

**COMPARISON OF INTRATHECAL MORPHINE AND EPIDURAL BUPIVACAINE
ANALGESIA FOR POST OPERATIVE ANALGESIA AFTER ELECTIVE ABDOMINAL
HYSTERECTOMY**

By

DR ANAFAIROS BINTI MD NAYAN

MD (USM)

MANUSCRIPT SUBMITTED IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF MASTERS OF MEDICINE

(ANAESTHESIOLOGY)



UNIVERSITI SAINS MALAYSIA

2016

ACKNOWLEDGEMENT

I would like to take this opportunity to thank everyone who was involved in making this manuscript possible.

First of all, I would like to express my gratitude to my supervisor, Dr Wan Nazaruddin bin Wan Hassan for his support, encouragement, advice and guide in completing this manuscript.

Special thanks to my co-supervisor, Dr Azmi bin Abu Hassan and Dr Rhendra Hardy bin Mohamad Zaini for their continuous support and courage.

Special thanks to all lecturers and colleagues from Department of Anesthesiology, Hospital University Sains Malaysia (HUSM) for their help and understanding. I also want to record my appreciation to Acute Pain Service nurses, operation theatre staffs and all nurses from wards that had help me during data collection and patient's review.

Finally, special thanks to my family for their unconditional love and patience.

Thank you.

TABLE OF CONTENTS

CONTENT	PAGE
Title	I
Acknowledgement	II
Table of contents	III
List of tables	IV
Abbreviations	V
Chapter 1: Introduction	1 – 7
Chapter 2: Study protocol	
• Document submitted for ethical approval	8 - 42
• Ethical approval letter	43 - 49
Chapter 3: Selected journal format	50 – 67
Chapter 4: Body (Manuscript)	
i Title	68
ii Abstract	68 – 69
iii Introduction	70 – 71
iv Methodology	72 – 73
v Results	74
vi Discussion	75 – 77
vii Conclusion	78
viii References	79 – 80
ix Correspondence	81
x Tables	82 – 85
Chapter 5: Appendix	86 – 88

LIST OF TABLES

<u>TABLE</u>		<u>PAGE</u>
Table 1	Demographic data	82
Table 2	The post-operative pain score over 24 hours	83
Table 3	The comparison of mean difference total morphine consumption, time to early mobilization, length of stay and time for first PCA morphine demand	84
Table 4	The side effects	85

ABBREVIATIONS

ITM	Intrathecal Morphine
EA	Epidural analgesia
HUSM	Hospital Universiti Sains Malaysia
VAS	Visual Analogue Scale
IV	Intravascular
PCA	Patient Controlled Analgesia
ASA	American Society of Anesthesiologists (Physical Status)
OT	Operation theatre
ECG	Electrocardiogram
ETT	Endotracheal tube
GA	General Anesthesia

CHAPTER 1: INTRODUCTION

Abdominal hysterectomy is the surgical removal of the uterus which may also involve removal of the cervix, ovaries, fallopian tubes and other surrounding structures. It is one of the most commonly performed gynaecological surgical procedures. The pain after this surgery is severe and the role of an effective post operative analgesia is very important for patient's comfort, haemodynamic stability, early ambulation and shorter hospital stay.

Epidural analgesia was one of the common techniques for post operative analgesia after this surgery and was previously thought to be gold standard analgesia. This technique is beneficial in reduction of cardiovascular and pulmonary complications. However, this procedure is more invasive which requires placement of catheter in epidural space. The placement of the epidural catheter may be time consuming, possibility of failure during insertion, may be contraindicated and pose several side effects. In patients who are potential to develop coagulopathy or require anti coagulant therapy, proper timing of epidural catheter removal can be affected and there is a potential risk of epidural haematoma.

Nowadays, with the present of other options and less invasive techniques, the options of analgesia for abdominal hysterectomy are wider. Intrathecal morphine (ITM) is one of the other potential alternatives to epidural. It has the advantages of being a single injection, easy to perform, less time consuming, safer technique and cost effective compared to epidural. This technique has been proven in previous studies as a good option to epidural analgesia in liver surgery and caesarean section but there is limited data for gynaecological surgery.

The aims of the study are to compare the analgesic efficacy between ITM and epidural bupivacaine for post operative analgesia undergoing elective abdominal hysterectomy.

LITERATURE REVIEW

Intrathecal morphine (ITM) for gynaecological surgery

Hein, A. et al. (2012) conducted a randomized placebo-controlled study on low dose ITM effects on post-hysterectomy pain. They compared the effects of morphine 0, 100, 200, or 300 mug added to intrathecal bupivacaine on first post-operative 24 h patient-controlled analgesia morphine (PCA-morphine) consumption after abdominal hysterectomy under general anaesthesia in 144 patients. Results showed that ITM reduced accumulated 24 h post-operative morphine consumption. Morphine 100 mug significantly reduced morphine consumption vs. placebo at 0-6 h, 6-12 h, and for the entire 0-24 h time interval post-operation. Morphine 200 mug further significantly reduced morphine consumption vs. morphine 100 mug at 0-6 h and for the entire 0-24 h post-operation. There was no further reduction of morphine consumption seen with morphine 300 mug. No serious side effects were seen. Emesis was similar in all groups, and pruritus was experienced only in the morphine groups. The study concluded that ITM supplementation to bupivacaine reduces first 24 h PCA-morphine consumption after abdominal hysterectomy under general anaesthesia, and they found no benefit from increasing the dose over 200 mug (1).

