COMPARING THE EFFECT OF ADDING INTRATHECAL MORPHINE VERSUS DEXMEDETOMIDINE AS ADJUVANT TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER LIMB ORTHOPAEDIC SURGERY

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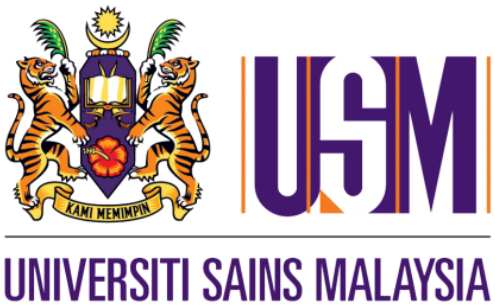
DISSERTATION SUBMITTED IN PARTIAL FULLFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (ANAESTHESIOLOGY)



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ABBREVIATIONS

ANOVA	Analysis of variance
ASA	American society of anaesthesiologists
BP	Blood pressure
dex	Dexmedetomidine
etCO2	End tidal carbon dioxide
HUSM	Hospital University Sains Malaysia
HR	Heart rate
IT	Intrathecal
IV	Intravenous
MAP	Mean arterial pressure
NIBP	Non-invasive blood pressure
OT	Operation theatre
PPV	Positive pressure ventilation
SD	Standard deviation
SAB	Subarachnoid block
SPSS	Statistical analysis software package
SPO2	Saturation of oxygen
PCA	Patient Controlled Analgesia

ABSTRAK

Perbandingan Kesan Penambahan Morfin Intratekal Berbanding Dexmedetomidine sebagai Pembantu kepada Bupivacaine dalam Pembiusan Spinal untuk Pembedahan Ortopedik di Anggota Kaki

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Abstrak

Pengenalan: Kami membandingkan kesan penambahan morfin intratekal berbanding dexmedetomidine sebagai pembantu kepada bupivacaine dalam pembedahan ortopedik di anggota kaki. Permulaan dan tempoh anestesia tulang belakang dinilai menggunakan pemeriksaan klinikal.

Metodologi: Tiga puluh enam pesakit, berumur 18-60 tahun, diklasifikasikan di bawah ASA 1-2, menjalani pembedahan ortopedik anggota kaki di bawah anestesia tulang belakang, telah di buat secara rawak kepada dua kumpulan: kumpulan morfin (n = 18) dan kumpulan dexmedetomidine (n-18). Anestesia tulang belakang diberikan untuk kumpulan masing-masing; 2.5 ml bupivacaine hiperbaric 0.5% dan 5 μg dexmedetomidine dalam 0.5 ml saline normal atau 2.5 ml 0.5% bupivacaine hyperbaric dengan 0.2 mg morfin dalam 0.5 ml saline normal. Pengukuran blok deria mengikut tahap dermatom dan skala Bromage untuk penilaian motor dan skor sakit pasca pembedahan direkodkan untuk analisis statistik. Data telah diuji oleh ujian -t dan analisis ANOVA berulang.

Keputusan: Tiada perbezaan masa yang signifikan untuk mencapai T10 antara morfin dan dexmedetomidine (p> 0.05). Terdapat perbezaan masa yang signifikan untuk mencapai Bromage 3 antara morfin dan dexmedetomidine (p <0.05). Purata (SD) masa untuk mencapai Bromage 3 untuk morfin ialah 4.56 (0.78) minit dan untuk dexmedetomidine adalah 3.83 (0.79) minit menunjukkan bahawa masa purata mencapai Bromage 3 adalah lebih rendah dalam kumpulan dexmedetomidine. Terdapat perbezaan masa yang signifikan untuk mencapai Bromage 0 antara kumpulan morfin dan dexmedetomidine (p <0.05). Purata (SD) masa untuk mencapai Bromage 0 untuk morfin ialah 134.44 (20.64) minit dan untuk dexmedetomidine adalah 276.67 (54.02) minit menunjukkan bahawa masa purata mencapai Bromage 0 lebih tinggi dalam dexmedetomidine. Untuk hasil interaksi rawatan masa dalam analisis ANOVA berulang, kami mendapati bahawa terdapat perbezaan purata yang signifikan dari skor rasa sakit antara kumpulan berdasarkan masa (F = 2.54, p = 0.031). Skor kesakitan lebih tinggi bagi mereka yang mengambil dexmedetomidine berbanding dengan morfin.

