REDUCING THE OCCURRENCE OF SHIVERING WITH INTRAVENOUS DEXMEDETOMIDINE IN PATIENTS UNDERGOING CAESAREAN DELIVERY UNDER SPINAL ANAESTHESIA: DOUBLE-BLINDED, RANDOMISED CONTROLLED TRIAL OF THE EFFICACY AND SAFETY

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

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All praise and thanks to Allah the Almighty who consistently guides me to the right path and providing strength for me to complete the journey as a postgraduate student.

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This dissertation would not be completed without the assisting hands of my colleague (doctors and staff nurses) especially during data collection period.

Hopefully, this dissertation would be a stepping stone towards a better and fruitful ride as an anesthesiologist.

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ASA	American Society Anesthesiologists
BMI	Body Mass Index
BP	Blood Pressure
CONSORT	Consolidated Standards of Reporting Trials
HR	Heart Rate
hr	hour
HREC	Human Research Ethics Committee
HUSM	Hospital University Sains Malaysia
IQR	interquartile range
IV	Intravenous
kg	kilogram
LSCS	Lower Segment Caesarean Section
m	metre
mcg	microgram
mg	milligram
min	minute
mls	millilitres
mmHg	millimiter of mercury
NIBP	Non-invasive Blood Pressure
PONV	Postoperative Nausea and Vomiting
RM ANOVA	Repeated Measure Analysis of Variance
RR	Respiratory Rate
SD	Standard Deviation
SpO2	Saturation of Oxygen

ABSTRAK

Latar Belakang

Kegigilan ialah satu pengalaman yang sangat tidak menyelesakan selepas menjalani bius separa badan, terutamanya pesakit yang menjalani pembedahan Caesarean. Penyelidikan ini bertujuan untuk mengkaji keberkesanan dan keselamatan ubat intravena (IV) dexmedetomidine sebagai pencegah kegigilan untuk pesakit-pesakit yang menjalani pembedahan Caesarean di bawah pembiusan separa badan.

Kaedah

Kajian prospektif ini ialah satu kajian rawak terkawal, melibatkan 62 pesakit yang menjalani pembedahan Caesarean di bawah pembiusan separa badan. Pesakit-pesakit ini dibahagikan kepada dua kumpulan; kumpulan D (n = 31) menerima IV dexdemedetomidine berdos 0.5mcg/kg dalam masa 10 minit diikuti dengan infusi berkadar 0.4mcg/kg/hr sehigga tamat pembedahan; manakala pesakit-pesakit dalam kumpulan C menerima infusi air garam pada kadar yang sebanding. Kadar kegigilan, tahap kesedaran pesakit dan tekanan darah serta denyutan jantung pesakit direkodkan sepanjang pembedahan.

Keputusan

Kadar kegigilan menurun dengan ketara di dalam kumpulan D jika dibandingkan dengan kumpulan C (3.2% vs 64.5%, $p < 0.001$). Pesakit-pesakit dalam kumpulan D mempunyai tahap kesedaran yang lebih rendah berbanding kumpulan C (51.6% vs 0%, $p < 0.001$). Tahap bacaan tekanan darah sistole dan diastole juga tidak mempunyai perbezaan ketara di antara kedua-dua kumpulan ini. Bacaan kadar denyutan jantung pesakit di dalam

kumpulan D adalah lebih rendah berbanding kumpulan C, namun bacaan ini masih lagi dalam paras normal fisiologi.

Kesimpulan

IV dexmedetomidine adalah berkesan untuk menurunkan kadar kegigilan tetapi mempunyai kesan sedasi yang ketara serta kadar denyutan jantung yang lebih rendah berbanding placebo. Namun, kadar denyutan jantung ini masih berada dalam julat normal.

ABSTRACT

Background

Shivering is a very discomforting experience following spinal anaesthesia, especially in patients undergoing caesarean delivery. The objective of this study was to investigate the efficacy and safety of intravenous (IV) dexmedetomidine in preventing shivering in patients undergoing caesarean delivery under spinal anaesthesia.

Methods

This was a prospective, double-blind, randomized trial involving 62 parturients undergoing caesarean delivery under spinal anaesthesia. They were divided into 2 groups; patients in group D (dexmedetomidine, n = 31) received 0.5mcg/kg IV dexmedetomidine over 10 minutes followed by infusion of 0.4mcg/kg/hr until end of surgery; whilst patients in group C (saline, n = 31) received equivalent loading and infusion volume of 0.9% saline. The occurrence of shivering, sedation score and haemodynamic parameters were recorded intraoperatively.

