Comparison of the Efficacy of Intrathecal Fentanyl 20mcg versus Intrathecal Morphine 0.2 mg as an adjuvant therapy in spinal anesthesia in lower limb surgery.

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#### LIST OF SYMBOLS AND ABBREVIATIONS

ASA American Society of Anaesthesiology

G Gauge

GOT General Operation theatre

HUSM Hospital University Sains Malaysia

ITF Intrathecal fentanyl

ITM Intrathecal Morphine

IV Intravenous

Mcg Microgram

Ml Millilitres

OT Operation theatre

SPSS Statistical package for the social sciences

TOT Trauma Operation theatre

VAS Visual analogue score

= Equal to

% Percent

< Less than

± standard deviation

#### **APPENDICES**

Appendix A: DATA COLLECTION SHEET

Appendix B : VISUAL ANALOGUE SCALE

Appendix C : PATIENT INFORMATION AND CONSENT

Perbandingan keberkesanan intrathecal fentanyl 20mcg berbanding dengan intrathecal morphine 0.2mg dalam buis setempat untuk pembedahan kaki.

#### **ABSTRAK**

#### Latar Belakang

Bius setempat spinal adalah bius yang diberi untuk pembedahan orthopedic melibatkan anggota badan kaki. Intrathecal morfin yang diberi boleh menjamin keselesaan pesakit yang berlanjutan selepas pembedahan. Objektif kajian ini adalah untuk mengaji keberkesanan intrathecal morfin 0.2mg sebagai ubat rawatan kesakitan selama 24 jam dan menilai komplikasi yang mungkin terjadi.

#### Kaedah

43 pesakit dijadual untuk menjalani pembedahan orthopedik kaki diteliti di dalam percubaan klinikal yang dikawal secara rawak. Pesakit ini dibahagikan kepada 2 kumpulan. Satu kumpulan pesakit akan menerima 2.8mls 0.5% hyperbaric bupicavaine dengan fentanyl 20mcg manakala satu kumpulan pesakit akan menerima 2.8mls 0.5% heavy Marcaine dengan 0.2mg morphine. Hasil kajian utama adalah untuk mengetahui tahap kesakitan dalan 24 jam selepas pembedahan , sementara hasil kajian kedua adalah untuk mengetahui komplikasi yang mungkin terjadi dalam 2 kumpulan pesakit .

#### Keputusan

Kumpulan Intrathecal morfin menunjukkan tahap kesakitan yang lebih rendah pada jam ke 6, 12, 18, dan 24. Secara keseluruhan , intrathecal morphine juga menunjukkan tahap kesakitan yang lebih rendah. Tiada perbezaan komplikasi loya dalam 2 kumpulan,

manakala komplikasi muntah dan gatal lebih tinggi di kalangan ITM. Kedua dua kumpulan tidak menunjukkan tanda kesukaran pernafasan.

.

## Kesimpulan

Intrathecal morfin memberikan kesan rawatan kesakitan yang lebih lama berbanding dengan intrathecal fentanyl. Tiada risiko ganguan pernafasan tetapi risiko muntah loya and gatal badan didapati berlaku dalam kumpulan intrathecal morfin.

# Comparison of the Efficacy of Intrathecal Fentanyl 20mcg versus Intrathecal Morphine 0.2 mg as an adjuvant therapy in spinal anesthesia in lower limb surgery

#### **ABSTRACT**

#### Background

Spinal anesthesia is the preferred method of anesthesia for majority of the lower limb surgery. Intrathecal Morphine is an adjuvant used to provide prolonged analgesia post operatively. The objective of this study was to investigate the efficacy of adding Intrathecal morphine 0.2mg by assessing the analgesic effect 24hours post spinal anesthesia and to assess the proportion of complication that ensues.