Kesimpulan: Dexmedetomidine intratekal secara ketara menyebabkan berpanjangan dalam deria dan blok motor berbanding dengan morfin intratekal. Walau bagaimanapun, untuk kawalan kesakitan selepas pembedahan morfin intratekal adalah lebih bagus

Kata kunci: anestesia tulang belakang, morfin intratekal, dexmedetomidine intratekal, ortopedik anggota kaki.

ABSTRACT

Comparing the Effect of Adding Intrathecal Morphine Versus Dexmedetomidine as Adjuvant to Bupivacaine in Lower Limb for Orthopaedic Surgery

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Abstract

Background: We studied the effect of adding intrathecal morphine versus dexmedetomidine as adjuvant to bupivacaine in lower limb orthopaedic surgery. The onset and the duration of spinal anaesthesia were assessed using clinical examination.

Methods: Thirty-six patients, aged 18-60 year old, classified under ASA 1-2, who underwent elective lower limbs orthopaedic surgery under spinal anaesthesia, were randomised into two groups: group morphine (n=18) and group dexmedetomidine (n=18). Spinal anaesthesia was performed and in group morphine 2.5 ml of 0.5% hyperbaric bupivacaine and 0.2 mg morphine in 0.5 ml of normal saline were administered intrathecally. In group dexmedetomidine, 2.5 ml of 0.5% hyperbaric bupivacaine and 5 µg dexmedetomidine in 0.5 ml normal saline. Measurement of sensory block according to dermatome level, Bromage scale for motor assessment and post operative pain score were recorded for statistical analysis. Data were tested by independent t-test and repeated measure ANOVA analysis.

Results: There was no significant difference with regard to the duration to reach T10 between morphine and dexmedetomidine ($p>0.05$). There was a significant difference with regard to time (mean) to reach Bromage 3 between morphine and dexmedetomidine ($p<0.05$). The time [mean (SD)] to reach Bromage 3 for morphine was 4.56 (0.78) minutes and for dexmedetomidine was 3.83 (0.79) minutes indicating that the time to reach Bromage 3 was lower in dexmedetomidine. There was a significant difference with regard to time taken to reach Bromage 0 between morphine and dexmedetomidine ($p<0.05$). The [mean (SD)] to reach Bromage 0 for morphine was 134.44 (20.64) minutes and for dexmedetomidine was 276.67(54.02) minutes indicating that the time to reach Bromage 0 was higher in dexmedetomidine. For time-treatment interaction results in repeated measure ANOVA analysis, we found that there was a significant difference between pain score of groups based on time ($F= 2.54$, $p= 0.031$). The mean pain score was higher for those who took dexmedetomidine compared to morphine.

Conclusions: Intrathecal dexmedetomidine significantly cause prolonged in sensory and motor block in comparison with intrathecal morphine. However for post-operative pain control, intrathecal morphine gave better pain control post-operatively

Keywords: spinal anaesthesia, intrathecal morphine, intrathecal dexmedetomidine, orthopaedic, lower limb surgery,

SECTION 2

2.0 Introduction

Spinal anaesthesia is one of the methods of anaesthesia for lower limbs surgeries as it is very economical and easy to administer. Many studies have showed concerned about prolonging the duration of spinal anaesthesia by adding different adjuvant. One of these additives are morphine and dexmedetomidine, which have been proved in many studies to prolong the duration of peripheral blocks both in animal and human studies (1, 2). This technique of anaesthesia 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 anaesthesia for lower limbs surgery (3) .

The commonest drug that is being used for spinal anaesthesia is heavy marcaine 0.5% and with the dose of 5-20mg. The duration of spinal anaesthesia ranged between 90-120 minutes (4). By looking at the duration of action of heavy marcaine it is relatively short duration and the patient may have poor pain controlled postoperatively. There are various factors affecting local anaesthetic potency and its effect. The factors include dose, volume, baricity and the amount of adjuvant given. Four factors play important role in the uptake of local anaesthetics from the subarachnoid space into neuronal tissue, concentration of local anesthetic in CSF, surface area of nerve tissue exposed to CSF, lipid content of nerve tissue, and blood flow to nerve tissue (5) .