Rebel, A. et al. (2011) retrospectively studied on high-dose intrathecal morphine for analgesia after pelvic surgery. The effectiveness of intrathecal opioids (ITOs) for postoperative analgesia has been limited by reduced opioid dosing because of opioid-related side effects, most importantly respiratory depression. To overcome these limitations, this study compared combination of high-dose intrathecal morphine with a continuous intravenous (IV) postoperative naloxone infusion with IV opioid analgesia alone. They concluded that high-dose IT opioids in combination with a postoperative IV naloxone

infusion provided excellent analgesia for major pelvic surgery. The IV naloxone infusion combined with high-dose ITOs appeared to control opioid side effects without affecting analgesia (2).

Massicotte, L. et al. (2009) conducted a study to compare morphine consumption with patient-controlled analgesia (PCA) between spinal anesthesia (SA) (bupivacaine, morphine and fentanyl) and general anesthesia (GA) (sufentanil) after an abdominal hysterectomy. 40 women were randomly assigned to receive SA with bupivacaine 15 mg, 0.15 mg of intrathecal morphine and 15 microg of fentanyl or GA with sufentanil, both combined with PCA. It was concluded that intrathecal morphine 0.15 mg with 15 microg of fentanyl decreases post-operative pain and morphine consumption by PCA without increasing adverse reactions for women undergoing an abdominal hysterectomy. Post operative care unit (PACU) and hospital stay were also significantly reduced in SA group (3).

Niruthisard, S et al (2007) studied the effect of IV parecoxib in addition to intrathecal morphine and bupivacaine. The results showed that the addition of parecoxib to intrathecal morphine and bupivacaine significantly reduced cumulative morphine consumption, Visual Analog Pain scores, and increased patient satisfaction for 24 h postoperatively without an obvious decrease of adverse side effects (4).

Karaman, S. et al. (2006) studied on the effects of preoperative intrathecal morphine on perioperative hemodynamics, stress response, and postoperative analgesia was evaluated in patients undergoing abdominal hysterectomy with general anesthesia. A total of 24 patients

were randomly assigned to the morphine group (n=12) or the control group (n=12). Patients in the morphine group were given intrathecal 5 microg/kg(-1) morphine before surgery. In all patients, general anesthesia was induced and all patients received intravenous morphine patient-controlled analgesia after surgery. Intra operative hemodynamic was similar in both groups, but postoperative HR and MAP values at 4 h, 8 h, 12 h, and 20 h were significantly lower in the morphine group ($P < .05$). Postoperative VAS scores, total morphine consumption, and plasma epinephrine, norepinephrine, and glucose levels were significantly lower in the morphine group than in the control group ($P < .05$). This study concluded that preoperative intrathecal morphine enhanced the quality of postoperative analgesia, decreased morphine consumption, and depressed the systemic stress response in patients undergoing total abdominal hysterectomy with general anesthesia (5).

Intrathecal morphine (ITM) versus epidural analgesia (EA)

Kasivisvanathan, R. et al. (2014) conducted a prospective observational study to compare peri/post-operative outcomes of thoracic epidural analgesia (TEA) versus intrathecal morphine and fentanyl patient-controlled analgesia (ITM+fPCA) for 73 patients undergoing a hepatic resection (36 TEA and 37 ITM+fPCA). The median (IQR) post-operative LoS was 13 (11-15) and 11 (9-13) days in the TEA and ITM+fPCA groups, respectively ($P = 0.011$). There was significantly lower median intra-operative central venous pressure ($P < 0.001$) and blood loss ($P = 0.017$) in the TEA group, and a significant reduction in the time until mobilization ($P < 0.001$), post-operative intra-venous fluid/vasopressor requirement ($P < 0.001/P = 0.004$) in the ITM+fPCA group. Pain scores were lower at a clinically significant level 12 h post-operatively in the TEA group ($P < 0.001$); otherwise there were no differences

out to day five. There were no differences in quality of recovery or postoperative morbidity/mortality between the two groups (6).

Mercadante, S. et al. (2008) conducted a randomized-controlled study of intrathecal versus epidural thoracic analgesia in patients undergoing abdominal cancer surgery. They concluded that ITA and ETA produced the same levels of analgesia, without relevant complications (7).

