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

By

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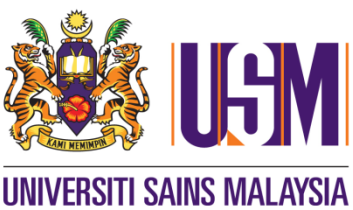
(ANAESTHESIOLOGY)



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

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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.

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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 t he 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 c omfort, haemodynamic stability, early ambulation and shorter hospital stay.

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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 t o 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.

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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).

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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).

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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

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INTRODUCTION

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GENERAL OBJECTIVES

To compare the analgesic efficacy between ITM and EB (epidural bupivacaine) for post oper ative 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 anaest hesia
    - 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 sam ples 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 pencan 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 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 patien t 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 follo wing 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 r eport 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

Approval from Ethics Committee

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Preoperative assessment & screening

↓

Enrollment of the patients (based on inclusion and exclusion criteria) & written consent

↓

Premedication (midazolam 7.5mg orally)

↓

In operation theatre:

- Standard monitoring will be attached (NIBP, SPO_2, ECG, $ETCO_2$)
- Preoxygenation
- block Randomization technique into 2 groups

<u>Group I (ITM):</u>

- intrathecal morphine 0.2mg with 0.5% bupivacaine 2.5mls

<u>Group E (EB)</u>

- About 10-12mls of 0.25% plain bupivacaine

↓

Assessment:

1. Intraoperative hypotensive episodes
2. Intraoperative total fluid intake
3. Intensity of visual analog scale (VAS)
4. Time for first patient-controlled analgesia (PCA) de mand
5. Total morphine consumption
6. Time to early mobilization
7. Length of hospital stay
8. Proportion of side effects

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