#### Methods

43 patients scheduled for various lower limb orthopedic surgery were studied in a prospective, single blinded controlled clinical trial. They were divided into 2 groups; Patient in ITF group receive 2.8mls of 0.5% hyperbaric bupivacaine with 20mcg of fentanyl added whilst patient in ITM group received 2.8mls of 0.5% hyperbaric bupivacaine with 0.2 mg of morphine added. The primary outcome was the pain score within 24 hours post operatively while the secondary endpoint was to determine the proportion of complications (nausea, vomiting, pruritus sedation and respiratory depression between the 2 groups.

#### Results:

Intrathecal morphine group revealed significantly lower median pain score at 6th, 12th, 18th and 24th hour post op. There was a significant difference in VAS score between the ITF and ITM group over 24 hours post operatively. There is no difference in terms of incidence of nausea between 2 groups (p=0.098), higher incidence of vomiting (n=9, 39.1%, p=0.002) and pruritus (n=10, 43.5%, p=0.001) in ITM group, No incidence of respiratory depression was recorded in both ITF and ITM group.

#### Conclusion:

Intrathecal morphine 0.2 mg as an adjuvant to spinal anesthesia provided prolonged 24 hours analysesia with no respiratory depression but at the expense of increased vomiting and pruritus which can be prophylactically treated with antiemetics.

#### **4.2.3 Keyword**

Intrathecal Morphine, Intrathecal fentanyl, spinal anesthesia, lower limb surgery

**CHAPTER 1: INTRODUCTION** 

Chapter 1

1.1 Introduction

Background

Most lower limb fractures occur following an accident, a fall or a sporting injury. These

acute traumas related to femoral or tibia fibula fractures usually require surgical

intervention to reduce the fractures and for stabilization. Surgical intervention of such

fractures usually caused some degree of pain and has the potential to lengthen the duration

of hospital stay and increases morbidity and mortality

Lower limb surgery can be done under general anesthesia, regional anesthesia or by local

anesthesia infiltrated at site of operation. This regional technique of anesthesia was first

performed by August Bier in Germany in 1889 and six month later Dr J.B Scldwitch in St

Petersburg Russia, reported four cases of spinal anesthesia for lower limbs surgery.

This subarachnoid block is often employed as there was a tendency towards a lower

incidence of myocardial infarction, confusion and postoperative hypoxia in the regional

anesthetic group compared to general anaesthesia.

Heavy bupivacaine 0.5% is currently employed as the local anesthetic of choice in spinal

anesthesia as it confers faster onset of sensory block at T10 compared to ropivacaine

Adjuncts opioids that were added to local anesthesia acts to synergistically alter the effect

of local anesthetic bupivacaine.

1

Intrathecal opioids that are injected into the cerebrospinal fluid, diffuses across the meninges into the spinal cord. They act on the u and k receptors in the substantial geletinosa of the dorsal horn to decrease transmission of pain fibers.

As fentanyl is 600x more lipid soluble than morphine, fentanyl has faster onset and shorter duration of action compared to morphine. Duration of action of morphine is estimated to be roughly 24 hours and hence is expected to produced longer analysis effects as compared to fentanyl. However, the use of Intrathecal morphine may be associated with many side effects such as pruritus, urinary retention, nausea and vomiting, and potentially life-threatening adverse effects i.e. delayed respiratory depression.

#### 1.2 Study rationale

In HUSM the current practice is to administer Intrathecal fentanyl with intrathecal bupivacaine in patients going for lower limb surgery. These patients would be discharged back to ward post-operatively with either oral or iv analgesics.

By conducting this study, we aim to challenge the current practice in our hospital setting by administering Intrathecal morphine instead of Intrathecal fentanyl as it was observed in other studies that Intrathecal morphine analgesic properties last more than 24 hours. This will allow patients pain level to be at minimal within the first 24 hours, for the oral analgesics effect to take effect.

We also aim to prove that the rate of respiratory depression that is feared most with Intrathecal morphine occurs very infrequently. While the other complications such as pruritus, nausea and vomiting do occur but at a insignificant rate. Hence Intrathecal morphine is safe to be administered in these group of patients.