De Pietri, L. et al (2006) studied the use of intrathecal morphine for postoperative pain relief after liver resection in comparison with epidural analgesia. In this study, they tested a single-shot intrathecal morphine technique and compared it to a continuous epidural morphine infusion for postoperative analgesia in liver surgery. Fifty patients were randomly assigned to an epidural analgesia group (EP group; n = 25) and an intrathecal analgesia group (IN group; n = 25). The quality of analgesia assessed by a visual analogue scale (VAS), the side effects, and the additional IV analgesic requirements were recorded. They did not observe any signs of cord compression. Time to first pain drug requirement was longer in the EP group compared to the IN group (25 +/- 18.5 h versus 12 +/- 10.3 h; $P < 0.05$). In both groups, the VAS remained less than 30 mm throughout the 48-h follow-up period. Consumption of IV morphine with a patient-controlled analgesia device in the IN group was larger (mostly from 24 to 48 h after surgery) than the EP group (12.0 +/- 5.54 mg versus 3.1 +/- 2.6 mg, respectively; $P < 0.01$). The incidence of vomiting was 4% in both groups, whereas the incidence of pruritus (16% versus 0%) and nausea (16% versus 4%) was more frequent in the IN group. No postdural puncture headache and no spinal hematoma occurred. They concluded that a single dose of intrathecal morphine followed by patient-controlled morphine analgesia can provide satisfactory postoperative pain relief after liver resection. The quality

of this treatment, according to the VAS, is not inferior to continuous epidural analgesia up to 48 h after surgery (8).

Duale, C. et al. (2003) studied on epidural versus intrathecal morphine for postoperative analgesia after Caesarean section. Combined spinal-epidural anaesthesia with 6 mg of IT hyperbaric bupivacaine plus sufentanil 5 microg, and additional ED lidocaine was used. Additionally, each patient received either 2 mg (2 ml) of ED morphine plus 1 ml of IT normal saline (ED group, n=28), or 0.075 mg (1 ml) of IT Morphine plus 2 ml of ED normal saline (IT group, n=25). Additional postoperative analgesia was given in the form of propacetamol and ketoprofen, plus self-administered IV morphine. Results showed that; no major respiratory depression occurred. Time to first demand of morphine was similar in the ED (307.5 min) and IT (310 min) groups, as was the incidence of side-effects such as sedation, pruritus, nausea, and vomiting. During the first 24 postoperative hours, VAS pain scores were greater in the IT group ($P=0.032$), as was additional morphine consumption (4 vs 1.5 mg) ($P=0.03$). The study concluded that the ED protocol was more effective than the IT protocol, whilst side-effects were similar (9).

Abouleish, E et al (1991) conducted a study to compare the efficacy and side effects of 0.2 mg intrathecal (IT) morphine with 0.125% epidural bupivacaine in 62 women in labor. They were randomly divided into three groups: group 1 (n = 20) received IT morphine; group 2 (n = 22) received epidural bupivacaine; and group 3 (n = 20) received a combination of both using a combined spinal-epidural (CSE) technique. According to a visual analogue scale for assessing analgesia, neither IT 0.2 mg morphine nor 10 ml 0.125% epidural bupivacaine was effective in producing adequate pain relief in labor, whereas the combination produced excellent analgesia. The use of IT morphine significantly reduced the dosage requirement of

epidural bupivacaine. The incidence of nausea, vomiting, and pruritus was significantly higher when IT morphine had been administered, whereas that of urinary retention did not differ. No serious respiratory depression occurred in any of the patients. When the course of labor was studied, the prior use of IT morphine significantly prolonged the duration of the first stage of labor and the total duration of labor. They conclude that the administration of 0.2 mg IT morphine in combination with epidural administration of 0.125% bupivacaine provides better analgesia than the administration of either drug alone (10).

CHAPTER 2: STUDY PROTOCOL

DISSERTATION PROPOSAL (SUBMITTED FOR ETHICAL APPROVAL)

TITLE

COMPARISON OF INTRATHECAL MORPHINE AND EPIDURAL BUPIVACAINE AN
ALGESIA FOR POST OPERATIVE ANALGESIA AFTER ELECTIVE ABDOMINAL HY
STERECTOMY

NAME OF STUDENT:

DR ANAFAIROS BINTI MD NAYAN

MMed (Anaesthesiology) Year 2

NAME OF SUPERVISOR:

DR WAN MOHD NAZARUDDIN BIN WAN HASSAN

Senior Lecturer, Department of Anaesthesiology & Intensive Care

NAME OF CO-SUPERVISORS:

1. DR AZMI BIN ABU HASSAN

(Consultant Anaesthesiologist, Hospital Sultanah Bahiyah, Alor Star,
Kedah)

2. DR RHENDRA HARDY BIN MOHAMAD ZAINI

(Senior Lecturer, Department of Anaesthesiology & Intensive Care)

INTRODUCTION

Abdominal hysterectomy is the surgical removal of the uterus which may also involve removal of the cervix, ovaries, fallopian tubes and other surrounding structures. It is one of the most commonly performed gynaecological surgical procedures. The pain after this surgery is severe and the role of an effective post operative analgesia is very important for patient's comfort, haemodynamic stability, early ambulation and shorter hospital stay.

