1968, when

Melzack and Wall (17) presented the gate control theory suggesting that the spinal cord was a potential site for the modulation of pain. Hindle (18) in a review, reported that Melzak and Wall's work inspired the finding of opioid receptors and their identification in the dorsal horn by Pert and colleagues. In 1976, Yaksh and Rudy (19), in an animal experiment showed that opioids modulate pain by direct action on the spinal cord. In 1979, Behar et al (20) published the first report on the epidural use of morphine to treat pain. In the same year, Wang et al (21) reported successful pain management with ITM in eight patients with genitourinary malignancy.

1.5.2 Contraindications to intrathecal morphine injection

Despite being an effective technique, ITM has contraindications. These include those of the intrathecal injection and of the morphine itself. Butterworth et al (9) classify the contraindications to an intrathecal injection as major, relative and controversial. The major contraindications are patient refusal, infection around the site of injection, a low platelet count or bleeding diathesis, elevated intracranial pressure, fixed cardiac output states, a known allergy to the substance to be injected and hypovolaemia (9). The relative contraindications are sepsis, an uncooperative patient, pre-existing neurological deficits, the presence of demyelinating lesions, the presence of stenotic valvular heart lesions, the presence of left ventricular outflow obstruction and severe spinal deformities (9, 22). The controversial contraindications are prior back surgery at the site of injection, anticipated complicated or prolonged operation, anticipated major blood loss and manoeuvres that compromise respiration (9, 22).

The only contraindication to the use of morphine is an allergy to the drug. Special caution should be applied with elderly patients, patients with signs and symptoms of sleep apnoea, obese patients, patients with chronic diseases such as diabetes, patients with chronic lung diseases, patients on chronic medication and the perioperative use of opioids and sedatives (4, 23).

1.5.3 Clinical approach to intrathecal morphine injection in the treatment of postoperative pain

Morphine and hydromorphone are the only medications that have been approved by the United States of America Food and Drugs Administration (24) as first-line neuraxial medications in the context of chronic pain. This is mainly due to their pharmacological properties. In this review, however, only morphine will be discussed.

Pharmacology of intrathecal morphine

The duration of ITM's analgesic properties is longer than all the other opioids commonly used, with an average duration of 18 – 24 hours compared to fentanyl at 1 – 4 hours and sufentanil 2 – 6 hours (25). This prolonged duration of action of ITM is due to its physicochemical properties that influence the pharmacodynamics (26).

Based on this model, intrathecal opioids are eliminated via either the epidural space or the spinal cord. In the epidural space, intrathecal opioids move in the dura mater of the spinal cord to reach the epidural space, where they are reabsorbed into blood vessels and the systemic circulation (18, 26). Bernards (26) states that this increase in the systemic concentration of opioids accounts for the early analgesic effects of hydrophobic opioids. Morphine is eliminated poorly via this route. In the latter route of elimination, spinal opioids move into the spinal cord. The spinal cord is surrounded by a thick fatty layer of Schwann cells that morphine penetrates slowly due to its physicochemical property (26).

Clearance of intrathecal morphine from the cerebrospinal fluid

Eisenach et al (27), using an equimolar dose of morphine and fentanyl intrathecally, demonstrated that the ratio of morphine to fentanyl changed to 2:1 and 4:1 at 36 and 104 minutes. This shows that the slow elimination of morphine from the cerebrospinal fluid (CSF) accounts for its high spinal bioavailability and higher and longer concentration of morphine in the CSF (27). Bernards (26) described the bioavailability of spinally administered opioids as "the ability of that opioid to distribute from its site of administration to its site of action".

The slow elimination of ITM accounts for its slow onset of action, its extensive and prolonged rostral spread, its broadband analgesia surrounding its site of injection and its relatively long duration of action (11). Morphine's high spinal bioavailability leads to a high proportion of molecules available to occupy receptors in the spinal cord and the distribution at multiple spinal levels producing a wider band of segmental analgesia (28, 29). The high proportion of molecules also results in a greater rostral spread to produce a greater supraspinal effect (central effect), which accounts for its delayed respiratory depression (28, 29).

Central nervous system spread of intrathecal morphine

The rostral spread of morphine depends on the patient's position, the volume and the baricity of the injected solution and the circulation of the CSF. The circulation of the CSF is subject to the pulsatile flow of blood in the central nervous system (30) and the fluctuating pressure changes in the thorax with respiration (18). The movement of the CSF drags along solutes (4, 26).

Central nervous system penetration of intrathecally administered opioids

Bujedo (30), in a review, reported that Von Cube and colleagues compared the central nervous system penetration of hydrophilic and hydrophobic opioids by injecting radiolabelled morphine and dihydromorphine (hydrophilic opioids) and fentanyl (hydrophobic opioid) in the CSF of rabbits at the level of the lateral cerebral ventricle. Morphine and dihydromorphine penetrated more deeply and had slower clearance from the CSF than fentanyl. This demonstrated the strong affinity of lipophilic opioids for the white matter and the strong affinity of hydrophilic opioids for the grey matter (30).

The white matter is composed mainly of axonal membranes wrapped by multiple layers of Schwann cells, which are lipid-rich. In contrast, the grey matter is lipid-poor and is the main location of opioid receptors in the dorsal horn at the Rexed laminae II, also known as the substantia gelatinosa of Rolando (30). Thus, the great affinity of morphine for the grey matter of the spinal cord facilitates the bonding of high-density opioid receptors. The same experiment conducted in pigs showed the same results (31).

Based on these experiments, it is an accepted theory that: “bioavailability at the spinal cord is inversely proportional to the degree of drug lipid solubility” (10). This accounts for morphine’s slow onset of action due to the slow crossing of the spinal fatty tissue, its band-like distribution of analgesia (11, 29) and its delayed risk of respiratory depression (32-35).

1.5.4 Mechanism of action of intrathecal morphine

According to Cosgrave et al (36), morphine binds to pre and postsynaptic G-protein-linked opioid receptors. The density of the receptors is greater in the presynaptic membrane compared to the postsynaptic membrane. The activation of these receptors stimulates a G-protein mediated opening of potassium channels via their interactions with mu and delta receptors. They also stimulate the closure of the calcium channels via interaction with the kappa receptors. The cell membrane thus becomes hyperpolarised. The hyperpolarisation of the cell membrane combined with a decrease in the intracellular concentration of calcium reduces presynaptic nociceptive C-fibre secretion of their neurotransmitters, namely substance P and glutamate. These two excitatory neurotransmitters are implicated in the transmission of nociceptive stimuli. Morphine thus directly decreases the transmission of nociceptive stimuli (36).

At the postsynaptic membrane, the activation of these receptors stimulates the opening of potassium channels and indirect activation of the descending pathway from the brainstem (26, 37). Other sites of action have been proposed for intrathecal opioids, such as the increase in adenosine concentration in the human CSF after morphine injection. Adenosine stimulates the opening of neural potassium channels, hyperpolarising their cell membranes, thus reducing their neuronal activity (38).

1.5.5 Intrathecal morphine dose in different type of surgery

ITM is a generally accepted anaesthetic technique that has been used in diverse type of surgeries ranging from obstetric (39, 40), urology (41), orthopaedic (13, 42), gynaecology (38, 43), cardiothoracic (44, 45) and general surgery (46, 47). Although being a technique offering effective analgesia for an extended period of 18 – 24 hours, the required dose of ITM should be titrated based on the type of

surgery (25, 47). The recommendation is to use an optimal dose based on the extent of the surgical intervention and the lowest efficacious dose to minimise the risk of respiratory depression (4, 23, 48) as there is a ceiling analgesic effect beyond which the risk of side effects outweighs the analgesic effect (25, 47). Different authors have estimated different doses for various surgical interventions and the exact most effective dose remains unknown (11, 25, 47, 48). The South African Acute Pain Guidelines (7) cite a dose of equal or more than 300 mcg as putting patients at risk of respiratory depression. On the other hand, Sultan et al (33) suggest that the optimal “single-shot” intrathecal dose appears to be between 75 – 150 mcg. Table 1 shows the recommended doses, as suggested by Bujedo (11) for different procedures.

Table 1: Recommended doses of intrathecal morphine (11)

Intrathecal morphine at low dose with local anaesthetic and regional anaesthesia	
Type of surgery	**Dose of intrathecal morphine**
Trans urethral resection of the prostate	50 µg (41)
Caesarean section delivery	100 µg (40, 49)
Hip replacement	200 µg (50)
Knee replacement	200 µg (51)
Intrathecal morphine at moderate dose with general anaesthetic	
Type of surgery	**Dose of intrathecal morphine**
Abdominal hysterectomy (plus local anaesthetic)	200 µg (38)
Abdominal colonic surgery	300 µg (47)
Spinal surgery	400 µg (52)
Intrathecal morphine at high dose with general anaesthesia	
Type of surgery	**Dose of intrathecal morphine**
Thoracotomy surgery	500 µg (53)
Abdominal aortic surgery and cardiac surgery	7 – 10 µg/kg (54-56)

ITM has proved to be an efficacious component of a multimodal analgesic strategy by improving analgesia and being opioid sparing in the first 24 hours

postoperatively (7, 57). Gwirtz et al (58), in a single large ITM study including the use of patient-controlled analgesia, found no increased risk of respiratory depression. The authors were of the opinion that using patient-controlled analgesia allowed for continuity of analgesia once the ITM effects had worn off and also increased patients' acceptance of intrathecal opioids (58).

ITM is not without limitations. It has been shown that in cardiac surgery, despite the use of a high dose of ITM, the postoperative sparing of morphine equates to patients who received acetaminophen (47). For orthopaedic procedures, although the dose of ITM proves excellent analgesia for hip arthroplasty, patients who have undergone knee arthroplasty report severe pain (25) and the best recommendation for this procedure is general anaesthesia combined with a femoral nerve block (14).

1.5.6 Complications and side effects of intrathecal morphine injection

The complications associated with ITM are inadequate or failed block, pneumocephalus, spinal hematoma, post-dural puncture headache, meningitis and arachnoiditis, nerve injury, hypotension (9, 22) and the complications specific to the use of ITM (22). Chaney (32) describes the side effects of morphine as classic and less common. The four classic side effects are nausea and vomiting, respiratory depression, pruritus and urinary retention. The less common side effects are mental status changes, central nervous system excitation, hyperalgesia, herpes simplex labialis virus reactivation, neonatal morbidity, sexual dysfunction, ocular dysfunction, water retention, cardiac dysrhythmia, hair loss, neurotoxicity and anaphylaxis (32).