#### 1.3 Literature review

Subarachnoid block

Subarachnoid block has become an integral mode of anesthesia for many types of surgery. As mentioned earlier, it was first used in 1898 by Karl august Bier using cocaine solution and it's usage has subsequently evolved since then. The anatomy, choice of Local anesthesia, the physiological effects of spinal anesthesia, the indication and contraindication, complications, the way the procedure is conducted, patient positioning must all be taken into consideration. Performing the SAB is the bread and butter skills that an anesthetist must acquire from the start of their training.

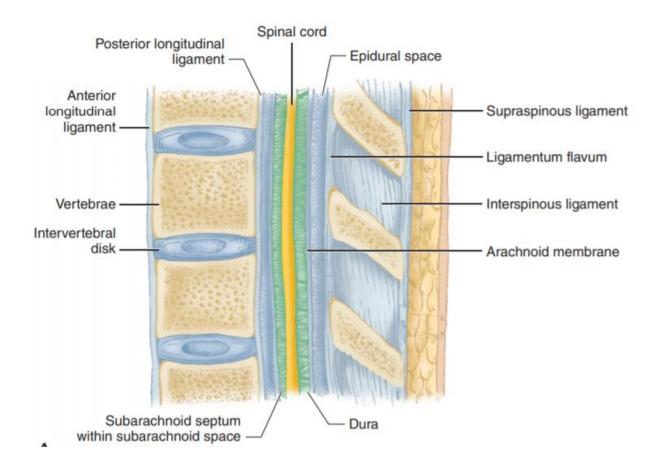
Neuraxial blocks have been given in lower limb, abdominal, inguinal, lower extremity surgery, rectal and urogenital surgery. It is contraindicated when patient does not consent to the procedure, bleeding disorder, raised ICP, infection at site of injection and hemodynamically unstable. Relative contraindications includes aortic and mitral stenosis, HOCM hypertrophic obstructive cardiomyopathy. (organ Mikail)

In reviewing the functional anatomy of the spinal anesthesia, an in depth knowledge of the spinal canal, the spinal cord and the spinal nerves needs to be present. The vertebral column consists of 33 vertebrae, 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal segments, with 3 curves present with the cervical and lumbar convex anteriorly and thoracic convex posteriorly. This vertebral column curves together with bauricity of Local anesthesia, patient positioning will determine the spread of anesthesia.

The 5 ligaments that hold the spinal column together includes the supraspinous ligament, interspinous ligaments, ligamentum flavum, anterior and posterior longitudinal ligaments. The three membranes that covers the spinal cord includes the dura mater, the arachnoid mater and the pia mater. The space between the arachnoid mater and the pia mater is known as the subarachnoid space.

When performing spinal anesthesia using midline approach, the layers of anatomy that are traversed includes skin, subcutaneous fat, supraspinous ligaments, interspinous ligaments, ligamentum flavum, dura mater, subdural spaces, arachnoid mater and finally the subarachnoid space.

Spinal anesthesia is given at the level of L3, L4 or L4, L5 to avoid spinal cord which ends at L1, L2.



Pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"

Opioids acts on opioid receptors that are present in spinal cord, brain and tissues such as the gastrointestinal tract, hence mitigating the vomiting side effect. Neuraxial opioids be it morphine or fentanyl binds to the pre and postsynaptic receptors in the substantia gelatinosa of the dorsal horn of the spinal cord. Activation of these presynaptic receptors on the primary afferent neurons results in decreased neurotransmitter release hence reducing signal transmission between primary and secondary neurons. While binding of opioid to the receptors present in the secondary afferent neurons results in hyperpolarization and decreased in action potential propagation.

The intrathecal opioids that is administered acts via 3 different mechanism to produce analysesic effect.

Firstly the act directly on the dorsal horn of the spinal cord, secondly via supra-spinally through CSF bulk flow where they act on the descending inhibitory pathways and finally a small amount diffuses across into the epidural space leading to systemic absorption and systemic side effects.

The onset and duration of action of these opioids are dependent on the lipid solubility and hence degree of cephalad spread. Highly lipid soluble opioids such as fentanyl diffuses into the spinal cord, binding to the receptors there and produces rapid onset of analgesia. As there is minimal cephalad spread, the risk of delayed respiratory depression is low with a short duration of action.