Epidural analgesia was one of the common techniques for post operative analgesia after this surgery and was previously thought to be gold standard analgesia. This technique is beneficial in reduction of cardiovascular and pulmonary complications. However, this procedure is more invasive which requires placement of catheter in epidural space. The placement of the epidural catheter may be time consuming, carries failure possibility, may be contraindicated and pose several side effects. In patients who are potential to develop coagulopathy or require anti coagulant therapy, proper timing of epidural catheter removal can be affected and there is a potential risk of epidural haematoma.

Nowadays, with the present of other options and less invasive techniques, the options of analgesia for abdominal hysterectomy are wider. Intrathecal morphine (ITM) is one of the other potential alternatives to epidural. It has the advantages of being a single injection, easy to perform, less time consuming, safer technique and cost effective compared to epidural. This technique has been proven in previous studies as a good option to epidural analgesia in liver surgery and caesarean section but there is limited data for gynaecological surgery.

The aims of the study are to compare the analgesic efficacy between ITM and epidural bupivacaine (EB) for post operative analgesia undergoing elective abdominal hysterectomy.

LITERATURE REVIEW

Intrathecal morphine (ITM) for gynaecological surgery

Hein, A. et al. (2012) conducted a randomized placebo-controlled study on low dose ITM effects on post-hysterectomy pain. They compared the effects of morphine 0, 100, 200, or 300 mug added to intrathecal bupivacaine on first post-operative 24 h patient-controlled analgesia morphine (PCA-morphine) consumption after abdominal hysterectomy under general anaesthesia in 144 patients. Results showed that ITM reduced accumulated 24 h post-operative morphine consumption. Morphine 100 mug significantly reduced morphine consumption vs. placebo at 0-6 h, 6-12 h, and for the entire 0-24 h time interval post-operation. Morphine 200 mug further significantly reduced morphine consumption vs. morphine 100 mug at 0-6 h and for the entire 0-24 h post-operation. There was no further reduction of morphine consumption seen with morphine 300 mug. No serious side effects were seen. Emesis was similar in all groups, and pruritus was experienced only in the morphine groups. The study concluded that ITM supplementation to bupivacaine reduces first 24 h PCA-morphine consumption after abdominal hysterectomy under general anaesthesia, and they found no benefit from increasing the dose over 200 mug (1).

Rebel, A. et al. (2011) retrospectively studied on high-dose intrathecal morphine for analgesia after pelvic surgery. The effectiveness of intrathecal opioids (ITOs) for postoperative analgesia has been limited by reduced opioid dosing because of opioid-related side effects, most importantly respiratory depression. To overcome these limitations, this study compared combination of high-dose intrathecal morphine with a continuous intravenous (IV) postoperative naloxone infusion with IV opioid analgesia alone. They

concluded that high-dose IT opioids combined with a postoperative IV naloxone infusion provided excellent analgesia for major pelvic surgery. The IV naloxone infusion combined with high-dose ITOs appeared to control opioid side effects without affecting analgesia (2).

Massicotte, L. et al. (2009) conducted a study to compare morphine consumption with patient-controlled analgesia (PCA) between spinal anesthesia (SA) (bupivacaine, morphine and fentanyl) and general anesthesia (GA) (sufentanil) after an abdominal hysterectomy. 40 women were randomly assigned to receive SA with bupivacaine 15 mg, 0.15 mg of intrathecal morphine and 15 microg of fentanyl or GA with sufentanil, both combined with PCA. It was concluded that intrathecal morphine 0.15 mg with 15 microg of fentanyl decreases post-operative pain and morphine consumption by PCA without increasing adverse reactions for women undergoing an abdominal hysterectomy. Post operative care unit (PACU) and hospital stay were also significantly reduced in SA group (3).

Niruthisard, S et al (2007) studied the effect of IV parecoxib in addition to intrathecal morphine and bupivacaine. The results showed that the addition of parecoxib to intrathecal morphine and bupivacaine significantly reduced cumulative morphine consumption, Visual Analog Pain scores, and increased patient satisfaction for 24 h postoperatively without an obvious decrease of adverse side effects (4).

Karaman, S. et al. (2006) studied on the effects of preoperative intrathecal morphine on perioperative hemodynamics, stress response, and postoperative analgesia was evaluated in patients undergoing abdominal hysterectomy with general anesthesia. A total of 24 patients

were randomly assigned to the morphine group (n=12) or the control group (n=12). Patients in the morphine group were given intrathecal 5 microg/kg (-1) morphine before surgery. In all patients, general anesthesia was induced and all patients received intravenous morphine patient-controlled analgesia after surgery. Intraoperative hemodynamics was similar in both groups, but postoperative HR and MAP values at 4 h, 8 h, 12 h, and 20 h were significantly lower in the morphine group ($P < .05$). Postoperative VAS scores, total morphine consumption, and plasma epinephrine, norepinephrine, and glucose levels were significantly lower in the morphine group than in the control group ($P < .05$). This study concluded that preoperative intrathecal morphine enhanced the quality of postoperative analgesia, decreased morphine consumption, and depressed the systemic stress response in patients undergoing total abdominal hysterectomy with general anesthesia (5).