Dexmedetomidine is the drugs of choice of our research because it has unique anaesthetic properties. Dexmedetomidine is one of the recent drug which acts on α2-adrenergic receptors in the dorsal horn of the spinal cord to produce analgesic effects, it can be added and used as an adjuvant in spinal anaesthesia, prolonging both motor and sensory block. Various doses have been tried intrathecally (3, 5, 10μg) with favorable

outcomes of prolongation of sensory/motor block with preserved haemodynamics; however, the prolonged motor block may not be ideal for ambulatory surgeries(6).

Intrathecal (IT) opiates are useful options in patients undergoing lower limbs surgery especially knee arthroplasty, and can significantly reduce postoperative opioid requirements. However, the use of IT 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. The hydrophilic properties of morphine contribute to both the longevity of its analgesic action and also the risk of late respiratory depression due to rostral spread when administered intrathecally. Profound late respiratory depression has been reported in a number of earlier studies, albeit following larger doses of spinal morphine than is used in current practice (7).

2.1 Study Protocols

2.1.1 Background of the study

Lower limb surgery is one of the most common surgeries in orthopaedic specialty. There are various cases that involve lower limbs which include trauma and non trauma. Our study involved both groups of patient. One of the limiting factors of spinal anaesthesia is short duration of motor and sensory block. Our current practice in HUSM is using heavy bupivacaine which has relatively short duration of action. Thus this will be a major problem for long duration of orthopeadic surgery. To counter these problems a lot of studies had been done to solve this limitation.

There was a study done in Egypt (2012): Effects of intrathecal bupivacaine–fentanyl versus bupivacaine–dexmedetomidine in sixty diabetic surgical patients, who were submitted for elective lower limb orthopaedic surgery. Patients were randomly allocated to three groups (each group 20 patients). In bupivacaine group the patients received 2.5 ml of hyperbaric bupivacaine 0.5% plus 0.5 ml of normal saline, in bupivacaine – fentanyl group, the patients received 2.5 ml of hyperbaric bupivacaine 0.5% plus 25 μg fentanyl in 0.5 ml of normal saline and in bupivacaine–dexmedetomidine group the patients received 2.5 ml of hyperbaric bupivacaine 0.5%, plus 10 μg dexmedetomidine in 0.5 ml of normal saline. From this study the result shows the duration of sensory and motor block as well as duration of effective analgesia was significantly longer in the bupivacaine–dexmedetomidine group as compared with both bupivacaine–fentanyl and control bupivacaine groups (8).

In Canada (2013), there was a systematic review and meta-analysis on the facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block, from this analysis a total of 516 patients were analysed from nine RCTs. Five trials

investigated dexmedetomidine as part of spinal anaesthesia and four as part of a brachial plexus (BP) block. Sensory block duration was prolonged by 150 minutes with intrathecal dexmedetomidine. Perineural dexmedetomidine used in BP block may prolong the mean duration of sensory block by 284 minutes (95% CI: 1, 566, P<0.05), but this difference did not reach statistical significance. Motor block duration and time to first analgesic request were prolonged for both intrathecal and BP block. Dexmedetomidine produced reversible bradycardia in 7% of BP block patients, but no effect on the incidence of hypotension. No patients experienced respiratory depression. Dexmedetomidine is a potential LA adjuvant that can exhibit a facilitatory effect when administered intrathecally as part of spinal anaesthesia or peripherally as part of a BP block (9).

There was almost similar study done in India (2016), comparing intrathecal morphine and intrathecal dexmedetomidine in patients undergoing gynaecological surgeries under spinal anaesthesia. This was a prospective, randomised, double-blind study involving 25 patients in each group. Group morphine received 15 mg of 0.5% hyperbaric bupivacaine with 250 μg of morphine while group dexmedetomidine received 15 mg of 0.5% hyperbaric bupivacaine with 2.5 μg of dexmedetomidine. Time for first rescue analgesic (P = 0.056) and total analgesic demand was similar in both groups**.** Duration of sensory (P = 0.001) and motor (P = 000) block was significantly higher in dexmedetomidine group. Itching was noticed in 36% and nausea in 52% of patients in the morphine group, either of which was not seen in dexmedetomidine group. This study conclude that intrathecal dexmedetomidine produces prolonged motor and sensory blockade without undesirable side effects but intraoperative hypotension was more frequent in dexmedetomidine group (10) .