Nausea and vomiting

According to Chaney (32), nausea and vomiting are due to a cephalad migration of morphine in the CSF and interaction with the opioid receptors located in the area postrema of the brain. Other contributing factors are sensitisation of the vestibular system to motion and a decrease in gastric emptying due to opioids. The author reports an incidence of approximately 30% of nausea and vomiting and that it tends to be more common in females than males experiencing pain (32). Gwirtz et al (58) and the South African Acute Pain Guidelines (7) describe an incidence of

25%. The incidence of nausea and vomiting warrants the use of prophylaxis preoperatively using ondansetron, dexamethasone or haloperidol (59).

Pruritus

Pruritus, the most common side effect, is usually localised to the face, neck, or upper body and tends to occur a few hours after the injection. Chaney (32) in a review, concluded that the incidence varies widely between 0 – 100% and is usually elucidated by direct questioning of patients. Gwirtz et al (58) described an incidence at 37%, while the South African Acute Pain Guidelines (7) state an occurrence of up to 30%. Pruritus occurs more commonly in the obstetrics population as gestational hormones alter the opioid receptor distribution (32). Severe pruritus is unusual and has an incidence of approximately 1% (32). Pruritus is due to a cephalad migration of the opioids in the CSF and their interaction with opioid receptors in the trigeminal nucleus (32, 60). Although opioids are known to induce the release of histamine, this seems not to be the primary mechanism for the development of pruritus. Agents that can be used for prophylaxis and treatment include ondansetron, low dose propofol, antihistamines and opioids receptors antagonists such as naloxone and naltrexone (32, 60).

Urinary retention

The incidence of urinary retention varies between 0 – 80% and tends to occur more commonly in young male patients (32). A meta-analysis showed a dose-related increase in the incidence of urinary retention. In patients receiving doses of more than 0.3 mg of ITM, there is a fivefold increase in the risk (RR = 5.0) of developing urinary retention (59). Urinary retention is more common with epidural and ITM compared to oral, intravenous and intramuscular morphine. This is due to the interaction of morphine with opioid receptors in the sacral spinal cord, which stimulates relaxation of the detrusor muscle. Urinary retention can last for a period of up to 16 hours and is readily reversed with naloxone and catheterisation is required for all patients receiving intrathecal opioids (32).

Respiratory depression

Respiratory depression is the most dreaded side effect. There is no clear definition in the literature for respiratory depression. Ko et al (61), in a review, highlighted that only 25% of articles defined it in terms of the respiratory rate alone and 29% defined respiratory depression beyond respiratory rate alone. Using respiratory rate and pulse oximetry alone can be a poor indicator of respiratory depression. An assessment of the patients' sedation level and a blood gas analysis is more reliable (60). The American Society of Regional Anaesthesia and Pain Medicine (23) has listed a reduction in respiratory rate to a respiratory rate below 10 breaths per minutes, a reduced saturation to an arterial oxygen saturation below 90%, an increase in arterial carbon dioxide tension to above 50 mm Hg, a drop in tidal volume and the presence of drowsiness, sedation, periodic apnoea and cyanosis as parameters indicating the occurrence of respiratory depression.

Sultan et al (33), Gehling and Tryba (59) and Shapiro et al (62) estimated the incidence of respiratory depression to approximately 1%, which is similar to the incidence associated with the use of parenteral opioids. ITM induced respiratory depression can occur 3.5 – 12 hours post-administration (61) and can persist up to 24 hours. This is due to a cephalad migration of morphine in the CSF and binding to the opioid receptors in the ventral medulla (34).

Sultan et al (33) classified risk factors of respiratory depression as pharmacological, anaesthetic-related, patient-related and miscellaneous. Pharmacological risk factors are high doses of opioids, use of hydrophilic opioids such as morphine, repeated opioid administration, concomitant use of systemic opioids and co-administration of sedatives. Anaesthetic-related risk factors are general anaesthesia and thoracic epidurals. Patient-related risk factors are advanced age, female sex, co-existing cardiopulmonary disease, opioid-naïve patients, morbid obesity and genetics (OPRM1: c.118A > G polymorphism). Miscellaneous risk factors include the co-administration of magnesium, a high dose of opioids, the concurrent use of sedatives and opioids and increased intrathoracic pressure due to controlled ventilation, coughing and vomiting (33).

The American Society of Anesthesiologists Task Force on Neuraxial Opioids (4), the American Society of Regional Anaesthesia and Pain Medicine (23) and the South African Acute Pain Guidelines (7) recommend a 1 – 2 hourly assessment in the first 24 hours postoperatively. Where respiratory depression occurs or is suspected an intravenous line should be placed. Naloxone should be readily available in every postoperative care unit and used incrementally if required. Ventilatory support should be instituted using non-invasive positive pressure ventilation to improve ventilatory status when necessary. Airway patency should be maintained at all times. In the infrequent event of life-threatening apnoea, bag-mask ventilation should be started pending naloxone administration (7, 23, 63).

1.6 Summary

Neuraxial injection techniques are very effective in decreasing postoperative recovery time and perioperative morbidity (64). ITM, compared to epidural, which is the gold standard for postoperative pain management, is technically less difficult to perform and has a lower failure rate (65). It has a lower administration cost due to its simplicity and the cheaper price of the required equipment for its performance (58).

1.7 References

1. Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. Postgrad Med J. 2011;87(1030):535-541. doi:10.1136/pgmj.2010.107169

2. Mariano ER. Management of acute perioperative pain. Uptodate. (Accessed 3 November 2017). Available from: https://0-www.uptodate.com.innopac.wits.ac.za/contents/management-of-acute-perioperative-pain?source=search_result&search=acute%20pain%20management&selectedTitle=1~150.

3. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: What do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85-93. doi:10.1097/PRS.0000000000000671

4. Apfelbaum J, Ashburn M, Connis R, Gan T, Nickinovich D. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116(2):248-273. doi:10.1097/ALN.0b013e31823c1030

5. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982. doi:10.1097/j.pain.0000000000001939

6. Longnecker DE, Mackey SC, Newman MF, Sandberg WS, Zapol WM. Editors. Pain psychology for perioperative and chronic pain management. Anesthesiology, 3rd ed. New York, NY: McGraw-Hill Education; 2017. p. 1505-1509.

7. South African Society of Anaesthesiologists. South African Acute Pain Guidelines. Cramerview, South Africa: Medpharm Publications; 2017.

8. Alam A, Juurlink DN. The prescription opioid epidemic: An overview for anesthesiologists. Can J Anesth. 2016;63(1):61-68. doi:10.1007/s12630-015-0520-y

9. Butterworth JF, Mackey DC, Wasnick JD. Spinal, epidural and caudal blocks. Morgan and Mikhail's Clinical Anesthesiology, 5th ed. New York, NY: McGraw-Hill Education; 2013. p. 937 - 973.

10. Bujedo BM. Current evidence for spinal opioid selection in postoperative pain. Korean J Pain. 2014;27(3):200-209. doi:10.3344/kjp.2014.27.3.200

11. Bujedo B. A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat. 2012;2012(612145). doi:10.1155/2012/612145

12. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25(2):118-122. doi:10.1017/s0265021507001305

13. Fischer H, Simanski C. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. Anaesthesia. 2005;60(12):1189-1202. doi:10.1111/j.1365-2044.2005.04382.x

14. Fischer H, Simanski C, Sharp C, Bonnet F, Camu F, Neugebauer E, et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. Anaesthesia. 2008;63(10):1105-1123. doi:10.1111/j.1365-2044.2008.05565.x

15. Butterworth JF, Mackey DC, Wasnick JD. Local anesthetics. Morgan and Mikhail's Clinical Anesthesiology, 5th ed. New York, NY: McGraw- Hill Education; 2013. p. 263 - 276.

16. Brill S, Gurman GM, Fisher A. A history of neuraxial administration of local analgesics and opioids. Eur J Anaesthesiol. 2003;20(9):682-689. doi:10.1017/s026502150300111x

17. Melzack R, Wall PD. Pain mechanisms: A new theory. Science. 1965;150(3699):971-979. doi:10.1126/science.150.3699.971

18. Hindle A. Intrathecal opioids in the management of acute postoperative pain. BJA Educ. 2008;8(3):81-85. doi:10.1093/bjaceaccp/mkn016

19. Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. Science. 1976;192(4246):1357-1358. doi:10.1126/science.1273597

20. Behar M, Olshwang D, Magora F, Davidson JT. Epidural morphine in treatment of pain. Lancet. 1979;313(8115):527-529. doi:10.1016/S0140-6736(79)90947-4

21. Wang J, Nauss L, Thomas J. Pain relief by intrathecally applied morphine in man. Anesthesiology. 1979;50(2):149-151. doi:10.1097/00000542-197902000-00013

22. Atchabahian A, Gupta R, Torrillo T. Neuraxial anesthesia. The anesthesia guide. New York, NY: McGraw Hill Education; 2013. p. 510-517.

23. Apfelbaum J, Horlocker T, Agarkar M, Connis R, Hebl J, Nickinovich D, et al. Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration: An updated report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2016;124(3):535-552. doi:10.1097/aln.0000000000000975

24. Krames ES. A history of intraspinal analgesia, a small and personal journey. Neuromodulation. 2012;15(3):172-193. doi:10.1111/j.1525-1403.2011.00414.x

25. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. Anesth Analg. 2005;101(5 Suppl):S30-43. doi:10.1213/01.ane.0000177101.99398.22

26. Bernards CM. Understanding the physiology and pharmacology of epidural and intrathecal opioids. Best Pract Res Clin Anaesthesiol. 2002;16(4):489-505. doi:10.1053/bean.2002.0255

27. Eisenach JC, Hood DD, Curry R, Shafer SL. Cephalad movement of morphine and fentanyl in humans after intrathecal injection. Anesthesiology. 2003;99(1):166-173. doi:10.1097/00000542-200307000-00027

28. Bernards CM. Recent insights into the pharmacokinetics of spinal opioids and the relevance to opioid selection. Curr Opin Anaesthesiol. 2004;17(5):441-447. doi:10.1097/00001503-200410000-00015

29. Bujedo BM, Santos SG, Azpiazu AU. A review of epidural and intrathecal opioids used in the management of postoperative pain. J Opioid Manag. 2012;8(3):177-192. doi:10.5055/jom.2012.0114

30. Bujedo B. Spinal opioid bioavailability in postoperative pain. Pain Pract. 2014;14(4):350-364. doi:10.1111/papr.12099

31. Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology. 2000;92(3):739-753. doi:10.1097/00000542-200003000-00018

32. Chaney M. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42(10):891-903. doi:10.1007/bf03011037

33. Sultan P, Gutierrez M, Carvalho B. Neuraxial morphine and respiratory depression: Finding the right balance. Drugs. 2011;71(14):1807-1819. doi:10.2165/11596250-000000000-00000

34. Shook JE, Watkins WD, Camporesi EM. Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis. 1990;142(4):895-909. doi:10.1164/ajrccm/142.4.895

35. Smith H. Peripherally-acting opioids. Pain Physician. 2008;11(2 Suppl):S121-132.

36. Cosgrave D, Shanahan E, Conlon N. Intrathecal opioids. (Accessed 7 November 2017). Available from:

https://www.wfsahq.org/components/com_virtual_library/media/1c584515c16ff7ec67abe3244735326b-347-Intrathecal-morphine-revised.pdf.