Morphine on the other hand less lipid soluble, , binds slowly to the receptors in the dorsal horn of the spinal cord but more significant rostral spread via CSF bulk flow, hence translating into slower onset of action but more prolonged effects of analgesia.

Wolfgang C et al. Compared the Spinal Distribution and Clearance Kinetics of Intrathecally Administered Morphine, Fentanyl, Alfentanil, and Sufentanil. They concluded that these pharmacokinetic differences between different classes of opiods were largely responsible for the marked differences observed in clinical pharmacological of opiods administered intrathecally.

Gehling et al. conducted a randomized double blinded multicenter study in 188 orthopaedic patients to determine the adequate dose for ITM by randomizing them into

receiving intrathecally placebo, 0.1 mg morphine or 0.2 mg morphine in addition to bupivacaine. They noted that after 0.2 mg morphine, systemic opioid requirements at 24 h were significantly lower than those in patients with 0.1 mg morphine given intrathecal. They also noted that at 0.2mg of intrathecal morphine was not associated with an increased frequency of respiratory depression.

Refika Kılıçkaya et al.Conducted a prospective, randomized study to compare the effects of Intrathecal Fentanyl (0.5% heavy bupivacaine 2.5 ml + 25 mcg fentanyl 0.5 ml), and Intrathecal Morphine (0.5% heavy bupivacaine 2.5 ml + 0.1 mg of morphine 0.5 ml) on Pain in Elective Total Knee Replacement Surgery in 50 patients. This study concluded that the morphine group had lower pain scores in the 2nd, 6th, 12th, and 24th hours compared to the fentanyl group (Group F). The fentanyl group also required earlier first analgesic requirement times than did the morphine group. This study also noted in terms of nausea and vomiting, there was no statistically significant difference between the two groups. (8)

G Siti Salmah et al. did a study to compare Morphine 0.1 mg versus Fentanyl 25mcg added to intrathecal 0.5% hyperbaric bupivacaine for analgesia after caesarean section. This study was done to determine the effects in terms of analgesia and duration for postoperative pain relief after Caesarean section. Time to first demand of PCA morphine, cumulative PCA morphine requirement and opioid side effects were documented. The VAS for pain and the cumulative PCA morphine requirement and the time to first demand were both significantly lower in morphine group during the 24 hours study period. This study did demonstrate an increase risk of vomiting with ITM, however this are easily treated side effect with antiemetics that does not react with analgesics. In conclusion the

addition of 0.1mg morphine for spinal anaesthesia provided superior and longer postoperative analgesia after Caesarean section.(1)

#### **CHAPTER 2: STUDY OBJECTIVES**

#### 2.1.1General Objectives

To compare the efficacy of Intrathecal fentanyl 20mcg to intrathecal morphine 0.2mg as adjuvant therapy in spinal anesthesia in lower limb surgery.

#### 2.1.2 Specific Objectives

- To compare the total Visual analogue scale, VAS 24 hours post operatively between Intrathecal fentanyl and Intrathecal morphine spinal anesthesia block in lower limb surgery
- To determine the proportion of complications of nausea, vomiting, pruritus and sedation between Intrathecal morphine and Intrathecal fentanyl spinal anesthesia block in lower limb surgery

#### 2.1.3 Null hypothesis

- There is no difference in the total visual analogue scale, VAS 24 hours post operatively between Intrathecal fentanyl and Intrathecal morphine spinal anesthesia block in lower limb surgery
- There is no difference in the proportion of complications of nausea, vomiting, pruritus and sedation between Intrathecal fentanyl and Intrathecal morphine spinal anesthesia block in lower limb surgery

#### **CHAPTER 3: MANUSCRIPT**

#### 3.1 Title page

*Title* 

Comparison of the Efficacy of Intrathecal Fentanyl 20mcg versus Intrathecal Morphine 0.2 mg as an adjuvant therapy in spinal anesthesia in lower limb surgery

Running head:

Intrathecal morphine as an adjuvant for spinal anesthesia in lower limb surgery.