Intrathecal morphine (ITM) versus epidural analgesia (EA)

Kasivisvanathan, R. et al. (2014) conducted a prospective observational study to compare peri/post-operative outcomes of thoracic epidural analgesia (TEA) versus intrathecal morphine and fentanyl patient-controlled analgesia (ITM+fPCA) for 73 patients undergoing a hepatic resection (36 TEA and 37 ITM+fPCA). The median (IQR) post-operative LoS was 13 (11-15) and 11 (9-13) days in the TEA and ITM+fPCA groups, respectively ($P = 0.011$). There was significantly lower median intra-operative central venous pressure ($P < 0.001$) and blood loss ($P = 0.017$) in the TEA group, and a significant reduction in the time until mobilization ($P < 0.001$), post-operative intra-venous fluid/vasopressor requirement ($P < 0.001/P = 0.004$) in the ITM+fPCA group. Pain scores were lower at a clinically significant level 12 h post-operatively in the TEA group ($P < 0.001$); otherwise there were no differences

out to day five. There were no differences in quality of recovery or postoperative morbidity/mortality between the two groups (6).

Mercadante, S. et al. (2008) conducted a randomized-controlled study of intrathecal versus epidural thoracic analgesia in patients undergoing abdominal cancer surgery. They concluded that ITA and ETA produced the same levels of analgesia, without relevant complications (7).

De Pietri, L. et al (2006) studied the use of intrathecal morphine for postoperative pain relief after liver resection in comparison with epidural analgesia. In this study, they tested a single-shot intrathecal morphine technique and compared it to a continuous epidural morphine infusion for postoperative analgesia in liver surgery. Fifty patients were randomly assigned to an epidural analgesia group (EP group; n = 25) and an intrathecal analgesia group (IN group; n = 25). The quality of analgesia assessed by a visual analogue scale (VAS), the side effects, and the additional IV analgesic requirements were recorded. They did not observe any signs of cord compression. Time to first pain drug requirement was longer in the EP group compared to the IN group (25 +/- 18.5 h versus 12 +/- 10.3 h; $P < 0.05$). In both groups, the VAS remained less than 30 mm throughout the 48-h follow-up period. Consumption of IV morphine with a patient-controlled analgesia device in the IN group was larger (mostly from 24 to 48 h after surgery) than the EP group (12.0 +/- 5.54 mg versus 3.1 +/- 2.6 mg, respectively; $P < 0.01$). The incidence of vomiting was 4% in both groups, whereas the incidence of pruritus (16% versus 0%) and nausea (16% versus 4%) was more frequent in the IN group. No postdural puncture headache and no spinal hematoma occurred. They concluded that a single dose of intrathecal morphine followed by patient-controlled morphine analgesia can provide satisfactory postoperative pain relief after liver resection. The quality

of this treatment, according to the VAS, is not inferior to continuous epidural analgesia up to 48 h after surgery (8).

Duale, C. et al. (2003) studied on epidural versus intrathecal morphine for postoperative analgesia after Caesarean section. Combined spinal-epidural anaesthesia with 6 mg of IT hyperbaric bupivacaine plus sufentanil 5 microg, and additional ED lidocaine was used. Additionally, each patient received either 2 mg (2 ml) of ED morphine plus 1 ml of IT normal saline (ED group, n=28), or 0.075 mg (1 ml) of IT morphine plus 2 ml of ED normal saline (IT group, n=25). Additional postoperative analgesia was given in the form of propacetamol and ketoprofen, plus self-administered IV morphine. Results showed that; no major respiratory depression occurred. Time to first demand of morphine was similar in the ED (307.5 min) and IT. (310 min) groups, as was the incidence of side-effects such as sedation, pruritus, nausea, and vomiting. During the first 24 postoperative hours, VAS pain scores were greater in the IT group ($P=0.032$), as was additional morphine consumption (4 vs 1.5 mg) ($P=0.03$). The study concluded that the ED protocol was more effective than the IT protocol, whilst side-effects were similar (9).