37. McQuay H, Sullivan A, Smallman K, Dickenson A. Intrathecal opioids, potency and lipophilicity. Pain. 1989;36(1):111-115. doi:10.1016/0304-3959(89)90118-8

38. Hein A, Rosblad P, Gillis-Haegerstrand C, Schedvins K, Jakobsson J, Dahlgren G. Low dose intrathecal morphine effects on post-hysterectomy pain: A randomized placebo-controlled study. Acta Anaesthesiol Scand. 2012;56(1):102-109. doi:10.1111/j.1399-6576.2011.02574.x

39. Karaman S, Kocabas S, Uyar M, Hayzaran S, Firat V. The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. Eur J Anaesthesiol. 2006;23(4):285-291. doi:10.1017/s0265021505001869

40. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: A qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology. 1999;91(6):1919-1927. doi:10.1097/00000542-199912000-00045

41. Sakai T, Use T, Shimamoto H, Fukano T, Sumikawa K. Mini-dose (0.05 mg) intrathecal morphine provides effective analgesia after transurethral resection of the prostate. Can J Anaesth. 2003;50(10):1027-1030. doi:10.1007/bf03018367

42. Bowrey S, Hamer J, Bowler I, Symonds C, Hall JE. A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. Anaesthesia. 2005;60(5):449-452. doi:10.1111/j.1365-2044.2005.04174.x

43. Borendal Wodlin N, Nilsson L, Kjolhede P. The impact of mode of anaesthesia on postoperative recovery from fast-track abdominal hysterectomy: A randomised clinical trial. BJOG. 2011;118(3):299-308. doi:10.1111/j.1471-0528.2010.02697.x

44. Joshi GP, Bonnet F, Shah R, Wilkinson RC, Camu F, Fischer B, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg. 2008;107(3):1026-1040. doi:10.1213/01.ane.0000333274.63501.ff

45. Zangrillo A, Bignami E, Biondi-Zoccai GG, Covello RD, Monti G, D'Arpa MC, et al. Spinal analgesia in cardiac surgery: A meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2009;23(6):813-821. doi:10.1053/j.jvca.2009.07.002

46. Devys JM, Mora A, Plaud B, Jayr C, Laplanche A, Raynard B, et al. Intrathecal + PCA morphine improves analgesia during the first 24 hr after major abdominal surgery compared to PCA alone. Can J Anaesth. 2003;50(4):355-361. doi:10.1007/BF03021032

47. Meylan N, Elia N, Lysakowski C, Tramer MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: Meta-analysis of randomized trials. Br J Anaesth. 2009;102(2):156-167. doi:10.1093/bja/aen368

48. Popping DM, Elia N, Marret E, Wenk M, Tramer MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: A meta-analysis of randomized trials. Pain. 2012;153(4):784-793. doi:10.1016/j.pain.2011.11.028

49. Girgin NK, Gurbet A, Turker G, Aksu H, Gulhan N. Intrathecal morphine in anesthesia for cesarean delivery: Dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. J Clin Anesth. 2008;20(3):180-185. doi:10.1016/j.jclinane.2007.07.010

50. Murphy P, Stack D, Kinirons B, Laffey J. Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg. 2003;97(6):1709-1715. doi:10.1213/01.ANE.0000089965.75585.0D

51. Rathmell J, Pino C, Taylor R, Patrin T, Viani B. Intrathecal morphine for postoperative analgesia: A randomized, controlled, dose-ranging study after hip

and knee arthroplasty. Anesth Analg. 2003;97(5):1452-1457. doi:10.1213/01.ANE.0000083374.44039.9E

52. Ziegeler S, Fritsch E, Bauer C, Mencke T, Muller BI, Soltesz S, et al. Therapeutic effect of intrathecal morphine after posterior lumbar interbody fusion surgery: A prospective, double-blind, randomized study. Spine (Phila Pa 1976). 2008;33(22):2379-2386. doi:10.1097/BRS.0b013e3181844ef2

53. Liu N, Kuhlman G, Dalibon N, Moutafis M, Levron JC, Fischler M. A randomized, double-blinded comparison of intrathecal morphine, sufentanil and their combination versus IV morphine patient-controlled analgesia for postthoracotomy pain. Anesth Analg. 2001;92(1):31-36. doi:10.1097/00000539-200101000-00007

54. Fleron MH, Weiskopf RB, Bertrand M, Mouren S, Eyraud D, Godet G, et al. A comparison of intrathecal opioid and intravenous analgesia for the incidence of cardiovascular, respiratory, and renal complications after abdominal aortic surgery. Anesth Analg. 2003;97(1):2-12. doi:10.1213/01.ANE.0000066355.07482.0C

55. Zisman E, Shenderey A, Ammar R, Eden A, Pizov R. The effects of intrathecal morphine on patients undergoing minimally invasive direct coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2005;19(1):40-43. doi:10.1053/j.jvca.2004.11.007

56. Turker G, Goren S, Sahin S, Korfali G, Sayan E. Combination of intrathecal morphine and remifentanil infusion for fast-track anesthesia in off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2005;19(6):708-713. doi:10.1053/j.jvca.2005.08.011

57. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J. Acute pain management: Scientific evidence, fourth edition, 2015. Med J Aust. 2016;204(8):315-317. doi:10.5694/mja16.00133

58. Gwirtz KH, Young JV, Byers RS, Alley C, Levin K, Walker SG, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: Seven years' experience with 5969 surgical patients at Indiana University Hospital. Anesth Analg. 1999;88(3):599-604. doi:10.1097/00000539-199903000-00026

59. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: A meta-analysis. Anaesthesia. 2009;64(6):643-651. doi:10.1111/j.1365-2044.2008.05817.x

60. Hindle A. Intrathecal opioids in the management of acute postoperative pain. Br J Anaesth. 2008;8(3):81- 85. doi:10.1093/bjaceaccp/mkn016

61. Ko S, Goldstein DH, Vandenkerkhof EG. Definitions of "respiratory depression" with intrathecal morphine postoperative analgesia: A review of the literature. Can J Anaesth. 2003;50(7):679-688. doi:10.1007/BF03018710

62. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. J Clin Anesth. 2005;17(7):537-542. doi:10.1016/j.jclinane.2005.01.006

63. Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116(2):248-273. doi:10.1097/ALN.0b013e31823c1030

64. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: Results from overview of randomised trials. Br Med J. 2000;321(7275):1493. doi:10.1136/bmj.321.7275.1493

65. Stoelting RK. Intrathecal morphine: An underused combination for postoperative pain management. Anesth Analg. 1989;68(6):707-709.

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The following are sample references:

1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-

dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.

2. Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web. pdf.

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10. All numbers below ten, without percentages or units, must be written in words.
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Section 3: Draft article

Intrathecal morphine injection practice for acute perioperative pain management at a central hospital: A retrospective review

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Keywords: opioids, intrathecal morphine injection, analgesia, respiratory depression

Abstract

Background

Multimodal analgesia has proved to be an effective strategy for managing acute perioperative pain. Neuraxial anaesthesia, including intrathecal morphine injection (ITM), is an important component of multimodal analgesia. This study described the practice of ITM for acute perioperative pain management at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over one year.

Methods

A retrospective, contextual, descriptive research design was followed. The study population consisted of the records of ASA I – III patients 18 years and older who received ITM for postoperative analgesia at CMJAH between 1 January and 31 December 2017. The patients were divided into Group A (received ≤150 mcg ITM) and Group B (received >150 mcg ITM).

Results

In 2017, 131 (2.3%) out of 5 613 general, orthopaedic, vascular and urogynaecology surgery patients received ITM. Group A included 86 (65.6%) and group B 45 (34.4%) records of patients. The mean (SD) dose of ITM was 163.2 (44.1) mcg. ITM was used in combination with bupivacaine in 75 (56.3%) patients with a mean (SD) dose of 8 (3.6) mg in the total sample and 8.2 (3.7) mg for Group A and 7.4 (3.4) mg for Group B. Additional intraoperative analgesia included fentanyl, sufentanil, ketamine, morphine and intravenous paracetamol. Postoperatively, patient-controlled analgesia (PCA) using morphine was used in 12 (9.9%) of patients. The most common non-PCA postoperative pain strategy was a combination of oral tramadol and paracetamol. Of the 121 patients for whom postoperative data were recorded, 30 (24.8%) experienced side effects.

Conclusion

In this study, as a routine practise all patients who received ITM were sent to a high dependency area postoperatively for monitoring. This may have led to the underuse of ITM. The doses of ITM used were within the recommended safe range recommended by the South African Acute Pain Guidelines. The postoperative analgesia side effects experienced by patients were mild and manageable in an appropriately staffed and equipped general ward.

Introduction

"Acute pain management is not a luxury, it is a human right!" (1).

Postoperative pain carries serious physiologic and psychological consequences that impact morbidity and recovery in the perioperative period and has the potential to produce chronic pain syndromes (2). Since 1999, the United States of America has witnessed an acute increase in the consumption of opioids and the incidence of opioid-related deaths (3), leading the government to declare the opioid epidemic a public health emergency (4). Pain control has evolved from opioid-based analgesia to a multimodal analgesia approach due to problems associated with opioids (5).

Multimodal analgesia has proved to be an effective strategy for managing acute perioperative pain (5). The principle of multimodal analgesia is based on the use of medications of different classes administered via different routes and techniques (6). Neuraxial anaesthesia is an important component of multimodal analgesia (5, 7) and uses techniques such as intrathecal, caudal, paravertebral and epidural injection of drugs (5, 8). The drugs used primarily for neuraxial analgesia are local anaesthetics alone or in combination with lipophilic or hydrophilic opioids (1, 5) or opioids alone (9-11). Epidural injection has been deemed the gold standard for postoperative analgesia modalities. Intrathecal injection, however, is easier and cheaper to administer than epidural injection (12).