Results

The occurrence of shivering was significantly reduced in group D as compared to group C (3.2% vs 64.5%, $p < 0.001$). Patients in group D were more sedated as compared to group C (51.6% vs 0%, $p < 0.001$). There were no statistically significant difference in systolic and diastolic blood pressure between both groups. Heart rate in group D were significantly lower than group C but still within normal physiological range.

Conclusion

IV dexmedetomidine was effective in reducing the occurrence of shivering but with significant sedative effect and lowering of heart rate than placebo. However, the value of heart rate was still within normal range.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Shivering is a common complication following anesthesia, described as repetitive, non-voluntary movement. The incidence of shivering following anesthesia is reported as high as 70%.

Shivering is particularly of importance to be avoided since oxygen consumption may be increased as high as 4-fold as compared to non-shivering patients. This could be detrimental especially to post-operative patients. It has also been associated with increased carbon dioxide production, increase catecholamine release, pain aggravation and occasionally impeding regular monitoring devices.

There are several measures can be taken to prevent or reduce the incidence of shivering, including pharmacological interventions. Several drugs are known to help in minimizing the occurrence of shivering including pethidine, tramadol, clonidine and dexmedetomidine. However, the evidence of drugs efficacy in preventing shivering in patients undergoing elective caesarean delivery is certainly lacking.

1.2 STUDY RATIONALE

As mentioned earlier, shivering may increase the oxygen consumption up to 4-fold. Post-operative as well as intra-operative shivering is certainly not desirable, especially in parturient who already has physiologically increased oxygen consumption compared to normal person. Due to its high incidence, shivering is very discomforting to the patient, regarded as similar burden to post-operative pain and postoperative nausea and vomiting.

There is no study conducted to assess the efficacy and safety of the use of intravenous dexmedetomidine as prophylaxis in preventing shivering, specifically in patient undergoing caesarean delivery under spinal anesthesia.

If this study is found to be significant, and dexmedetomidine is proven to be efficacious and safe to be used as prophylaxis in preventing shivering in patients undergoing elective caesarean delivery, then it would provide an alternative to current drug used for the treatment of shivering following spinal anesthesia. Currently, the most commonly used agents for perioperative shivering is pethidine, which is associated with nausea, vomiting and respiratory depression (1). Furthermore, the use of pethidine is better avoided in patient already given intrathecal opioids to avoid an extra risk of respiratory depression and further sedation (2).

1.3 LITERATURE REVIEW

Shivering and Anaesthesia

Shivering is a common complication following anesthesia, described as repetitive, non-voluntary movement. The incidence of shivering following general or regional anesthesia has been reported as high as more than 70% (3). It has also been regarded as one of the most discomforting experience to patients undergoing anesthesia, alongside pain and post-operative nausea/vomiting (PONV) (4).

Shivering leads to increase in oxygen consumption as well as metabolic demand. This is potentially detrimental to patients with limited cardiorespiratory reserve, especially postoperative patients (4). It has also been associated with increased carbon dioxide production, pain aggravation and occasionally impeding regular monitoring devices (5).

Relationship between shivering and anesthesia centrals around thermoregulation system. Regional and general anesthesia inhibit vasoconstriction, which is important in regulation of body temperature (6).

Factors which will affect the incidence of shivering perioperatively includes patient's age, body size, duration of surgery and anesthesia, drug administration, operating room temperature and fluid temperature (7).

There are several measures can be taken to prevent or reduce the incidence of shivering, which includes non-pharmacological and pharmacological approach. Non-

pharmacological approach includes perioperative hypothermia prevention, fluid warming and patient warming technique (4).

Use of Dexmedetomidine for Perianaesthetic Shivering

Mechanism of action for dexmedetomidine (an alpha-2 agonist) in the management of shivering is still in the dark. It is said to alter the threshold for vasoconstriction and shivering (8), but sweating threshold is unchanged (4). Possible mechanisms include central thermoregulation and internal as well as external heat redistribution (1). Neural pathways in the development of shivering includes alpha-2 adrenergic neurotransmitter (6), hence the interest for the role of dexmedetomidine in perioperative shivering.

There are various ways of how dexmedetomidine has been used in the management of perioperative shivering. It has either been used as prophylaxis or treatment of shivering; and it has also been given as single slow-injection bolus, as infusion and combination of bolus-dose together with infusion.