2.1.2 Problem Statement and Rationale of Study

The most common practice of spinal anaesthesia for lower limbs surgery is solely using heavy marcaine 0.5 % in our local setting. However we encountered several limitations using this local anaesthesia. One of the major limitations is the duration of sensory and motor block which only last for 2 hours and may lead to inadequate anaesthesia intraoperatively and poor analgesia postoperatively. The consequences of inadequate anaesthesia may lead to conversion to general anaesthesia.

In order to solve this problem we conducted a research, with the aim of prolonging sensory and motor block and to improve post operative pain control. We have chosen dexmedetomidine as a drug of choice because this drug has good pharmacokinetic and pharmacodynamic profile.

2.2.2 RESEARCH OBJECTIVES

The study research objectives are divided into general and specific objectives:

General objective

The aim of this study is to compare the effect of adding morphine versus dexmedetomidine to bupivacaine in prolonging the duration of spinal anaesthesia and analgesia in lower limbs operations, and to evaluate for any possible side effects.

Specific objective

1. To compare the duration of the sensory block of 2.5 ml 0.5% hyperbaric bupivacaine with 0.2 mg morphine intrathecal versus 2.5 ml 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 ml administered intrathecally
2. To compare the duration of the motor block of 2.5 ml 0.5% hyperbaric bupivacaine with 0.2 mg morphine intrathecal versus 2.5 ml 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 ml administered intrathecally
3. To evaluate the presence of possible side effect experiences by study sample

2.2.3 RESEARCH HYPOTHESIS

Null hypothesis

There are no differences in the addition of morphine versus dexmedetomidine to bupivacaine in prolonging the duration of spinal anaesthesia and analgesia in lower limb operations.

Alternative hypothesis

There are differences in effect of adding morphine versus dexmedetomidine to bupivacaine in prolonging the duration of spinal anaesthesia and analgesia in lower limb operations.

2.2.4 BENEFITS OF THE STUDY

i. Improvement in neuraxial anaesthesia technique with drug adjuvant and to minimise the conversion to general anaesthesia.

ii. Improvement in patient satisfaction particularly in relation to post operative pain relief.

2.2.5 LIMITATIONS OF THE STUDY

i. Inadequate time to observe and clinical assessment in operating theatre recovery particularly for dexmedetomidine group.

ii. This study can only representative anaesthetic management of patient in Hospital Universiti Sains Malaysia (HUSM) as it is not representing the people in Kelantan.

2.2.6 METHODOLOGY

2.2.6.1 RESEARCH DESIGN

This is a prospective, randomized controlled double-blinded study in Trauma Operation Theatre and General Operation Theatre of Hospital Universiti Sains Malaysia (HUSM). Study period was from February 2017 to February 2018.

Reference population involved patients scheduled for elective lower limbs orthopaedic surgery in HUSM. This research was done in a single phase which involved data collection and thesis writing. Following completion of the data collection, analysis of the data available was done and compiled in a thesis.

2.2.6.2 SAMPLE SIZE CALCULATION

The sample size was calculated based on objective 1 and 2, using power and sample software version 3.1.2, with the information from previous study, comparative evaluation of intrathecal morphine and intrathecal dexmedetomidine in patients undergoing gynaecological surgeries under spinal anaesthesia by Pranjali et al., 2016.

For objective 1

1. To compare the duration of the sensory block of 2.5 ml 0.5% hyperbaric bupivacaine with 0.2 mg morphine intrathecal versus 2.5 ml 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 ml administered intrathecally.

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 61. If the true difference in the experimental and control means is 63, we need to study 16 experimental subjects and 16 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) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

For objective 2

1. To compare the duration of the motor block of 2.5 ml 0.5% hyperbaric bupivacaine with 0.2 mg morphine intrathecal versus 2.5 ml 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 ml administered intrathecally.