Intrathecal morphine injection (ITM), due to its pharmacological profile, offers effective analgesia that lasts on average 18 – 24 hours (13) and allows a decrease in the amount of total analgesia required in the postoperative period (14). Due to this property, it has been used in different types of surgery (15-22). Although an inexpensive and effective intervention, ITM has side effects, such as pruritus, respiratory depression, nausea and vomiting and urinary retention (23).

At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), there are no data regarding the use of ITM for postoperative pain and the associated complications. There is evidence suggesting that patients who receive an ITM can be sent to a ward postoperatively provided the ward staff is adequately trained and the ward is equipped to manage ITM side effects (24). However, due to the

anticipated side effects of morphine, patients who receive ITM are admitted to the high care or intensive care unit at CMJAH. These high dependency units are an expensive and scarce resource with limited bed availability. This practice deprives some patients of the benefits of this technique (25). The aim of this retrospective study was to describe the ITM practice for acute perioperative pain management at CMJAH over one year.

Methods

A retrospective, descriptive and contextual research design was followed in this study. Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) (M180607) at the University of the Witwatersrand and other relevant authorities.

The study population consisted of the records of ASA I – III patients 18 years and older who received ITM for postoperative analgesia at CMJAH between 1 January and 31 December 2017. ITM is only used at CMJAH for orthopaedic, general, urogynaecological and vascular surgery. The sample size was realised by the number of records available during the study period. Records of obstetric patients who received ITM for analgesia, illegible records and where ITM doses were not documented were excluded from the study. The patients were divided into two groups, Group A (received ≤150 mcg ITM) and Group B (received >150mcg ITM) for descriptive purposes (10, 26).

A draft data collection sheet was developed following a review of the literature and was reviewed by three senior anaesthesiologists. The comments of the reviewers were incorporated in the final document. The information required for the data collection sheet is shown in Table I.

Table I: Data collected

Demographics • Age • Weight • Sex • Type of surgery • Type of anaesthetic • Postoperative destination • ASA classification ITM • Morphine dose • Type of local anaesthetic and dose Additional analgesia • Intraoperative drug(s) and total dose • Postoperative drug(s) and total dose • Postoperative use of PCA Side effects of ITM Presence of respiratory depression and intervention taken

The postoperative period in this study reflects only the first 24 hours. Additional analgesia was any analgesic given intraoperatively or within the first 24 hours postoperatively as rescue analgesia or as standard practice. Data were collected by one author (DBV). The number of patients who received ITM was established using the anaesthetic records. Information regarding the ITM was then recorded using anaesthetic and high care or intensive care records.

Data were analysed in consultation with a bio-statistician using STATA (StataCorp, USA). Categorical variables were described using frequencies and percentages and continuous variables were described using means and standard deviations or medians and interquartile ranges depending on the distribution of the data.

Results

During the study period, a total of 132 of 5 613 patients received ITM for postoperative analgesia. Of these, 131 (2.3%) patients were included in the study. The patient excluded did not have an ITM dose documented. The patients' characteristics are shown in Table II.

Table II: Characteristics of patients

Characteristics	Group A	Group B	Total
	Number (%)		
Sex			
Male	38 (29.0)	34 (26.0)	72 (55.0)
Female	48 (36.6)	11 (8.4)	59 (45.0)
ASA status			
1	3 (2.3)	2 (1.5)	5 (3.8)
2	30 (22.9)	18 (13.7)	48 (36.6)
3	53 (40.5)	25 (19.1)	78 (59.6)
Type of anaesthesia			
Neuraxial only	16 (12.2)	2 (1.5)	18 (13.7)
Neuraxial and GA*	70 (53.4)	43 (32.8)	113 (86.3)
	Median (IQR)		
Weight (kg)	75 (60.0 – 90.0)	80 (65.0 – 90.0)	80 (64.5 – 90.0)
Age (years)	63 (50.0 – 72.0)	59 (48.0 – 67.0)	61 (49.0 – 71.0)

*GA: General anaesthetic

The type of surgery per ITM dose group is shown in Table III.

Table III: Type of surgery per ITM dose group

Type of surgery	Group	
	A	B
	Number (%)	
Orthopaedic	37 (28.2)	14 (10.7)
General surgery	20 (15.3)	12 (9.2)
Urogynaecology	15 11.5)	7 (5.3)
Vascular	14 (10.7)	12 (9.2)
Total	86 (65.6)	45 (34.4)

Of the 131 patients who received ITM, the mean (SD) dose of morphine was 163.2 (44.1) mcg and of bupivacaine was 8 (3.6) mg. No patients received lignocaine intrathecally. ITM was combined with bupivacaine in 75 (56.3%) patients and given

alone in 56 (43.7%) patients. The average dose of bupivacaine in Group A was 8.2 (3.7) mg and 7.4 (3.4) mg in Group B.

Table IV shows the additional intraoperative intravenous analgesia that the patients received per ITM dose group.

Table IV: Additional intraoperative intravenous analgesia per ITM dose group

Additional intravenous analgesic	Group	
	A	B
	Mean (SD)	
Morphine (mg)	6.2 (3.4)	6.9 (4.9)
Fentanyl (mcg)	255.8 (149.7)	378.2 (239.2)
Sufentanil (mcg)	28.6 (20.4)	29.4 (14.8)
Ketamine (mg)	32.9 (26.1)	35.8 (25.1)
Paracetamol (g)	1.0 (0.2)	1.1 (0.2)

The postoperative analgesia is presented for patients who received patient-controlled analgesia (PCA) and those who did not receive patient-controlled analgesia (non-PCA). The postoperative data of 10 patients were missing and are not included in the results. Of the remaining 121 patients, 12 (9.9%) received PCA with morphine. Table V shows the analgesics patients received in the first 24 hours postoperatively per PCA group and ITM dose group.

Table V: Postoperative analgesia given within the first 24 hours per PCA group and ITM dose group

Drug	PCA group Number			Non-PCA group Number			Total
	A	B	Total	A	B	Total	
Morphine ≤8 mg	1	0	1	8	5	13	14
Morphine >8 mg	0	0	0	5	6	11	11
Tramadol ≤400 mg	3	2	5	61	28	89	94
Tramadol >400 mg	0	0	0	1	0	1	1
PO* paracetamol ≤2 g	2	1	3	42	15	57	60
PO* paracetamol >2 g	1	2	3	19	8	27	30
IV† paracetamol ≤2 g	0	0	0	1	2	3	3
IV† paracetamol >2 g	0	0	0	0	0	0	0

*PO: Per os, †IV: Intravenous

Table VI shows the combinations of additional postoperative analgesia per PCA group and ITM dose group.

Table VI: Combinations of additional postoperative analgesia per PCA group and ITM dose group

Drug combination	PCA group			Non-PCA group			Total
	A	B	Total	A	B	Total	
	Number (%)						
Tramadol only	0 (0)	0 (0)	0 (0)	7 (46.7)	8 (53.3)	15 (100)	15 (100)
Tramadol IV* paracetamol	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	2 (100)	2 (100)
Tramadol PO† paracetamol	2 (3.3)	2 (3.3)	4 (6.7)	44 (73.3)	12 (20)	56 (93.3)	60 (100)
Tramadol Morphine	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	3 (100)	3 (100)
Tramadol PO† paracetamol Morphine	1 (6.7)	0 (0)	1 (6.7)	7 (46.7)	7 (46.7)	14 (93.3)	15 (100)
PO† paracetamol	0 (0)	2 (16.7)	2 (16.7)	9 (75)	1 (8.3)	10 (83.3)	12 (100)
PO† paracetamol Morphine	0 (0)	0 (0)	0 (0)	1 (25)	3 (75)	4 (100)	4 (100)
Morphine	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	2 (100)	2 (100)
IV* paracetamol morphine	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	1 (100)
Nil	1 (14.3)	1 (14.3)	2 (28.6)	3 (42.9)	2 (28.6)	5 (71.4)	7 (100)

*IV: Intravenous, †PO: Per os

Side effects to the postoperative analgesia received were experienced by 30 (24.8%) of the 121 patients within the first 24 hours. These side effects were nausea and vomiting in 22 (18,2%) patients, respiratory depression in 6 (4.9%) patients and pruritis in 2 (1.7%) patients. The side effects experienced by the 30 patients per PCA group and ITM dose group are shown in Table VII. The side effects per type of anaesthetic is also shown.

Table VII: Side effects of postoperative analgesia per PCA group and ITM dose group and per type of anaesthetic

Side effects	PCA group n= 2		Non-PCA group n= 28		Total n= 30
	A	B	A	B	
	Number (%)				Number (%)
Nausea and vomiting	1 (3.3)	1 (3.3)	14 (46.7)	6 (20)	22 (73.3)
Respiratory depression	0	0	5 (16.7)	1 (3.3)	6 (20)
Pruritus	0	0	2 (6.7)	0	2 (6.7)
	Neuraxial anaesthesia n= 4		Neuraxial and general anaesthesia n= 26		Total n= 30
Nausea and vomiting	1 (3.3)		21 (70)		22 (73.3)
Respiratory depression	3 (10)		3 (10)		6 (20)
Pruritus	0 (0)		2 (6.7)		2 (6.7)

Respiratory depression was experienced by 6 (20%) of the 30 patients with side effects and was defined as a drop in saturation to ≤90%. The therapeutic measure was to increase the nasal prong FiO_2 from 0.28 to 0.32. None of the patients needed to be given naloxone or to be intubated.

Discussion

ITM has proved to be an effective modality for perioperative analgesia due to its prolonged postoperative analgesic effect of 18 – 24 hours (1, 27). ITM also decreases postoperative opioid requirements (28, 29). ITM for postoperative pain management use in this study was 2.3% of patients having the surgeries for which this modality is commonly used. This is lower than the 21.3% shown in a survey of 270 anaesthetic departments in the United Kingdom (11). The low rate in this study could be explained in that all patients who received ITM were routinely admitted to a high dependency unit as the standard of care. Patients can be monitored in a general ward if the staff are adequately trained and regular monitoring is provided (11). In a study by Lim and Macintyre (24), patients who received ITM were admitted into high dependency areas due to their comorbid status, surgery-related factors and anaesthetic concerns. The difference in

practise in this study could be explained by the absence of an acute pain service and the lack of a standard ITM postoperative protocol at CMJAH. The routine admission of patients to a high dependency unit after ITM might contribute to the underutilisation of this effective and affordable method of postoperative analgesia.