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#### 3.2 Abstract

*Background* Spinal anesthesia is the preferred method of anesthesia for majority of the lower limb surgery. Intrathecal Morphine is an adjuvant used to provide prolonged analgesia post operatively. The objective of this study was to investigate the efficacy of adding Intrathecal morphine 0.2mg by assessing the analgesic effect 24hours post spinal anesthesia and to access the proportion of complication that ensues.

#### Methods

43 patients scheduled for various lower limb orthopedic surgery were studied in a prospective, single blinded controlled clinical trial. They were divided into 2 groups; Patient in ITF group receive 2.8mls of 0.5% hyperbaric bupivacaine with 20mcg of fentanyl added whilst patient in ITM group received 2.8mls of 0.5% hyperbaric bupivacaine with 0.2 mg of morphine added. The primary outcome was the pain score within 24 hours post operatively while the secondary endpoint was to determine the proportion of complications (nausea, vomiting, pruritus and sedation) between the 2 groups.

#### Results:

Intrathecal morphine group revealed significantly lower median score at 6<sup>th</sup>, 12<sup>th</sup>, 18<sup>th</sup> and 24<sup>th</sup> hour post op. There was a significant difference in VAS score between the ITF and ITM group over 24 hours post operatively. There is no difference in terms of incidence of nausea between 2 groups (p=0.098), higher incidence of vomiting (n=9, 39.1%, p=0.002) and pruritus (n=10, 43.5%, p=0.001) in ITM

group, No incidence of respiratory depression was recorded in both ITF and ITM group.

#### Conclusion:

Intrathecal morphine 0.2 mg as an adjuvant to spinal anesthesia provided prolonged 24 hours analgesia with no respiratory depression but at the expense of increased nausea, vomiting and pruritus which can be prophylactically treated with antiemetics,

## Keyword:

Intrathecal Morphine, Intrathecal fentanyl, spinal anesthesia, lower limb, surgery

#### 3.3 Introduction

Lower limb surgeries are performed by orthopedic surgeons on a daily basis. Most lower limb fractures occur following an accident, a fall or a sporting injury. These acute traumas that require surgical intervention usually caused some degree of pain. Acute post-operative pain that is not well controlled can potentially effect multi systemic organ leading to a multitude of negative impact. Uncontrolled post-operative pain causes an activation of the neurohumoral stress response, causing a surge in the cortisol levels, potentially increasing the risk of HAI and subsequently surgical site infections.(2)

Regional anesthesia is often employed over general anesthesia as it was associated with a reduced in-hospital mortality and length of hospitalization.(3) General anesthesia was also associated with increased occurrence of adverse event, namely prolonged ventilator use post operatively, unplanned intubation, stroke, cardiac arrest, and increase in need for blood transfusion following elective primary total hip arthroplasty. (4)

Heavy bupivacaine 0.5% is currently employed as the local anesthetic of choice in spinal anesthesia as it confers faster onset of sensory block at T10 compared to ropivacaine at 3.2minutes versus 4.3 minutes, with a longer duration of sensory block with bupivacaine than ropivacaine at 190 mins vs 120 mins. This allows surgery of longer duration to be done under spinal anesthesia otherwise not possible with ropivacaine.(5) Adjuncts opioids that were added to local anesthesia acts to synergistically alter the effect of local anesthetic bupivacaine. These adjuncts confers postoperative pain relief beyond the duration of motor block from local anesthesia, while permitting the use of local anesthetic at a lower dosage.(6)

Intrathecal opioids that are injected into the cerebrospinal fluid, diffuses across the meninges into the spinal cord. They act on the u and k receptors in the substantial gelatinosa of laminae I and II of the dorsal horn to decrease transmission of pain fibers.

As fentanyl is 600x more lipid soluble than morphine, fentanyl has faster onset and shorter duration of action compared to morphine. As morphine is more hydrophilic compared to fentanyl, duration of action of morphine is estimated to be roughly 24 hours and hence is expected to produce longer analysesic effects as compared to fentanyl.