When dexmedetomidine is used for treatment of shivering, the dose most frequently used is 0.5mcg/kg given over 10 minutes. This dose has been investigated in several studies published between 2014 until 2016 (9-12). Most of these studies found dexmedetomidine to be more effective in the treatment of post spinal anaesthesia shivering. However, depending on the rate it is infused, some has reported more episodes of hypotension and bradycardia as, which is treatable. A recent study by Kundra and Kaur published in 2017 found out that the minimum dose of dexmedetomidine required to abolish shivering is less than 0.3mcg/kg of intravenous dexmedetomidine (13).

As for prophylaxis, the studies are divided between population undergoing general anesthesia as well as regional anesthesia. For general anesthesia, use of single bolus dexmedetomidine of 1mcg/kg was studied in patients undergoing laparoscopic surgical procedures (7). The optimal dose for dexmedetomidine as shivering prophylaxis was studied and published in 2013, which suggest that the dose of 0.75 or 1.0 mcg/kg provides effective prophylaxis against shivering (14). Another study use a combination of 1.0mcg/kg bolus followed by infusion of 0.4mcg/kg/hr in patients undergoing general anesthesia, although this has been associated with higher episodes of bradycardia (15).

As for prophylaxis for patients undergoing regional anaesthesia, two different ways has been studies. First, the use of single dose dexmedetomidine of 0.5mcg/kg (16); and secondly combination of loading dose (0.5mcg/kg or 1mcg/kg) followed by infusion of 0.4mcg/kg/hr (1, 6). All these studies showed significant reduction in the incidence of shivering post regional anesthesia.

Shivering and Pregnancy

Incidence of shivering in parturients undergoing caesarean delivery under regional anesthesia was as high as 62% (17). Several drugs has been studied for management of shivering in caesarean delivery which includes clonidine, tramadol, pethidine, ephedrine, amitryptilline and sufentanil, either through intravenous or intrathecal administration. (2, 5, 17-21).

There is no standard drug being used today routinely for shivering prophylaxis. Common

practice nowadays involves the use of pethidine to treat shivering when it occurs. However, it can be associated with nausea, vomiting, sedation and respiratory depression (1, 2), especially with administration of another opioid (fentanyl with or without morphine) intrathecally.

Clonidine has also been useful in the management of perioperative shivering but it is associated with episodes of bradycardia, hypotension and sedation (2). Tramadol was associated with nausea and vomiting. Since it is also considered as weak opioid, its administration for patients already receiving intrathecal opioid should always warrant extra caution.

Since other drugs has been associated with several unwarranted side effects, dexmedetomidine (which is relatively new compared to others) appears to be a better choice in the management of shivering.

Use of Dexmedetomidine in Parturients

Dexmedetomidine is not commonly used during caesarean section. However, there are several studies as well as case reports involving use of dexmedetomidine in caesarean delivery. A study published in 2012 was done to investigate the use of intravenous dexmedetomidine in caesarean delivery under general anesthesia (22). In this study, the aim of study drug was for suppression of cardiovascular and hormonal responses during the operation. It is important to note from this study that no maternal or neonatal complications were reported throughout the period. Additionally, there were additional benefits of improved uterine relaxation, reduced requirement of oxytocin requirement as

well as lower incidence of post-operative nausea/vomiting (22).

Use of dexmedetomidine in epidural has also been studied for patients undergoing caesarean delivery under regional anesthesia (23). It is important to note the absence of significant maternal or neonatal side effects during the study. Furthermore, this study showed a reduced incidence of intra-operative shivering with epidural dexmedetomidine (23).

CHAPTER 2: STUDY OBJECTIVES

2.1 GENERAL OBJECTIVES

To study the efficacy and safety of dexmedetomidine as prophylaxis to prevent shivering in patients undergoing caesarean delivery under spinal anesthesia

2.2 SPECIFIC OBJECTIVES

a) To determine the efficacy of dexmedetomidine infusion to reduce the incidence of shivering when given prophylactically in patients undergoing caesarean delivery under spinal anesthesia

b) To assess the effect of dexmedetomidine infusion on sedation status when given intraoperatively in patients undergoing caesarean delivery under spinal anesthesia

c) To assess the haemodynamic response of dexmedetomidine infusion when given intraoperatively in patients undergoing caesarean delivery under spinal anesthesia

2.3 RESEARCH HYPOTHESES (NULL HYPOTHESES)

a) There is no significant difference in the incidence of shivering when dexmedetomidine is given prophylactically (compared to placebo) in patients undergoing caesarean delivery under spinal anaesthesia.

b) There is no significant difference on sedation status when dexmedetomidine is given prophylactically (compared to placebo) in patients undergoing caesarean delivery under spinal anaesthesia.

c) There is no significant difference on haemodynamic response when dexmedetomidine is given prophylactically (compared to placebo) in patients undergoing caesarean delivery under spinal anaesthesia.