Historically, safety was the principal factor limiting the use of ITM and it has been shown that the incidence of side effects is directly related to the dose used (13, 14). In the past, the doses of ITM used were in the range of 500 – 1 000 mcg, which proved to have a high incidence of respiratory depression and profound sedation (30). The South African Acute Pain Guidelines (1) endorsed by SASA recommend a dose of ITM of ≤300 mcg as the upper limit to decrease the occurrence of these side effects (1). The mean dose of ITM in this study was 163.2 mcg and 65.6% of doses were ≤150 mcg which is within the South African Acute Pain Guidelines (1) recommended dose range. The dose of 150 mcg has been described by Sultan et al (26) as the dose at which maximal analgesia is achieved with minimal side effects. Beyond this dose, analgesia does not improve, but side effects become more frequent.

The use of ITM in combination with local anaesthetic agents for a longer-lasting analgesic effect is well described (27). In this study, ITM was used in combination with bupivacaine in 56.3% of cases. The average dose of bupivacaine was 8.2 mg for Group A and 7.4 mg for Group B. The use of bupivacaine and morphine in ITM has proved its effectiveness in general (31) and orthopaedic surgery (32, 33). The combination of a local anaesthetic agent with ITM has a synergistic effect, which improves the quality of the analgesia while allowing a decrease in the dose of the local anaesthetic agent required, therefore improving safety (34).

The use of ITM has been described in general, orthopaedics, vascular, urogynaecology, thoracic (29) and cardiac surgery (35). In this study, ITM was used in all of these disciplines except for cardiac and thoracic surgeries. ITM is not used in cardiac and thoracic surgery at CMJAH. Myelan et al (14) have shown that in cardiac surgery, despite the use of a high dose of ITM, the postoperative sparing of morphine equates to patients who received acetaminophen.

ITM in this study was mostly used for postoperative analgesia in patients who had received a general anaesthetic (86.3%). The drugs most commonly used for intraoperative analgesia were fentanyl, sufentanil, ketamine, morphine and intravenous paracetamol. The combination of drugs used for intraoperative analgesia is similar to the combination of drugs used in a study that looked at the efficacy of ITM in fast-track abdominal hysterectomy (36) and abdominal aortic aneurysm repair (37) and the doses were within similar ranges.

In this study, during the postoperative period, PCA was used in 9.9% of patients. The decision to institute PCA postoperatively was not guided by a standardised acute pain management protocol but was at the discretion of the anaesthetist and the treating doctor in the high dependency area. In the study by Lim and Macintyre (24), morphine PCA in combination with other agents, was only instituted as rescue analgesia under the supervision of an acute pain service and not routinely (24). Only 24 patients out of a total of 409 patients were prescribed PCA (24). In contrast, in the study by Gwirtz et al (29), all patients were routinely prescribed PCA, in the form of reduced-dose morphine, for approximately 15 hours following discharge from the postanaesthesia care unit (29).

Non-PCA based postoperative pain strategies after ITM vary widely across studies internationally (38, 39). The South African Acute Pain Guidelines (1) recommend the use of multimodal analgesia. In this study, the practice adhered to the guidelines and the most commonly used analgesic combination in this study was oral tramadol and paracetamol, which was used by patients mainly in the non-PCA group.

Respiratory depression in this study was reported in 4.9% of 121 patients, which is higher than the respiratory depression rate of around 1% found in two other studies (26, 40). This could possibly be explained by the lack of a standardised definition for respiratory depression (41, 42). In this study, all the patients who developed respiratory depression developed mild respiratory depression, which was characterised by a decrease in oxygen saturation, necessitating an increase in FiO_2 from 0.28 to 0.32.

Nausea and vomiting were the most common side effects reported at 18.2%. This incidence is below the incidence of 29.2% reported by Chaney (23) but similar to other studies (4,9). Patients in Group A experienced more nausea and vomiting than patients in Group B. This might be explained by the fact that more patients in Group A and the non-PCA group received rescue analgesia in the postoperative period, which included tramadol, a known emetogenic agent.

Pruritus is a frequent side effect associated with the use of opioids regardless of the route of administration (27). In this study, the incidence of pruritus was low at 1.6% compared to the incidence of 29.2% described by Popping et al (28). This low incidence might be due to the fact that pruritus is mostly elucidated upon questioning (23) and as this study was retrospective, patients could not be asked about this side effect.

A limitation of this study was that it was retrospective, relying on patients' records and, therefore, the efficacy of ITM analgesia could not be assessed. This study was also done contextually at CMJAH and the results may not be generalisable to other patient populations. The authors recommend the implementation of a perioperative ITM protocol and the establishment of an acute pain service at CMJAH to increase the use of ITM.

Conclusion

In this study, as a routine practise all patients who received ITM were sent to a high dependency area postoperatively for monitoring. This may have led to the underuse of ITM. The doses of ITM used were within the recommended safe range recommended by the South African Acute Pain Guidelines (1). The postoperative analgesia side effects experienced by patients were mild and manageable in an appropriately staffed and equipped general ward.

Conflict of interest

The authors declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

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References

1. South African Society of Anaesthesiologists. South African Acute Pain Guidelines. Cramerview, South Africa: Medpharm Publications; 2017.

2. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North America. 2005;23(1):21-36. doi:10.1016/j.atc.2004.11.013

3. Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician. 2012;15(3 Suppl):9-38.

4. Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: the role of the anesthesiologist. Perioper Med (Lond). 2018;7:16. doi:10.1186/s13741-018-0097-4

5. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: What do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85-93. doi:10.1097/PRS.0000000000000671

6. Heitz JW, Witkowski TA, Viscusi ER. New and emerging analgesics and analgesic technologies for acute pain management. Curr Opin Anaesthesiol. 2009;22(5):608-617. doi:10.1097/ACO.0b013e32833041c9

7. Nordquist D, Halaszynski TM. Perioperative multimodal anesthesia using regional techniques in the aging surgical patient. Pain Res Treat. 2014;2014:902174. doi:10.1155/2014/902174

8. Butterworth JF, Mackey DC, Wasnick JD. Spinal, epidural and caudal blocks. Morgan and Mikhail's Clinical Anesthesiology, 5th ed. New York, NY: McGraw-Hill Education; 2013. p. 937 - 973.

9. Bujedo BM. Current evidence for spinal opioid selection in postoperative pain. Korean J Pain. 2014;27(3):200-209. doi:10.3344/kjp.2014.27.3.200

10. Bujedo B. A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat. 2012;2012(612145). doi:10.1155/2012/612145

11. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25(2):118-122. doi:10.1017/s0265021507001305

12. Stoelting RK. Intrathecal morphine: An underused combination for postoperative pain management. Anesth Analg. 1989;68(6):707-709.

13. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. Anesth Analg. 2005;101(5 Suppl):S30-43. doi:10.1213/01.ane.0000177101.99398.22

14. Meylan N, Elia N, Lysakowski C, Tramer MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: Meta-analysis of randomized trials. Br J Anaesth. 2009;102(2):156-167. doi:10.1093/bja/aen368

15. Chetty S, Paruk F, Kamerman P. Low dose intrathecal morphine reduces post-operative opioid requirements after caesarean section. Anesth Analg. 2016;123(3S):238-239. doi:10.1213/01.ane.0000492590.47304.36

16. Hein A, Rosblad P, Gillis-Haegerstrand C, Schedvins K, Jakobsson J, Dahlgren G. Low dose intrathecal morphine effects on post-hysterectomy pain: A randomized placebo-controlled study. Acta Anaesthesiol Scand. 2012;56(1):102-109. doi:10.1111/j.1399-6576.2011.02574.x

17. Fischer H, Simanski C. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. Anaesthesia. 2005;60(12):1189-1202. doi:10.1111/j.1365-2044.2005.04382.x

18. Bowrey S, Hamer J, Bowler I, Symonds C, Hall JE. A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. Anaesthesia. 2005;60(5):449-452. doi:10.1111/j.1365-2044.2005.04174.x

19. Sakai T, Use T, Shimamoto H, Fukano T, Sumikawa K. Mini-dose (0.05 mg) intrathecal morphine provides effective analgesia after transurethral resection of the prostate. Can J Anaesth. 2003;50(10):1027-1030. doi:10.1007/bf03018367

20. Sakowska M, Docherty E, Linscott D, Connor S. A change in practice from epidural to intrathecal morphine analgesia for hepato-pancreato-biliary surgery. World J Surg. 2009;33(9):1802-1808. doi:10.1007/s00268-009-0131-2

21. Boezaart AP, Eksteen JA, Spuy GV, Rossouw P, Knipe M. Intrathecal morphine: Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. Spine (Phila Pa 1976). 1999;24(11):1131-1137. doi:10.1097/00007632-199906010-00013

22. Turker G, Goren S, Sahin S, Korfali G, Sayan E. Combination of intrathecal morphine and remifentanil infusion for fast-track anesthesia in off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2005;19(6):708-713. doi:10.1053/j.jvca.2005.08.011

23. Chaney M. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42(10):891-903. doi:10.1007/bf03011037

24. Lim PC, Macintyre PE. An audit of intrathecal morphine analgesia for non-obstetric postsurgical patients in an adult tertiary hospital. Anaesth Intensive Care. 2006;34(6):776-781. doi:10.1177/0310057X0603400601

25. Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. Anesthesiology. 1991;75(3):452-456. doi:10.1097/00000542-199109000-00012

26. Sultan P, Gutierrez M, Carvalho B. Neuraxial morphine and respiratory depression: Finding the right balance. Drugs. 2011;71(14):1807-1819. doi:10.2165/11596250-000000000-00000

27. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J. Acute pain management: Scientific evidence, fourth edition, 2015. Med J Aust. 2016;204(8):315-317. doi:10.5694/mja16.00133

28. Popping DM, Elia N, Marret E, Wenk M, Tramer MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: A meta-analysis of randomized trials. Pain. 2012;153(4):784-793. doi:10.1016/j.pain.2011.11.028

29. Gwirtz KH, Young JV, Byers RS, Alley C, Levin K, Walker SG, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: Seven years' experience with 5969 surgical patients at Indiana University Hospital. Anesth Analg. 1999;88(3):599-604. doi:10.1097/00000539-199903000-00026

30. Samii K, Chauvin M, Viars P. Postoperative spinal analgesia with morphine. Br J Anaesth. 1981;53(8):817-820. doi:10.1093/bja/53.8.817

31. Wongyingsinn M, Baldini G, Stein B, Charlebois P, Liberman S, Carli F. Spinal analgesia for laparoscopic colonic resection using an enhanced recovery after surgery programme: Better analgesia, but no benefits on postoperative recovery: A randomized controlled trial. Br J Anaesth. 2012;108(5):850-856. doi:10.1093/bja/aes028

32. Murphy P, Stack D, Kinirons B, Laffey J. Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg. 2003;97(6):1709-1715. doi:10.1213/01.ANE.0000089965.75585.0D