However, the use of Intrathecal morphine may be associated with potential side effects, such as pruritus, urinary retention, nausea and vomiting, and life-threatening adverse effects i.e. delayed respiratory depression. These side effects are concentration dependent hence balancing between the analgesic dose versus the risk of side effects.(7-9)

The objective of this study was to compare the efficacy of intrathecal fentanyl 20mcg to intrathecal morphine 0.2mg as adjuvant therapy in spinal anesthesia in lower limb surgery. This study aim to compare the total VAS at 1<sup>st</sup>, 6<sup>th</sup> 12<sup>th</sup> 18<sup>th</sup> and 24<sup>th</sup> hour between intrathecal fentanyl and intrathecal morphine and to determine the proportion of complications of nausea, vomiting, pruritus and sedation among the 2 different adjuvant drugs.

#### 3.4 Methodology:

After ethical approval from USM ethics committee and written consent, 44 patients aged 18 to 70 years old ASA 1 and ASA 2, scheduled for elective lower limb surgery were enrolled. This is a prospective, randomized, single blinded controlled trial. The surgeries included surgical fixation for open or closed fractures of the lower limb, repair of tendon cut, ligament tears and injuries to the vessels, and wound debridement of the diabetic foot ulcers and abscesses involving the lower limb.

Using a computer-generated randomizer, patients were randomized into 2 groups of 22 patients each as: Group ITF received 2.8 mls of heavy Marcaine 0.5% with fentanyl 20 mcg and Group ITM received 2.8mls of heavy Marcaine 0.5% with morphine 0.2mg.

Sample size for VAS at different time intervals were calculated using independent T test based on study by Refika et al(10) While sample size for proportion of complications of PONV and pruritus was calculated using dichotomous test based on study by Siti Salmah et al(1). With an anticipated dropout rate of 10%. we concluded that 40 patients, 20 per group were needed.

Consent was taken during preoperative assessment 1 day prior to surgery. All patients were fasted for at least 6 hours. When patient arrived in OR, there was a sealed envelope containing which group patient was allocated to. Once in the OR, the patient was put on standard anesthesia monitoring Ie: non invasive blood pressure, heart rate, pulse oximetry and cardiac monitoring. IVD normal saline 10mls/kg was given as preloading fluid prior to spinal. The drug for the spinal was prepared by the operator based on the randomization in the envelope. Both the patient and the assessor were blinded in this study.

The patient was seated on the OT table, and spinal anesthesia was done under aseptic technique. The lumbar area cleaned using chlorhexidine and draped accordingly, while anatomic landmarks at L3, L4 identified. Local anesthetics with 2ml of 2% lidocaine given at the indicated site. A 25 G Spinocan passed through the anesthetized area, and stopped when the presence of CSF is obtained. Then the drug was given slowly into the intrathecal space.

Spinal anesthesia was established when there is a sensory block up to T4 level using pin prick test with a short bevel needle and complete motor block. Patient was subsequently positioned for surgery and placed on 3L of oxygen via a nasal prong. Systolic blood pressure, diastolic blood pressure, heart rate were recorded every 5 mins as per standard intraoperative monitoring.

After the operation, patient was assessed for the pain score at 1<sup>st</sup> hour in recovery, 6<sup>th</sup> hour, 12<sup>th</sup> hour, 18<sup>th</sup> hour and 24<sup>th</sup> hour in the ward based on visual analogue scale (VAS), 1-10 Assessment of pain score were done by medical colleague who were blinded to the study. Presence of any complications such as pruritus, nausea and vomiting and sedation score (Ramsay score) were documented.

Any patient who vomited or complained of nausea were given a single dose of IV metoclopramide 10mg while those who complained of itching were given a single dose of Pririton 4mg stat.

#### 3.5 Results

#### 3.5.1 Demographics

A total of 43 participants were recruited for this study. 21 were randomized into group intrathecal fentanyl while the remaining 22 were randomized into intrathecal morphine group. All participants were Malay with a median age of (27 ± 21) years old. There were total 35 males (n=35, 81%). There were 31 fracture (n=31, 74%) versus 12 non fracture cases (n=12, 36%). 39 patients were ASA 1 (n=39, 88%) the remaining 4, 1 had hypertension and another 3 had diabetes mellites. There was 1 incomplete data in the Intrathecal fentanyl group.