Abouleish, E et al (1991) conducted a study to compare the efficacy and side effects of 0.2 mg intrathecal (IT) morphine with 0.125% epidural bupivacaine in 62 women in labor. They were randomly divided into three groups: group 1 (n = 20) received IT morphine; group 2 (n = 22) received epidural bupivacaine; and group 3 (n = 20) received a combination of both using a combined spinal-epidural (CSE) technique. According to a visual analogue scale for assessing analgesia, neither IT 0.2 mg morphine nor 10 ml 0.125% epidural bupivacaine was effective in producing adequate pain relief in labor, whereas the combination produced excellent analgesia. The use of IT morphine significantly reduced the dosage requirement of

epidural bupivacaine. The incidence of nausea, vomiting, and pruritus was significantly higher when IT morphine had been administered, whereas that of urinary retention did not differ. No serious respiratory depression occurred in any of the patients. When the course of labor was studied, the prior use of IT morphine significantly prolonged the duration of the first stage of labor and the total duration of labor. They conclude that the administration of 0.2 mg IT morphine in combination with epidural administration of 0.125% bupivacaine provides better analgesia than the administration of either drug alone (10).

GENERAL OBJECTIVES

To compare the analgesic efficacy between ITM and EB (epidural bupivacaine) for post operative analgesia undergoing elective abdominal hysterectomy

SPECIFIC OBJECTIVES

1. To assess intensity of post operative pain using visual analogue scale (VAS) at 1 hour, 4 hour, 8 hour, 12 hour, 16 hour and 24 hour post surgery.
2. To compare the time for first patient-controlled analgesia (PCA) demand between the two groups
3. To compare total morphine consumption
4. To compare length of hospital stay and time to early mobilization

HYPOTHESIS

1. Intensity of visual analogue scale (VAS) is less in ITM
2. Time for first patient-controlled analgesia (PCA) demand is earlier in ITM
3. Total morphine consumption is more in EB

4. Length of hospital stay and time to early mobilization is less in ITM

RESEARCH METHODOLOGY

- Study design: Prospective, randomized, observer-blinded, controlled clinical trial
- Study period: August 2014 – August 2016
- Study population: Elective surgical patients who are planned for general anaesthesia with endotracheal intubation in Hospital Sultanah Bahiyah Alor Setar and Hospital Universiti Sains Malaysia (HUSM)
- Study setting: General Operation theater Hospital Sultanah Bahiyah, Alor Setar, Kedah and General Operation Theater (OT) HUSM
- Inclusion criteria:
 - ASA I – II undergoing elective abdominal hysterectomy under general anaesthesia
 - Age 18 -60 years old
- Exclusion criteria:
 - Patient with chronic pain treated with opioids
 - Patient with Coagulopathy
 - Patient who is contraindicated to spinal/epidural technique (bleeding disorder, neurologic dysfunction, systemic/local infection)
 - Known allergic to study drugs
- Withdrawal criteria :
 - patient decided to withdraw from study
 - If adverse event occurs

- Death not related to study conducted which occurs during study period

SAMPLE SIZE CALCULATION

The sample size calculation is based on study by De Pietri, L. et al. (2006) which resulted a significant difference in consumption of iv morphine with a patient-controlled analgesia device in the intrathecal analgesia group was larger (mostly from 24 to 48 hour after surgery) than the Epidural analgesia group (12.0 +/- 5.54 mg versus 3.1 +/- 2.6 mg, respectively; $P < 0.01$)(8). We used Power and sample size software version 3.0.10 for the calculation and the outcome was as below:

- We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. In a previous study the response within each subject group was normally distributed with standard deviation 5.5. If the true difference in the experimental and control means is 8.9, we will need to study 13 experimental subjects and 13 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.01.

If we consider 20% drop out, the additional samples will be 5.2 (~ 6). Therefore the total samples will be 32, which is 16 patients per group

METHODOLOGY

- Approval from Ethics Committee of Universiti Sains Malaysia (USM) will be taken before enrollment of the patients
- Eligibility of the patients will be screening during preoperative assessment round which is normally done at least a day prior to scheduled surgery
- Written consent will be obtained from all selected patients who fulfill the inclusion and the exclusion criteria
- All patients will be premedicated with midazolam 7.5mg orally on the operation day (given in 1 hour before induction of anesthesia).
- Consented Patients will be randomized into 2 arm group I (ITM) and group E (EB) using block randomization as below :
 - 6 ballot cards will be put inside the envelope. Each of the cards state 6 different sequences of grouping (AABB, BBAA, ABAB, BABA, ABBA, and BAAB).
 - 1 card will be randomly taken each time by any nurse who assists general anaesthesia to decide the group for the first four patients. This will be followed by other cards until all 6 sequences are completed. This means that at the end of 6 randomized sequences, there will be an equal 12 patients in each groups with the total number of 24 samples.
 - The randomization will be continued again as above until the total samples of collection are completed
- All patients will be given fluid preload 10 ml/kg normal saline or Hartman's before going to OT in preoperative waiting area.