33. Essving P, Axelsson K, Aberg E, Spannar H, Gupta A, Lundin A. Local infiltration analgesia versus intrathecal morphine for postoperative pain management after total knee arthroplasty: A randomized controlled trial. Anesth Analg. 2011;113(4):926-933. doi:10.1213/ANE.0b013e3182288deb

34. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases. 2017;5(8):307-323. doi:10.12998/wjcc.v5.i8.307

35. Parlow JL, Steele RG, O'Reilly D. Low dose intrathecal morphine facilitates early extubation after cardiac surgery: Results of a retrospective continuous quality improvement audit. Can J Anesth. 2005;52(1):94-99. doi:10.1007/BF03018588

36. Borendal Wodlin N, Nilsson L, Kjolhede P. The impact of mode of anaesthesia on postoperative recovery from fast-track abdominal hysterectomy: A randomised clinical trial. BJOG. 2011;118(3):299-308. doi:10.1111/j.1471-0528.2010.02697.x

37. Blay M, Orban JC, Rami L, Gindre S, Chambeau R, Batt M, et al. Efficacy of low-dose intrathecal morphine for postoperative analgesia after abdominal aortic surgery: A double-blind randomized study. Reg Anesth Pain Med. 2006;31(2):127-133. doi:10.1016/j.rapm.2005.11.010

38. Kuchalik J, Granath B, Ljunggren A, Magnuson A, Lundin A, Gupta A. Postoperative pain relief after total hip arthroplasty: A randomized, double-blind comparison between intrathecal morphine and local infiltration analgesia. Br J Anaesth. 2013;111(5):793-799. doi:10.1093/bja/aet248

39. Nuri Deniz M, Erhan E, Ugur G. Intrathecal morphine reduces postoperative tramadol consumption in patients undergoing radical retropubic prostatectomy: A randomized trial. Eur Rev Med Pharmacol Sci. 2013;17(6):834-838.

40. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. J Clin Anesth. 2005;17(7):537-542. doi:10.1016/j.jclinane.2005.01.006

41. Ko S, Goldstein DH, Vandenkerkhof EG. Definitions of “respiratory depression” with intrathecal morphine postoperative analgesia: A review of the literature. Can J Anaesth. 2003;50(7):679-688. doi:10.1007/bf03018710

42. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: A meta-analysis. Anaesthesia. 2009;64(6):643-651. doi:10.1111/j.1365-2044.2008.05817.x

Section 4: Proposal

Intrathecal morphine injection practice for acute perioperative pain management at a central hospital: A retrospective review

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4.1 Introduction and problem statement

“Acute pain management is not a luxury, it is a human right!” (1). This statement was made by Dr Milton Raff Chairperson of the World Federation of Societies of Anaesthesiologists Pain Relief Committee in his preface of the first edition of the South African Acute Pain Guidelines. The control of pain has evolved from an “opioid based analgesia” to a multimodal analgesia approach due to problems associated with opioids, namely their potential for abuse and dependence and their side effects profile (2). From the year 1999 to date, the United States of America has witnessed an acute increase in the consumption of opioids and the incidence of opioid-related deaths (3) leading the government to declare the opioid epidemic a public health emergency (4). The principle of multimodal analgesia is based on the use of medications of different classes administered via different routes and techniques (5). Neuraxial anaesthesia is an important component of multi-modal analgesia (6, 7).

Neuraxial anaesthesia uses techniques such as intrathecal, caudal, paravertebral and epidural injection of drugs (2, 8). The drugs used primarily for neuraxial analgesia are local anaesthetics alone or in combination with opioids such as fentanyl, sufentanil, hydromorphone and morphine (1, 2) or opioids alone (9-11). Epidural injection has been deemed the gold standard for postoperative analgesia modalities. Intrathecal injection, however, is easier and cheaper to administer than epidural injection (12).

Intrathecal injection for analgesia is done with medication of different classes such as local anaesthetics, opioids and alpha-2 agonists, to name a few (13). These can be used in combination or alone. Two groups of opioids have been used for neuraxial anaesthesia: the lipophilic opioids, fentanyl and sufentanil and the hydrophilic opioids, morphine and hydromorphone. Of the opioids, morphine is the only drug approved by the Food and Drug Administration for use for intrathecal anaesthesia in the context of chronic pain (13).

Neuraxial morphine, due to its pharmacological profile, offers effective analgesia that lasts on average 18 – 24 hours (13) and allows a decrease in the amount of total analgesia required in the postoperative period (14). Due to this property, it

has been used in different type of surgeries, such as caesarean sections (15), hysterectomies (16), hip and knee arthroplasty (17, 18), transurethral resection of the prostate (19), colo-rectal surgery, hepatectomy (20), lumbar spinal fusion (21) and coronary artery bypass surgery (22). Although an inexpensive and effective intervention, intrathecal morphine injection (ITM) has side effects. Four classic side effects have been cited namely pruritus, respiratory depression, nausea and vomiting and urinary retention (23). Of these, respiratory depression is the most serious with an incidence of about 1%, which is similar to that of parenteral morphine (24) and it often occurs 3.5 – 12 hours after injection (25).

Postoperative management after ITM should be in wards where monitoring equipment is available and medical staff are educated regarding the risk of occurrence of respiratory depression. These wards should also keep resuscitation equipment and drugs to reverse respiratory depression (1, 26). The staff should be educated with regards to the need for additional monitoring and caution when prescribing or administering any additional dose of parenteral sedatives, hypnotics, opioid and magnesium sulphate as these increased the risk of respiratory depression (26). The South African Acute Pain Guidelines states that " A multimodal plan alternatives should be in place to prevent (preferably) or treat rebound pain"(1). Routine observation should be conducted hourly for the first 12 hours and two hourly for the second 12 hours (26, 27).

Postoperative pain carries serious physiologic and psychological consequences that impact morbidity and recovery in the perioperative period and has the potential to produce chronic pain syndromes (28).

Multimodal analgesia has proved to be an effective strategy for the management of acute perioperative pain (2). As a component of multimodal analgesia, intrathecal injection, according to Meylan et al (14), is a modality that "is simple, quick, and with a relatively low risk of technical complications or failure."

The practice of ITM varies in terms of the dose used and the type of surgery. At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), there are no data regarding the use of ITM for postoperative pain and its complications.

There is some evidence in the literature that suggests that patients who receive an ITM can be sent to an ordinary ward postoperatively provided the unit is adequately trained and equipped to manage ITM side effects (29). However, due to the anticipated side effects of morphine, most notably respiratory depression, patients who receive ITM are admitted to the high care or intensive care unit at CMJAH. These high dependency units are an expensive and scarce resource with limited bed availability. The postoperative high care or intensive care unit admission of patients post ITM limits access of sick patients to this much needed and sought-after resource. This practice also deprives some patients of the benefits of this technique (30).

4.2 Aim and objectives

4.2.1 Aim

The aim of this retrospective study is to describe the intrathecal morphine injection practice for acute perioperative pain management at CMJAH over one year.

4.2.2 Objectives

The objectives of this study are to:

- estimate the number of intrathecal morphine injections performed at CMJAH over one year
- describe the type of surgeries for which it is done
- determine the dose of intrathecal morphine and local anaesthetic used
- describe the type and dose of additional analgesia given intraoperatively and within the first 24 hours postoperatively
- estimate the incidence of side effects of intrathecal morphine injections in the first 24 hours postoperatively.

4.3 Research assumptions

The following definitions will be used in the study.

Intrathecal morphine injection: is a technique where morphine, with or without local anaesthetic, is injected intrathecally.

Additional analgesia: is any analgesic given intraoperatively or within the first 24 hours postoperatively as rescue analgesia or standard practice.

Records: will include anaesthetic and high care or intensive care records.

Essential information: is the documentation of intrathecal morphine doses.

4.4 Demarcation of study field

The study will be conducted at CMJAH, which is affiliated to the University of the Witwatersrand. CMJAH is a 1 200-bed central hospital. The hospital has 23 theatres where on average 23 000 cases are done annually.

4.5 Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Permission to conduct the study at CMJAH will be obtained from the Chief Executive Officer prior to the commencement of the study (Appendix 1). Further approval was obtained from the gatekeepers of the anaesthetic (Appendix 2), high care and intensive care records (Appendix 3).

A list with patient names, hospital numbers and study numbers will be generated and filed separately. No identifying information will be recorded on the data collection sheet, only the study number. Confidentiality will be maintained as only the researcher and supervisors will have access to the raw data.

All data collected will be stored securely for six years after completion of the study on a password-protected database. This study will be conducted according to the principles of the Declaration of Helsinki (31) and the South African Guidelines for Good Clinical Practice (32).

4.6 Research methodology

4.6.1 Research design

A retrospective, descriptive and contextual research design will be followed in this study.

A retrospective study measures variables that have occurred in the past (33). This study will obtain data from anaesthetic charts, high care or intensive care unit records over a one-year period from 1 January to 31 December 2017.

Descriptive studies are, according to Brink et al (33), “research studies in which phenomena are described, or the relationship between variables is examined; no attempt is made to determine cause-and-effect relationships.” This study will describe ITM practice at CMJAH.

Contextual studies, according to de Vos et al (34), are studies “conducted in ‘small-scale worlds’ are, *inter alia*, gangs, hospital wards, public drinking places, school classrooms, restaurants, clubs and cults.” The study will be conducted at CMJAH in patients who have received ITM for postoperative pain management.

4.6.2 Study population

The study population consists of the records of patients 18 years and older who received ITM for postoperative analgesia at CMJAH in 2017.

4.6.3 Study sample

Sample size

All the records of the patients who received ITM for postoperative analgesia between 1 January and 31 December 2017 will be included. The sample size will be realised by the number of records available during the study period. On average, 120 patients receive ITM per annum.

Sampling method

In this study, a consecutive, convenience sampling method will be used. Convenience sampling involves all individuals or units readily available to the researcher (33). Endacott and Botti (35) define consecutive sampling as “A version of convenience sampling where every available individual or event within an accessible population is chosen.” and the authors further state that it is: “The best choice of non-random sampling.” All the records of the patients who received ITM from 1 January to 31 December 2017 for postoperative analgesia will be used in the study.

Inclusion and exclusion criteria

The inclusion criteria for this study are the records of:

- ASA I, II and III patients
- 18 years and older
- who received intrathecal morphine injection for postoperative analgesia.

Exclusion criteria for this study are:

- obstetric patients who received intrathecal morphine injection for analgesia
- illegible records
- if morphine dose is missing.