#### 3.5.2 VAS

In the comparison of median VAS scores between the two treatment groups, ITM revealed significantly lower median score at 6<sup>th</sup>,12<sup>th</sup>, 18<sup>th</sup> and 24<sup>th</sup> hours post operation, as compared to that of ITM group. Repeated measure ANOVA was used to analyze the Visual analogue score across 24 hours. There was a significant difference in VAS scores between the intrathecal fentanyl and intrathecal morphine groups over 24 hours (p< 0.001), as shown in Table 1.

#### 3.5.3 Complications

There is no significant difference (P=0.098) in the incidences of nausea between ITF and ITM. However, there were significant differences (P<0.002) in the incident distribution of vomiting and (P<0.001) in the pruritus group between ITM and ITF. Incidence of vomiting and pruritis are higher in ITM group (Table 2) No incident of respiratory depression was documented in both study groups.

#### 3.6 Discussion

From the results obtained and analyzed, we were able to prove that intrathecal intrathecal morphine does indeed provides superior analgesic effects within 24 hours, as pain score at 6<sup>th</sup>, 12<sup>th</sup>,18<sup>th</sup>, 24<sup>th</sup> hour is significantly lower. This is in keeping with morphine's pharmacokinetics that is hydrophilic in nature, binding to nonspecific receptors in spinal cord, crosses the dura to the epidural space, while slowly entering the plasma. As a consequence, morphine results in slower onset, prolonged and extensive rostral spread providing and a relatively longer duration of action.

The optimal dosing of intrathecal morphine for postoperative analgesia has been a matter of much debate. In a cross surgical specialties European collaborative (PROSPECT) has recommended ITM 0.1 to 0.2 mg after Total Hip replacement. Hence in this study, an intrathecal morphine dosage of 0.2 mg was chosen as compared to 0.1mg as it was deemed able to provide more superior analgesic effect without increasing the risk of respiratory depression. This finding correlates with the study of Gehling et al.(11) Indeed, all patients in the study did not experience any respiratory depression within the 24 hours period.

As analgesic properties of intrathecal morphine is expected to last approximately 24 hours, therefore this study only monitored VAS up to 24 hours. The potential for ITM to produce analgesic effect past 24 hours is beyond the scope of this study. Acute nociceptive pain from orthopedic surgery is expected to last up 7 days or more. Hence during this period, multimodal analgesic should be employed, and oral analgesia initiated early to ensure adequate pain relief is achieved to allow for early mobilization and physiotherapy.

In this study none of the patient developed respiratory depression. Nevertheless, it is important to be able to prevent, detect and manage respiratory depression. If respiratory depression does occur, then naloxone should be given as an intravenous infusion. Guideline by ASA task force for prevention detection and management of respiratory depression associated with intrathecal morphine should be strictly adhered at all times.(12)

The occurrence of vomiting in ITF and ITM is statistically insignificant. Although ITF in general is not known to cause nausea, there may be other confounding factors leading to nausea in this group of patients. Female, previous PONV, history of motion sickness, non-smoker, intense preoperative anxiety, dehydration may all be contributing factors for developing post op nausea and vomiting.(13) Managing all these factors may decrease the patient's risk of PONV.

Experiencing post-operative nausea and vomiting can be equally as distressing as post-operative pain. Hence PONV should not be taken lightly and necessary preventions should be taken to minimize these occurrences. The outcome of this study does indeed confirm that the risk of nausea vomiting in patients receiving intrathecal morphine is high with 65% of patients suffered from nausea and another 39% suffered from vomiting. Prophylactically treating patients at risk of PONV with antiemetic therapy is effective, and the latest guidelines recommended 2 antiemetics in patient at risk of PONV(14). Nonpharmacologic strategies such as acupuncture may also play an important role.(15, 16) If PONV does occurs in the immediate postoperative period, a different class of antiemetics from that given prophylactically should be considered.