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 126.62. If the true difference in the experimental and control means is 176, we need to study 9 experimental subjects and 9 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) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

The highest value of estimated sample size is: 36 samples (16x2) + 10% dropout)

2.2.6.3 SAMPLING METHOD

For this research, random sampling was used from the source population as mentioned before.

2.2.6.4 INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA:

1. Consented patient
2. ASA 1 - ASA 2 patient.
3. Patient age: more than 18 years old and less than 60 years old.
4. Haemodynamically stable patient (stable blood pressure and heart rate).
5. Expected duration of surgery of less than 2 hours
6. All orthopaedic elective surgeries involve lower limbs including trauma and non-trauma cases.

EXCLUSION CRITERIA;

1. Patient refusal to spinal anaesthesia.
2. Allergy to dexmedetomidine/morphine and local anaesthesia.
3. Pregnancy.
4. History of previous spine injury.
5. History of chronic pain, those that was treated with chronic analgesic medication.
6. Coagulapathy.
7. Systemic infection or local infection at site of the injection.

8. Patients with history of long-term steroid therapy.

WITHDRAWAL CRITERIA

1. Patient developed local anaesthetic toxicity.
2. Patient developed haemodynamic instability (bradycardia/hypotension).
3. Patient developed anaphylaxis.

DATA COLLECTION

Sample was obtained from Trauma operation Theatre (TOT) and General Operation Theatre (GOT) HUSM in stipulated time by means of universal sampling. Consent was taken from sample that was undergoing elective lower limbs surgery. Sampling randomization was done using 'RESEACHERS RANDOMIZATION SOFTWARE'. The consented patients were randomized into two arms group morphine and group dexmedetomidine. The card was put inside the box. One card was randomly taken each time by nurse that assists spinal anaesthesia.

The elective orthopaedic patients who meet the study criteria were approached to participate in this study. Each patient was given a thorough explanation along with a copy of patient information sheet. All questions were answered to their satisfaction before consent was obtained by signing the consent form.

RESEARCH TOOL

1. Drugs study: morphine and dexmedetomidine.
2. Diluted intravenous atropine (0.2 mg/ml) in 5 mls syringe (to standby at patient's bedside in case of symptomatic bradycardia). Ephedrine 6mg/ml diluted in 5ml normal saline. Thiopentone 25mg/ml in 10 ml normal saline also prepared for patient who failed spinal anaesthesia as an induction agent or as an anti-convulsion if patient develop seizure due to local anaesthetic toxicity.
3. Spinocan 25 G for spinal anaesthesia.
4. Short bevel needle for sensory assessment during intraoperative.
5. Bromage score for motor assessment, Ramsay scale for sedation scoring and for postoperative pain assessment using visual analogue scale.
6. Standard monitoring devices that already available at study area to monitor patient's haemodynamic parameters.

METHODOLOGY

1. Approval for Ethics Committee of Universiti Sains Malaysia (USM) was obtained before enrollment of the patients.
2. Eligibility for the patients was screened during preoperative assessment. Written consent was obtained from all selected patients that fulfill the inclusion and the exclusion criteria.
3. Premedication was not prescribed in the morning of the surgery and patients were randomized using computer generated randomization.
4. Upon arrival in the OT, all patients were monitored based on standard anaesthesia monitoring (non invasive blood pressure, pulse oximetry (spO2), electrocardiography (ECG) and baseline BP, HR were documented before the procedures.
5. IV excess at least 20 G was inserted on the other hand.
6. IV loading with Ringer's Lactate solution 10 ml/kg was given before performing the block.
7. Spinal anaesthesia was performed in the operating theatre.
8. Drugs regime for spinal anaesthesia was prepared:
    - 2 ml of lignocaine 2% for skin infiltration
    - 2.5 ml of 0.5% hyperbaric bupivacaine with 0.2 mg morphine in 0.5 ml of normal saline ----- Group M
    - 2.5 ml of 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 ml of normal saline ---Group D
9. Other standard equipments were used for the block:
    - Spinocan 25G