4.6.4 Data collection

Data collection sheet

A data collection sheet was designed following a review of the literature and was reviewed by three senior anaesthesiologists. The comments of the reviewers were incorporated in the final document. The following information will be documented on the data collection sheet (Appendix 4):

- demographics
    - age
    - weight

    - type of anaesthetic
    - sex
    - ASA classification
    - postoperative admission (high care, ward or intensive care)
- type of surgery
- intrathecal morphine injection
    - morphine dose
    - local anaesthetic and dose
- additional analgesia intraoperatively and 24 hours postoperative
    - drug
    - total dose
- side effects of intrathecal morphine
    - nausea and vomiting
    - pruritus
    - respiratory depression and treatment
    - other.

Data collection process

Once the relevant approvals have been obtained, data will be collected from CMJAH by the researcher. The theatre statistics will be used to determine the number of surgeries done at CMJAH during the study period. Thereafter, the number of patients who received intrathecal morphine injections will be established using the anaesthetic records. The next step will be to record the information regarding the intrathecal morphine injection using the anaesthetic, high care and intensive care records. Data will be captured directly onto a Microsoft Excel spreadsheet. No records will be removed from the hospital premises.

4.6.5 Data analysis

Descriptive statistics will be used to analyse the data. Categorical variables will be described using frequencies and percentages and continuous variables will be described using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. The patients will be divided into two groups, Group A (received ≤150 mcg ITM) and Group B (received >150 mcg ITM) for descriptive purpose (10, 24).

4.6.6 Significance of the study

This study by, analysing the data on ITM, will give a better understanding of this practice at CMJAH. It will estimate the incidence of the side effects of ITM and may allow more patients to receive ITM without requiring a high care or intensive care unit admission.

4.7 Validity and reliability of the study

The validity of a study is the extent to which it accurately reflects the variables being measured and the reliability is the consistency of the measures achieved (36).

Measures to ensure the validity and reliability of this study are:

- using an appropriate study design
- a retrospective design ensures that anaesthetists are not able to change their practice in response to the study
- a single researcher collecting data on a standardised data collection sheet
- every tenth data entry will be checked for accuracy of capture
- data analysis will be done in consultation with a biostatistician.

4.8 Potential limitations

Limitations are those restrictions or problems that reduce the assumptions that can be made from the findings of a study (33).

The study is contextual as it is limited to CMJAH patients who received ITM for postoperative analgesia. The results may therefore not be generalisable to other hospitals in South Africa.

A further potential limitation is the reliance on completed anaesthetic, high care and intensive care records.

4.9 Project outline

4.9.1 Time frame

	May-Jun 2018	Jul-Aug 2018	Sep-Oct 2018	Nov 2018 – Mar 2020	Apr 2020 - Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021
Proposal									
Literature review									
Proposal submission									
Ethics committee submission									
Graduate Study Committee submission									
Data collection									
Data analysis									
Article preparation									
Editing									

Submission									

4.9.2 Budget

The Department of Anaesthesiology will bear the cost of printing and paper for the proposal, ethics and postgraduate approvals.

Items	**Numbers**	**Cost**	**Total**
Printing	1000	R1/page	R1000
Binding	4	R 200	R800
Total			R1800

4.10 References

1. South African Society of Anaesthesiologists. South African Acute Pain Guidelines. Cramerview, South Africa: Medpharm Publications; 2017.

2. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: What do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85-93. doi:10.1097/PRS.0000000000000671

3. Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician. 2012;15(3 Suppl):9-38.

4. Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: the role of the anesthesiologist. Perioper Med (Lond). 2018;7:16. doi:10.1186/s13741-018-0097-4

5. Heitz JW, Witkowski TA, Viscusi ER. New and emerging analgesics and analgesic technologies for acute pain management. Curr Opin Anaesthesiol. 2009;22(5):608-617. doi:10.1097/ACO.0b013e32833041c9

6. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: What do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85S-93S. doi:10.1097/PRS.0000000000000671

7. Nordquist D, Halaszynski TM. Perioperative multimodal anesthesia using regional techniques in the aging surgical patient. Pain Res Treat. 2014;2014:902174. doi:10.1155/2014/902174

8. Butterworth JF, Mackey DC, Wasnick JD. Spinal, epidural and caudal blocks. Morgan and Mikhail's Clinical Anesthesiology, 5th ed. New York, NY: McGraw-Hill Education; 2013. p. 937 - 973.

9. Bujedo BM. Current evidence for spinal opioid selection in postoperative pain. Korean J Pain. 2014;27(3):200-209. doi:10.3344/kjp.2014.27.3.200

10. Bujedo B. A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat. 2012;2012(612145). doi:10.1155/2012/612145

11. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25(2):118-122. doi:10.1017/s0265021507001305

12. Stoelting RK. Intrathecal morphine: An underused combination for postoperative pain management. Anesth Analg. 1989;68(6):707-709.

13. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. Anesth Analg. 2005;101(5 Suppl):S30-43. doi:10.1213/01.ane.0000177101.99398.22

14. Meylan N, Elia N, Lysakowski C, Tramer MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: Meta-analysis of randomized trials. Br J Anaesth. 2009;102(2):156-167. doi:10.1093/bja/aen368

15. Chetty S, Paruk F, Kamerman P. Low dose intrathecal morphine reduces post-operative opioid requirements after caesarean section. Anesth Analg. 2016;123(3S):238-239. doi:10.1213/01.ane.0000492590.47304.36

16. Hein A, Rosblad P, Gillis-Haegerstrand C, Schedvins K, Jakobsson J, Dahlgren G. Low dose intrathecal morphine effects on post-hysterectomy pain: A randomized placebo-controlled study. Acta Anaesthesiol Scand. 2012;56(1):102-109. doi:10.1111/j.1399-6576.2011.02574.x

17. Fischer H, Simanski C. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. Anaesthesia. 2005;60(12):1189-1202. doi:10.1111/j.1365-2044.2005.04382.x

18. Bowrey S, Hamer J, Bowler I, Symonds C, Hall JE. A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. Anaesthesia. 2005;60(5):449-452. doi:10.1111/j.1365-2044.2005.04174.x

19. Sakai T, Use T, Shimamoto H, Fukano T, Sumikawa K. Mini-dose (0.05 mg) intrathecal morphine provides effective analgesia after transurethral resection of the prostate. Can J Anaesth. 2003;50(10):1027-1030. doi:10.1007/bf03018367

20. Sakowska M, Docherty E, Linscott D, Connor S. A change in practice from epidural to intrathecal morphine analgesia for hepato-pancreato-biliary surgery. World J Surg. 2009;33(9):1802-1808. doi:10.1007/s00268-009-0131-2

21. Boezaart AP, Eksteen JA, Spuy GV, Rossouw P, Knipe M. Intrathecal morphine: Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. Spine (Phila Pa 1976). 1999;24(11):1131-1137. doi:10.1097/00007632-199906010-00013

22. Turker G, Goren S, Sahin S, Korfali G, Sayan E. Combination of intrathecal morphine and remifentanil infusion for fast-track anesthesia in off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2005;19(6):708-713. doi:10.1053/j.jvca.2005.08.011

23. Chaney M. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42(10):891-903. doi:10.1007/bf03011037

24. Sultan P, Gutierrez M, Carvalho B. Neuraxial morphine and respiratory depression: Finding the right balance. Drugs. 2011;71(14):1807-1819. doi:10.2165/11596250-000000000-00000

25. Ko S, Goldstein DH, Vandenkerkhof EG. Definitions of “respiratory depression” with intrathecal morphine postoperative analgesia: A review of the literature. Can J Anaesth. 2003;50(7):679-688. doi:10.1007/bf03018710

26. Apfelbaum J, Horlocker T, Agarkar M, Connis R, Hebl J, Nickinovich D, et al. Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration: An updated report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2016;124(3):535-552. doi:10.1097/aln.0000000000000975

27. Apfelbaum J, Ashburn M, Connis R, Gan T, Nickinovich D. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain

Management. Anesthesiology. 2012;116(2):248-273. doi:10.1097/ALN.0b013e31823c1030

28. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North America. 2005;23(1):21-36. doi:10.1016/j.atc.2004.11.013

29. Lim PC, Macintyre PE. An audit of intrathecal morphine analgesia for non-obstetric postsurgical patients in an adult tertiary hospital. Anaesth Intensive Care. 2006;34(6):776-781. doi:10.1177/0310057X0603400601

30. Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. Anesthesiology. 1991;75(3):452-456. doi:10.1097/00000542-199109000-00012

31. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

32. Department of Health. Guidelines for good practice in the conduct of clinical trials in human participants in South Africa Pretoria, South Africa. (Accessed 14 May 2018). Available from: http://www.kznhealth.gov.za/research/guideline1.pdf.

33. Brink H, Van der Walt C, Van Rensburg G. Fundamentals of research methodology for healthcare professionals. Third edition ed. Cape Town, South Africa: Juta; 2012.

34. De Vos A S, Strydom H, Fouche C B, Poggenpoel M, Schurink E, W. S. Research at grass roots, A primer for the caring professions. Cape Town, South Africa: Van Schaik; 2000.

35. Endacott R, Botti M. Clinical research 3: Sample selection. Accid Emerg Nurs. 2007;15(4):234-238. doi:10.1016/j.aaen.2006.12.006

36. Burns N, Grove SK. Understanding nursing research. Philadelphia, PA: Saunders; 2003.

4.11 Appendices

Appendix 1 Letter to the CEO of CMJAH

Dr DB Voka

Department of Anaesthesiology

University of the Witwatersrand

Attention: The CEO of Charlotte Maxeke Johannesburg Academic Hospital

Johannesburg, 22 May 2018

Re: Audit of morphine spinal for postoperative analgesia at Charlotte Maxeke Johannesburg academic hospital

Dear Ms Gladys Bogoshi

I am a registrar in the Department of Anaesthesiology. The research component of my MMED is a non-human study. I propose to do a retrospective audit of the practice of intrathecal morphine injection for postoperative pain at Charlotte Maxeke Johannesburg Academic Hospital. Approval for the study will be requested at the Human Research Ethics committee (Medical) and the University of the Witwatersrand Graduate Study Committee. The audit will involve the anaesthetic charts, the high care and the intensive care unit records of patients who received intrathecal morphine injection for postoperative pain management during the period of 01 January 2017 to 31 December 2017. No identifiable information of patients and medical staff will be recorded. Records will be reviewed on the premises and not removed from the hospital. There will be no financial implications for CMJAH or the Gauteng Department of Health. A copy of the final report, should you request it, will be made available to you.