In this study, one limitation is that we were not able to obtain a homogenous sample of orthopedic surgery. Although majority of the cases 32 cases (74.4 %) were fracture related, there were 11 non fracture cases included. Hence certain procedures may invoke more pain compared to the other procedures conducted.

#### 3.7 Conclusion

Intrathecal morphine 0.2mg as an adjuvant to spinal anesthesia provided prolonged 24 hours analysesia with no respiratory depression but at the expense of increased nausea, vomiting and pruritus which can be prophylactically treated with antiemetics.

#### 3.8 References

- 1. Siti GS, Choy YC. Comparison of morphine with fentanyl added to intrathecal 0.5% hyperbaric bupivacaine for analgesia after caesarean section. The Medical journal of Malaysia. 2009;64(1):71-4.
- 2. van Boekel RLM, Warlé MC, Nielen RGC, Vissers KCP, van der Sande R, Bronkhorst EM, et al. Relationship Between Postoperative Pain and Overall 30-Day Complications in a Broad Surgical Population: An Observational Study. Annals of surgery. 2019;269(5):856-65.
- 3. Van Waesberghe J, Stevanovic A, Rossaint R, Coburn M. General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. BMC Anesthesiology. 2017;17(1):87.
- 4. Basques BA, Toy JO, Bohl DD, Golinvaux NS, Grauer JN. General compared with spinal anesthesia for total hip arthroplasty. J Bone Joint Surg Am. 2015;97(6):455-61.
- 5. Kulkarni KR, Deshpande S, Namazi I, Singh SK, Kondilya K. A comparative evaluation of hyperbaric ropivacaine versus hyperbaric bupivacaine for elective surgery under spinal anesthesia. Journal of anaesthesiology, clinical pharmacology. 2014;30(2):238-42.
- 6. Bujedo BM, Santos SG, Azpiazu AU. A review of epidural and intrathecal opioids used in the management of postoperative pain. Journal of opioid management. 2012;8(3):177-92.
- 7. Sultan P, Gutierrez MC, Carvalho B. Neuraxial Morphine and Respiratory Depression. Drugs. 2011;71(14):1807-19.

- 8. Dominguez JE, Habib AS. Prophylaxis and treatment of the side-effects of neuraxial morphine analgesia following cesarean delivery. Current Opinion in Anesthesiology. 2013;26(3):288-95.
- 9. Chinachoti T, Nilrat P, Samarnpiboonphol P. Nausea, vomiting and pruritus induced by intrathecal morphine. J Med Assoc Thai. 2013;96(5):589-94.
- 10. Kılıçkaya R, Orak Y, Balcı MA, Balcı F, Ünal İ. Comparison of the Effects of Intrathecal Fentanyl and Intrathecal Morphine on Pain in Elective Total Knee Replacement Surgery. Pain Res Manag. 2016;2016:3256583.
- 11. Gehling M, Luesebrink T, Kulka P, Tryba M. The effective duration of analgesia after intrathecal morphine in patients without additional opioid analgesia: a randomized double-blind multicentre study on orthopaedic patients. European Journal of Anaesthesiology | EJA. 2009;26(8):683-8.
- 12. 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):535-52.
- 13. Chandrakantan A, Glass PSA. Multimodal therapies for postoperative nausea and vomiting, and pain. BJA: British Journal of Anaesthesia. 2011;107(suppl\_1):i27-i40.
- 14. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesthesia and analgesia. 2020;131(2):411-48.
- 15. El-Deeb AM, Ahmady MS. Effect of acupuncture on nausea and/or vomiting during and after cesarean section in comparison with ondansetron. Journal of Anesthesia. 2011;25(5):698.

16. Cheong KB, Zhang J-p, Huang Y, Zhang Z-j. The Effectiveness of Acupuncture in Prevention and Treatment of Postoperative Nausea and Vomiting - A Systematic Review and Meta-Analysis. PLOS ONE. 2013;8(12):e82474.