CHAPTER 3: STUDY PROTOCOL & ETHICAL APPROVAL

3.1 STUDY PROTOCOL

Research design: Prospective, double-blind, randomised controlled trial.

Study area: Operation Theatre, HUSM, Kubang Kerian, Kelantan.

Study population:

Reference population – Patients undergoing Caesarean delivery in Malaysia

Source population – Patients undergoing Caesarean delivery in Kelantan

Target population – Patients undergoing Caesarean delivery in HUSM

Sampling frame – Patients undergoing Caesarean delivery in HUSM between November 2017 until April 2018

Subject criteria

Inclusion criteria:

a) age 18-45 years old

b) patients undergoing LSCS under spinal anesthesia

c) ASA I-III with stable haemodynamic parameter

Exclusion criteria:

a) height < 1.5m

b) morbid obesity (BMI > 40kg/m^2)

c) shivering occurs prior to fetal delivery

d) known allergy to dexmedetomidine

e) use of epidural catheter

f) significant cardiac, liver or renal problem

g) pre-existing hypo/hyperthermia (< 36C or >38C)

Withdrawal criteria: a) conversion to general anaesthesia intraoperatively

b) blood loss of more than 1L, or administration of blood products

c) duration of surgery more than 2 hours

Operational Terms

Dexmedetomidine infusion refers to infusion of dexmedetomidine at the dose of 0.4mcg/kg/hr, preceded by loading infusion of 0.5mcg/kg over 10 minutes.

Incidence of shivering is assessed by using grades of shivering used in earlier study (Tsai and Chu 2001), which ranges from grade 0 to 4.

Sedation status is assessed by using modified Wilson Sedation Scale, ranging from score 1-4.

Haemodynamic response refers to the systolic and diastolic blood pressure as well as heart rate of the patients.

Sample size estimation

1st Objective

Significance level, α = 0.05 (two-sided)

Power of study 0.8

Based on previous study on the incidence of shivering for patients undergoing Caesarean delivery under spinal anaesthesia, the incidence of shivering in control group is 62.5% (17). With the use of dexmedetomidine, the incidence of shivering is expected to be reduced to 25%. From the calculation using PS software, we would need to study 26 experimental subjects and 26 control subjects to be able to reject the null hypothesis.

2nd objective

Significance level, α = 0.05 (two-sided)

Power of study 0.8

There is minimal incidence of sedation occurring in patients undergoing caesarean delivery under spinal anesthesia. In previous study, use of dexmedetomidine for post spinal anaesthesia shivering was associated with 24% incidence of sedation (10). Calculation using PS software indicated that we would need to study 28 experimental subjects and 28 control subjects to be able to reject the null hypothesis.

3rd objective

Significance level, α = 0.05 (two-sided)

Power of study 0.8

Based on previous study (12), the standard deviation for heart rate, systolic BP and diastolic BP within dexmedetomidine group were 4.95, 8.48 and 6.35 respectively. The anticipated differences are 5bpm for heart rate, 10mmHg for systolic BP and 5mmHg for diastolic BP. Calculating using PS software, for a study of continuous response variable from independent control and experimental subjects, we would require different number of experimental and control subjects to be able to accept alternative hypothesis, as followed:

a) 16 experimental subjects and 16 control subjects for changes in heart rate

b) 12 experimental subjects and 12 control subjects for changes in heart rate

c) 26 experimental subjects and 26 control subjects for changes in heart rate

*The highest sample study required is 28 for each group, with additional 10% for dropout rate, this study would require 31 patients in each group, giving a total of 62 patients.

Sampling method and subject recruitment

Sampling method is based on time frame and target number of subjects. Subject recruitment is done during pre-anaesthetic assessment in the ward for elective cases or at the receiving bay of operation theatre for emergency cases.

Research tool

This research involves the study of three group of variables.

Shivering Status

Shivering is graded based on its severity, using grading system validated in an earlier study (2). Shivering is considered absent for grade 0 or 1, and considered present if the grade is 2, 3 or 4.