Yours sincerely

DR Di Betu Voka

0826690386

Appendix 2 Letter from the gate keeper of the CMJAH Department of Anaesthesiology

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF ANAESTHESIA
CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
UNIVERSITY OF THE WITWATERSRAND
TEL: 011 488 4344
FAX: 011 488 4343

22 May 2018

Dr DB Voka
Registrar: Department of Anaesthesiology
University of the Witwatersrand

Dear Dr Voka

RE: PERMISSION TO COLLECT DATA FOR MMED STUDY

Your request for permission to collect data for an MMed study refers.

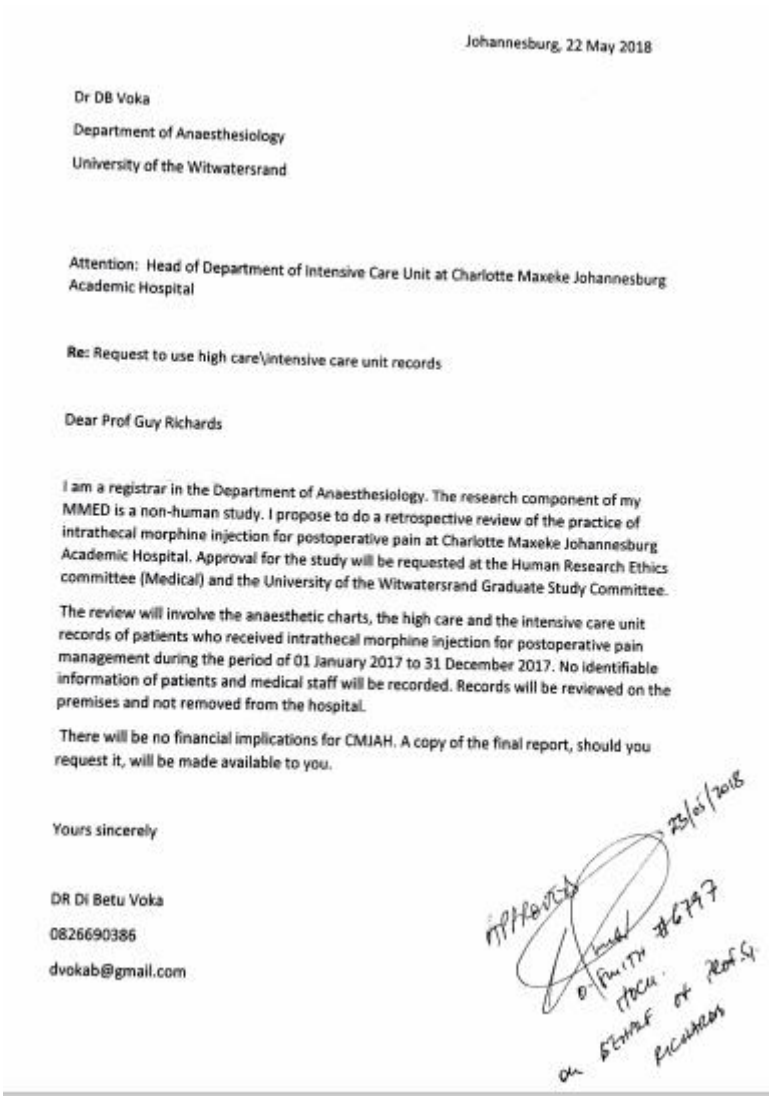
Approval is granted to collect data from anaesthesia records for your study titled: A retrospective review of the practice of intrathecal morphine for postoperative pain at CMJAH. This approval is subject to gaining the necessary clearances from other involved parties, including ethical approval.

I am looking forward to the results of your study.

Yours sincerely,

Prof EE Oosthuizen
Clinical Head: Department of Anaesthesia
Charlotte Maxeke Johannesburg Academic Hospital

Appendix 3 Letter from the gate keeper of the CMJAH Department of High care and intensive care unit



Johannesburg, 22 May 2018

Dr DB Voka

Department of Anaesthesiology

University of the Witwatersrand

Attention: Head of Department of Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital

Re: Request to use high care\intensive care unit records

Dear Prof Guy Richards

I am a registrar in the Department of Anaesthesiology. The research component of my MMED is a non-human study. I propose to do a retrospective review of the practice of intrathecal morphine injection for postoperative pain at Charlotte Maxeke Johannesburg Academic Hospital. Approval for the study will be requested at the Human Research Ethics committee (Medical) and the University of the Witwatersrand Graduate Study Committee.

The review will involve the anaesthetic charts, the high care and the intensive care unit records of patients who received intrathecal morphine injection for postoperative pain management during the period of 01 January 2017 to 31 December 2017. No identifiable information of patients and medical staff will be recorded. Records will be reviewed on the premises and not removed from the hospital.

There will be no financial implications for CMJAH. A copy of the final report, should you request it, will be made available to you.

Yours sincerely

DR Di Betu Voka

0826690386

dvokab@gmail.com

Appendix 4 Data collection sheet

Study number

1. Demographics

Age in years			
Weight in kg			
Type of surgery			
Sex	Male	Female	
Anaesthetic	GA	Intrathecal	
Ward	HC	ICU	
ASA	1	2	3

2. Intrathecal morphine dose

Morphine dose	
Local anaesthetic dose	Marcaine
	Lignocaine

3. Additional analgesia

Intraoperatively

Drug	Dose

Postoperatively

Drug	Dose

4. Side effects of intrathecal morphine

Nausea and vomiting	Pruritus
Respiratory depression or Apnoea	Other

If other please specify

……
……

If respiratory depression or apnoea, intervention taken:

Nasal prong	Face mask	Ventilation

Section 5: Annexures

5.1 Ethics approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Di Betu Voka et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180607

NAME: (Principal Investigator)	Dr Di Betu Voka et al
DEPARTMENT:	Anaesthesiology Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Intrathecal morphine injection practice for acute perioperative pain management at a central hospital: a restrospective review
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Mrs Helen Perrie
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/09/2018

This clearance certificate is valid for 5 years from 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 Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due 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 07/03/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

5.2 Graduate studies approval

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

23 August 2018
Person No: 0211230Y
PAG

Dr DB Voka
Unit Number 4
300 Surrey Avenue
Randburg
2194
South Africa

Dear Dr Voka

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Intrathecal morphine injection practice for acute perioperative pain management at a central hospital: A retrospective review*. has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Approval from CEO of Charlotte Maxeke Johannesburg academic hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gautemg.gov.za
21 September 2018

GP_201808_038

Dear Dr. Di Betu Voka

STUDY TITLE: Intrathecal Morphine Injection Practice for Acute Perioperative Pain Management at Central Hospital: A Retrospective Review.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

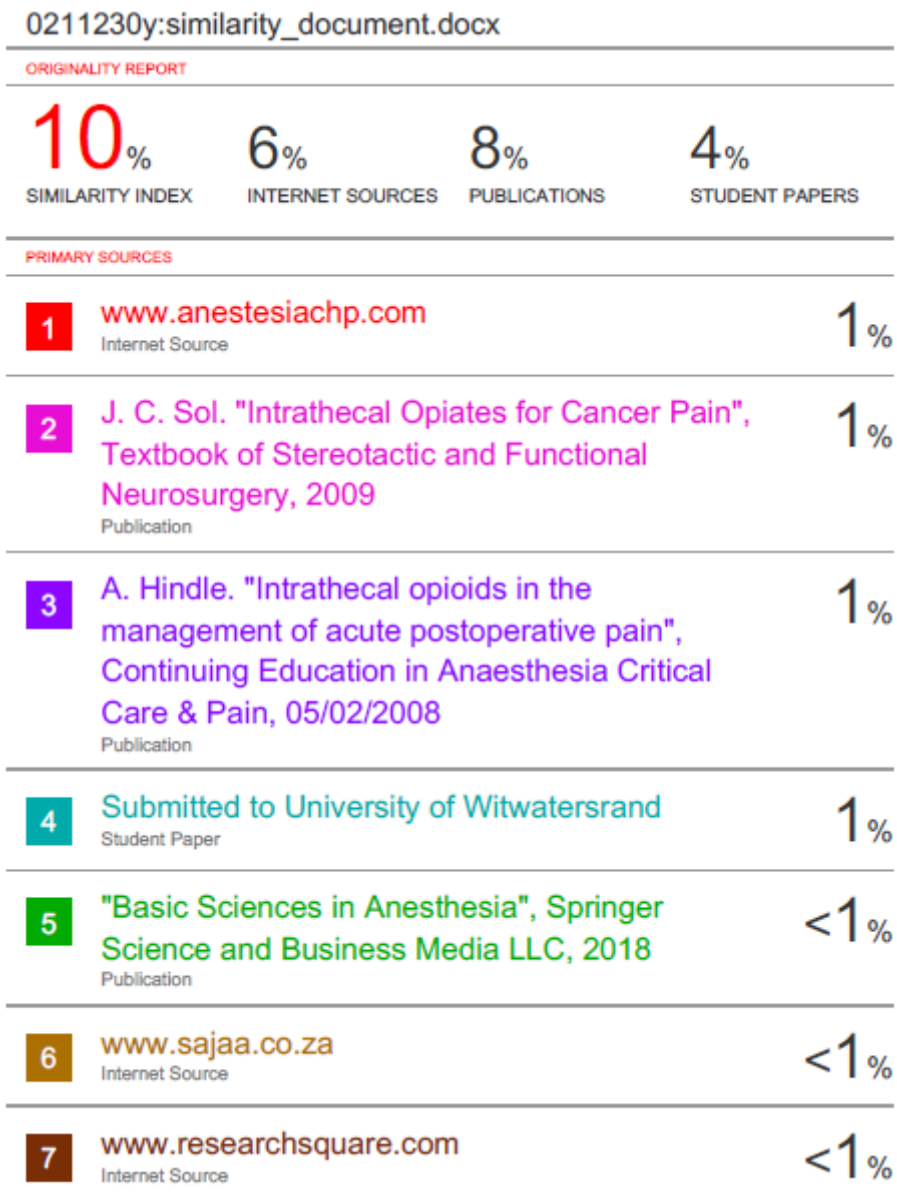
Supported / ~~not supported~~

Dr. M.T. Mofokeng
Clinical Director
DATE: 21/09/2018

Approved/~~not approved~~

Ms. G. Bogoshi
Chief Executive Officer
Date: 25/09/2018

5.4 Turnitin report



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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

2nd February, 2021

The Chairperson
Graduate Studies Committee
Faculty of Health Sciences
University of the Witwatersrand

Dear Madam,

Re: M Med: **Intrathecal morphine injection practice for acute perioperative pain management at a central hospital: A retrospective review**

Dr Di Betu Voka, student number: 0211230Y, has submitted his research report to Turnitin which revealed a similarity index of 10%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the topic of the research.

Yours sincerely,

H Perrie

Helen Perrie
Supervisor