- In OT, standard monitoring will be placed (ECG, oxygen saturation, non invasive blood pressure, capnography).
- Group I will receive:
 - Patient will receive single injection of intrathecal morphine 0.2mg with 0.5% bupivacaine 2.5mls.
 - Spinal anaesthesia will be conducted under aseptic technique in sitting position.
 - Site will be identified at the level L3/L4 or L4/L5 based on anatomical landmark.
 - Local anesthetic (lidocaine hydrochloride) 2mls will be injected for skin infiltration.
 - Using spinal needle either spinocan 25G or pengan 27G, 0.2mg morphine with 2.5ml 0.5% bupivacaine will be given intrathecally after CSF backflow is obtained.
- Group E will receive:
 - Patient will receive epidural analgesia.
 - Epidural catheter will be inserted at the level of L3/L4 or L4/L5 using loss of resistance technique with Touhy needle 18G after infiltration of local anaesthesia.
 - Distance from skin to epidural space is marked and epidural catheter will be inserted into epidural space with bevel of the needle directed cephalad.
 - Then a test dose of 3mls lidocaine 2% + adrenaline 1:200,000 will be injected via the catheter to confirm placement and to exclude inadvertent intravascular or intrathecal placement.
 - About 10-12 mls of 0.25% bupivacaine will be given in titration before induction.

- Both groups will be assessed the level of analgesia, at least up to T6 dermatomes before starting general anaesthesia
- The anaesthetic management of all patients will be standardized. For all patients, they will induce with IV propofol 2 mg/kg, IV fentanyl 2-3mcg/kg, IV rocuronium 0.9mg/kg. Proper ETT size will be use for tracheal intubation. Anaesthesia will be maintained with sevoflurane in a 50% oxygen; air mixture with minimal flow ventilation.
- Intraoperative analgesia, the epidural group will be provided continuous epidural infusion 0.1% bupivacaine + fentanyl 2 µg/ ml, run at 6-12 ml/hr.
- a decrease in blood pressure by more than 30% less than preoperative value in both group will be corrected with fluids , IV ephedrine or both.
- Post operatively, patient will be observed in the recovery area. In epidural group, epidural analgesia continues with infusion 0.1% bupivacaine + fentanyl 2 µg/ ml at 6-12ml/hr.
- Both groups will be prepared, IV PCA morphine pump with lockout time 5 minutes, dilution 1mg/ml. No background infusion will be provided.
- In the ward, pain assessment will be done during 1st hour post operative and then 4 hourly up to 24hrs. VAS with 0 (no pain) to 10 (worst pain) will be used.
- First PCA demand and total consumption of rescue PCA morphine will be recorded.
- Post operative nausea/vomiting will be recorded and IV metoclopramide 10mg every 8 hours and chlorpeneramine will be given for pruritus. Other side effects will be noted.
- Patient's outcome and patient satisfaction regarding pain management will be evaluated.

ASSESSMENT

- Pain score using VAS (visual analog scale) in both group
- The total morphine consumption post operative
- Haemodynamic parameters: post administration of drugs (intrathecal morphine / epidural). Blood pressure and heart rate will be monitored every 5 minutes intraoperatively.
- Side effect of the drugs will be recorded including nausea, vomiting, pruritus, respiratory depression and patient sedation.
- Patient's satisfaction and outcome will be noted

ADVERSE EVENT

Adverse effects reported from drug product information are listed below:

MORPHINE

- Nausea
- Vomiting
- Constipation
- Drowsiness
- Respiratory depression
- Hypotension
- Pruritus, urticaria
- Difficulty in micturition, sweating, vertigo
- Facial flushing , palpitation, dependence, miosis

PIVIKAN (plain bupivacaine)

- High / total spinal blockade
- Acute systemic toxicity
- Allergy
- Neurological reaction

Should any adverse reaction occurred, the symptoms will be managed accordingly and patient will be followed up until symptoms resolved

SERIOUS ADVERSE EVENT

A serious adverse event is considered when any adverse events that result in any of the following outcomes:

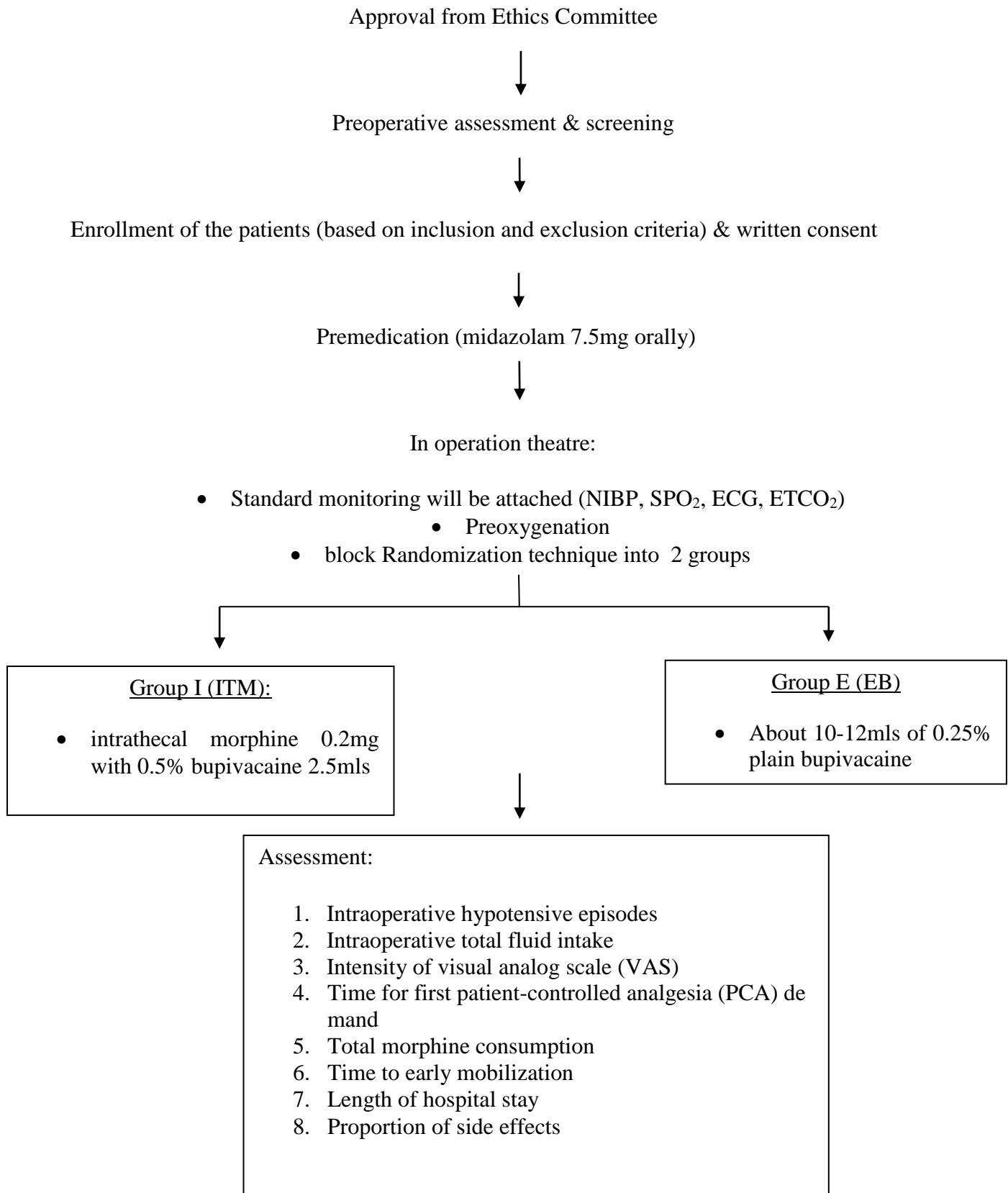
- Death
- A life threatening adverse event
- In patient hospitalization or prolonging existing hospitalization
- A persistent or significant disability/incapacity

Should any of those incident happen, relevant action will be taken and investigator will send report to relevant body base on guideline provide by CRC

STATISTICAL ANALYSIS

All analysis will be using SPSS software version 19. Data were tested for normal distribution. Demographic and clinical data were compared by means of Independent samples Student's t-test, or chi-square test if appropriate. Differences were considered as significant with $P < 0.05$.

FLOW CHART



REFERENCES

1. 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 anaesthesiologica Scandinavica*. 2012;56(1):102-9.
2. Rebel A, Sloan P, Andrykowski M. Retrospective analysis of high-dose intrathecal morphine for analgesia after pelvic surgery. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur*. 2011;16(1):19-26.
3. Massicotte L, Chalaoui KD, Beaulieu D, Roy JD, Bissonnette F. Comparison of spinal anesthesia with general anesthesia on morphine requirement after abdominal hysterectomy. *Acta anaesthesiologica Scandinavica*. 2009;53(5):641-7.
4. Niruthisard S, Werawataganon T, Bunburaphong P, Ussawanophakiat M, Wongsakornchaikul C, Toleb K. Improving the analgesic efficacy of intrathecal morphine with parecoxib after total abdominal hysterectomy. *Anesthesia and analgesia*. 2007;105(3):822-4.
5. Karaman S, Kocabas S, Uyar M, Zincircioglu C, Firat V. Intrathecal morphine: effects on perioperative hemodynamics, postoperative analgesia, and stress response for total abdominal hysterectomy. *Advances in therapy*. 2006;23(2):295-306.
6. Kasivisvanathan R, Abbassi-Ghadi N, Prout J, Clevenger B, Fusai GK, Mallett SV. A prospective cohort study of intrathecal versus epidural analgesia for patients undergoing hepatic resection. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2014.
7. Mercadante S, Villari P, Casuccio A, Marrazzo A. A randomized-controlled study of intrathecal versus epidural thoracic analgesia in patients undergoing abdominal cancer surgery. *Journal of clinical monitoring and computing*. 2008;22(4):293-8.
8. De Pietri L, Siniscalchi A, Reggiani A, Masetti M, Begliomini B, Gazzì M, et al. The