Table 3.1: Grade of shivering

Grade	Description
0	no shivering
1	piloerection or peripheral vasoconstriction but no visible shivering
2	Muscular activity in only one muscle group
3	Muscular activity in more than one muscle group but not generalised shivering
4	Shivering involving the whole body

Sedation Status

Sedation status is assessed based on Modified Wilson sedation scale which ranges from 1 to 4. This is assessed by the attending anaesthesiologist or the medical officer. The assessment is done every 10 minutes from the administration time of study drug for total of 1 hour. The modified Wilson sedation scale provides a simple and reliable method of

monitoring for sedation during regional anesthesia, with inter-rater agreement of 84% (24). Sedation is considered present if the score is 2 or more.

Table 3.2: Modified Wilson Sedation Scale

Modified Wilson Sedation Scale
1: Oriented; eyes may be closed but can respond to "Can you tell me your name?" "Can you tell me where you are right now?"
2: Drowsy; eyes may be closed, rousable only to command: "(name), lease open your eyes."
3: Rousable to mild physical stimulation (earlobe tug)
4: Unrousable to mild physical stimulation

Haemodynamic Response

Haemodynamic response which includes BP and HR is recorded every 10 minutes from the administration time of study drug for total of 1 hour. Measurements are done by using standard monitoring device in operation theatre. Bradycardia is defined as heart rate of less than 50 beats per minute. Hypotension is defined as mean arterial pressure reduction of more than 20% from baseline.

Study Protocol & Methods

This is a single-centre, double-blinded, randomised placebo-controlled parallel group study. After the written consent has been taken, patients will be randomly assigned to 2 groups in 1:1 ratio.

Patient are allocated into two groups: dexmedetomidine group (D) and control group (C). For this study, patient will be randomised according to blocked randomisation technique. For every block of 10 patients, 5 would be allocated to each arm. The order of interventions within each block will vary randomly, determined by computer random number generator. This technique is chosen to ensure similar numbers of patients in each group at any point during trial.

The allocation sequence is enclosed in opaque envelopes and revealed once patient is already inside the operation theatre.

Patients in group D (intervention group) will receive loading dose of intravenous dexmedetomidine of 0.5mcg/kg over 10 minutes, and continued intravenous infusion afterwards at the rate of 0.4mcg/kg/min. Dexmedetomidine solution will be diluted at 4mcg/ml.

Patients in group C (placebo control group) will receive normal saline intravenous infusion with equivalent infusion rate to the intervention group according to patient's weight.

Study drugs will be prepared in an equivalent 20mls syringe which will contain similar colourless solution in either group. The preparation will be done by principal investigator which is not blinded.

For this study, the blinding applies to the patients and the attending anaesthesiology officer who will be responsible for administration of the study drug as well as assessing the outcome of the study.

In Operation Theatre, patient is attached to standard monitoring and initial parameters are taken, which includes non-invasive blood pressure (NIBP), oxygen saturation (SpO2), respiratory rate (RR) and heart rate (HR). Patient is preloaded with 10mls/kg of crystalloid fluids before the administration of spinal anaesthesia.

Spinal anesthesia is administered (heavy bupivacaine 0.5% 2.0mls, fentanyl 15mcg, total volume 2.3mls) at the level of L3/L4 or 1 level adjacent under aseptic condition. Patient was asked to lie supine following spinal anesthesia administration with slight left lateral tilt. Supplementary oxygen is given via face mask with oxygen flow rate of 5L/min.

Operation would commence after level of spinal blockade is adequate for the operation. Level of blockade is assessed by using Bromage Score and testing for light touch using cotton wool. Intraoperatively, patient would be regularly monitored for vital signs every 5 minutes. After fetal delivery, IV pitocin 5 units slow bolus is given followed by 40 units infused over next 8 hours.

The study drug infusion is then started 5 minutes after fetal delivery, the dosage and infusion rate as explained earlier. The infusion rate according to patient's weight is summarised in following table:

Table 3.3: Summary of intraoperative weight-based infusion rate

Weight	Infusion Rate (mls/hr)		Weight	Infusion Rate (mls/hr)	
	1st 10 minutes	After 10 minutes		1st 10 minutes	After 10 minutes
35	26.3	3.5	70	52.5	7.0
40	30	4.0	75	56.25	7.5
45	33.8	4.5	80	60	8.0
50	37.5	5.0	85	63.75	8.5
55	41.25	5.5	90	67.5	9.0
60	45	6.0	95	71.25	9.5
65	48.75	6.5	100	75	10.0

All fluids given were preheated to 37°C in fluid warmer. Operation theatre temperature is maintained at 20-24°C. Patient warming methods are standardised which include and restricted to the use of air warming blanket.

The temperature of the patient is recorded preoperatively, intraoperatively and postoperatively (measurements every 30 minutes) by using an infra-red tympanic membrane thermometer.

For both study groups, infusion will be continued until the operation is completed. Intravenous dexamethasone 4mg is given as prophylaxis for postoperative nausea and vomiting.

Incidence of shivering is observed from the time after the study drug is given until patient is discharged from recovery. Similar observations are made with regards to sedation score and haemodynamic parameter.

Patients who developed grade 4 shivering for more than 10 minutes (after infusion is started) during the study would be administered with IV pethidine 0.2-0.4mg/kg as rescue therapy.

Side effects such as nausea, vomiting, hypotension and bradycardia, and sedation scores are documented and treated if necessary. The incidences of bradycardia and hypotension requiring treatment are documented. Bradycardia is treated with IV atropine 0.6mg and hypotension is treated with IV ephedrine 6mg, with additional repeated doses if necessary.

Urgent unblinding will be considered in the following events:

a) suspected allergic reaction to study drugs

b) refractory bradycardia or hypotension, not responding to treatment

Data collection is done based on data collection form (see appendix A). Assessments of shivering status, sedation status and haemodynamic parameter are labelled with respect to the time it is measure (T_0, T_{10}, T_{20}, T_{30}, T_{40}, T_{50} and T_{60}).

Patient would be monitored at recovery room for 1 hour before discharged to postnatal ward. In the ward, patient continues to be monitored as per usual protocol.

Study flow chart is as follows:

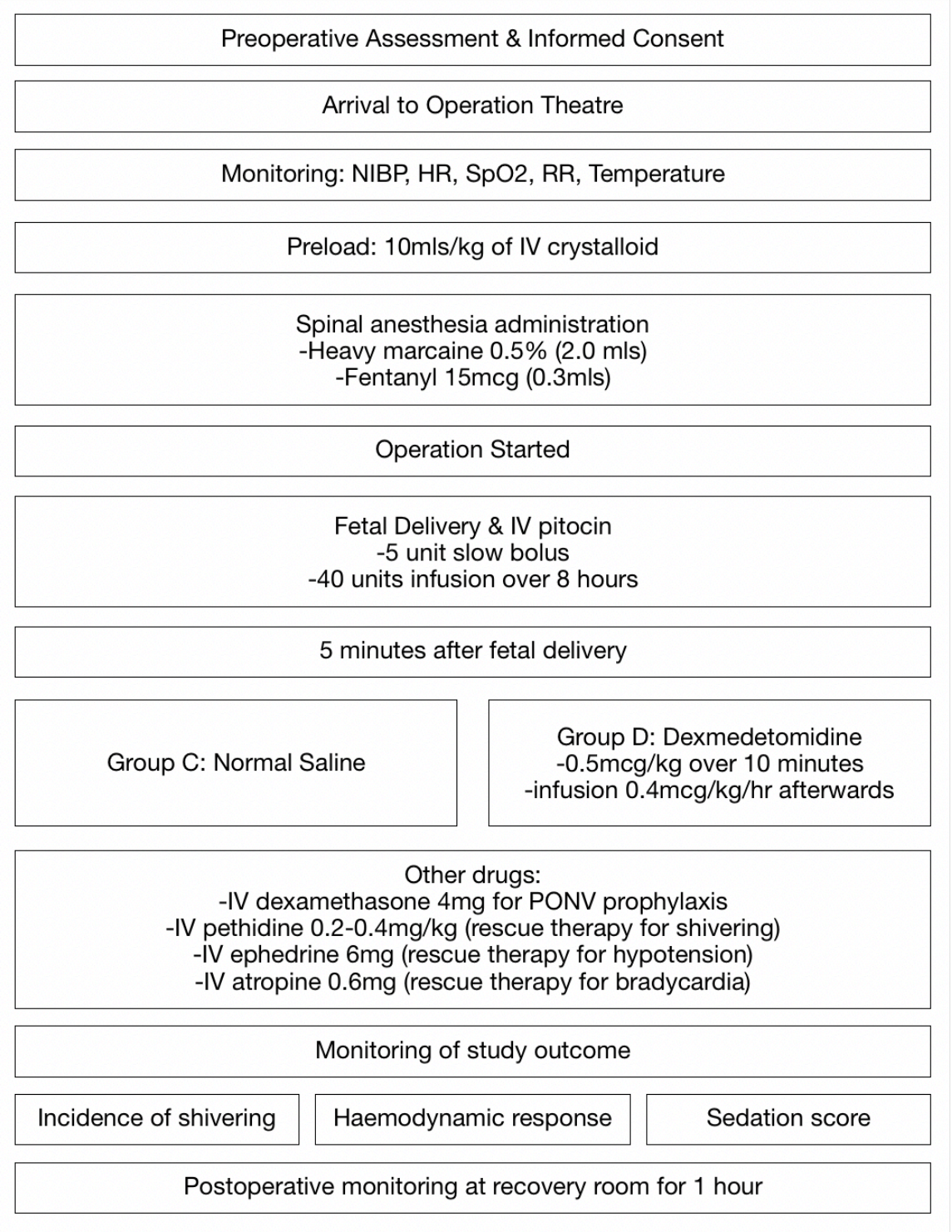

Figure 3.1: Study flow chart

Study flow diagram:

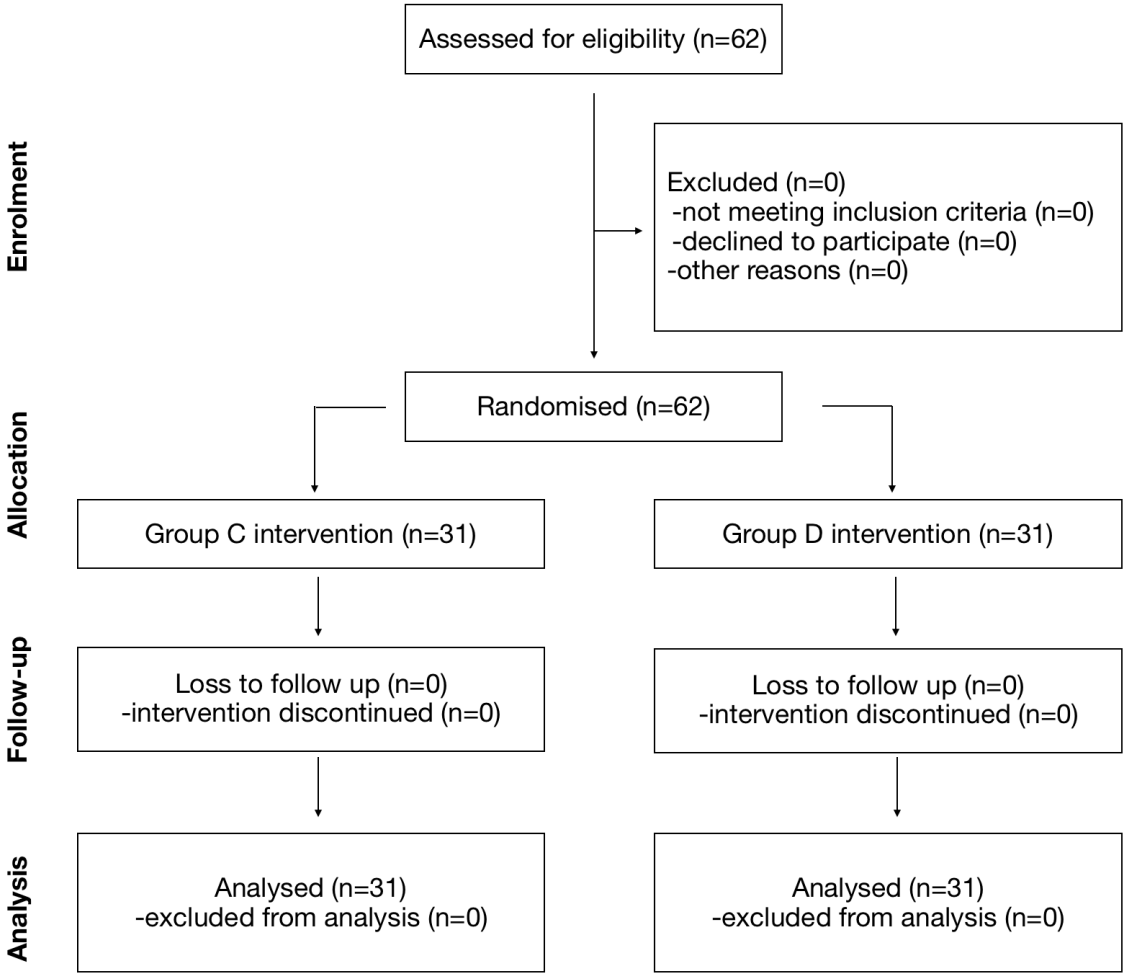

Figure 3.2: Study flow diagram (prepared according to CONSORT 2010 Guidelines)

Data analysis

Data will be entered and analysed using SPSS version *22*. Descriptive statistics will be used to summarise the socio-demographic characteristics of subjects. Numerical data will be presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data will be presented as frequency (percentage).

Table 3.4: Intended Statistical Analysis:

Objective	Parameter	Statistical Analysis
Objective 1	Incidence of shivering	Chi square
Objective 2	Sedation status	Chi square
Objective 3	Blood pressure (Systolic, Diastolic) and Heart Rate	Repeated Measure ANOVA

Gantt Chart

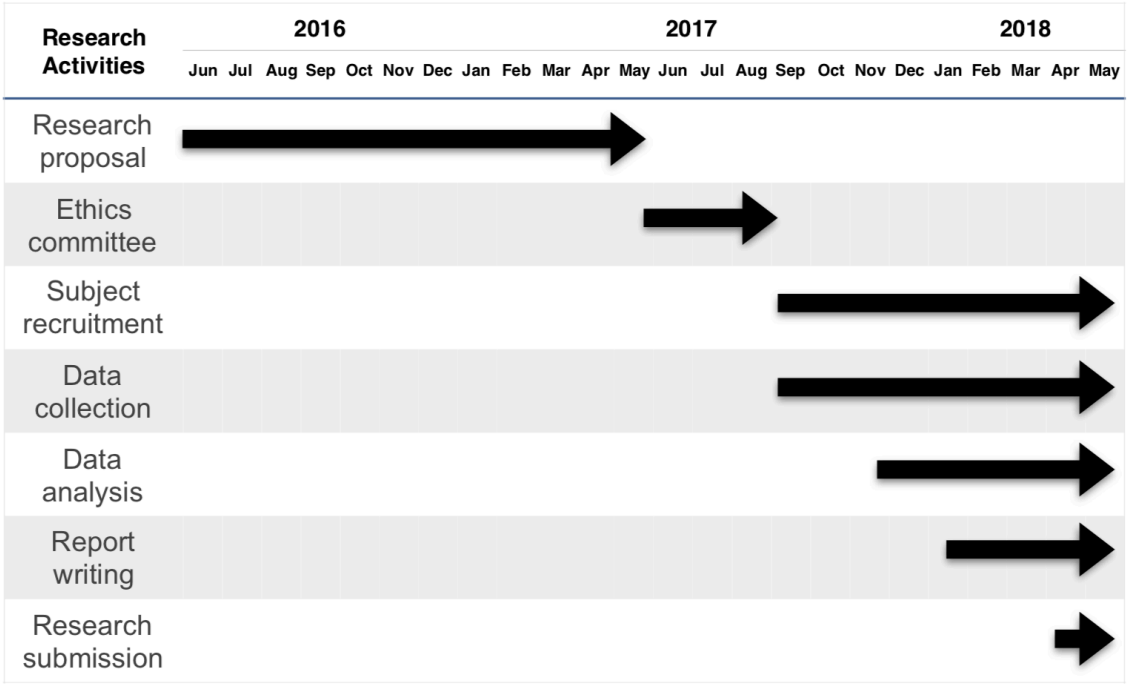

Figure 3.3: Gantt Chart

3.2 ETHICAL APPROVAL LETTER

UNIVERSITI SAINS MALAYSIA

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

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30th October 2017

Dr. Wan Ahmad Asyraf Wan Md Adnan
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JEPeM Code : USM/JEPeM/17060303
Protocol Title : Reducing Incidence of Shivering with Intravenous Dexmedetomidine in Patients Undergoing Caesarean Delivery under Spinal Anaesthesia: Double Blind, Randomized Controlled Trial of Efficacy and Safety.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/17060303**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **30th October 2017** until **29th October 2018.**

Study Site: Hospital Universiti Sains Malaysia.

The following researchers also involve in this study:

1. Dr. Mohd Erham Mat Hassan
2. Dr. W Mohd Nazaruddin W Hassan

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Patient Information Sheet and Consent Form (English version)
2. Patient Information Sheet and Consent Form (Malay version)
3. Data Collection Form

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2017: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**

CERTIFIED BY: National Pharmaceutical Regulatory Agency (NPRA) | Forum for Ethical Review Committees in Asia & Western Pacific Region