THE EFFICACY OF DEXMEDETOMIDINE 100MCG AS AN ADJUVANT TO 0.25% ROPIVACAINE VERSUS 0.5% PLAIN ROPIVACAINE FOR SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK IN ARTERIOVENOUS FISTULA SURGERY

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

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ACKNOWLEDGEMENT

Firstly, I wish to thank GOD for giving me the wisdom and confidence to complete this study. I also would like to take this opportunity to extend my utmost appreciation and gratitude to those who helped me from the beginning till the completion of my dissertation.

- Dissertation supervisor: Dr Ariffin Marzuki, (Senior Lecturer, Consultant Cardiac Anesthesiologist, Department of Anesthesiology and Intensive Care, Hospital University Sains Malaysia)
- Dissertation co- supervisor: Associate Professor Dr Wan Mohd Nazaruddin (Senior Lecturer, Head of Department & Consultant Neuroanesthesiologist, Department of Anesthesiology and Intensive Care, Hospital University Sains Malaysia)
- All the Anesthesiologist and Lecturer, Department of Anesthesiology and Intensive Care, Hospital University Sains Malaysia.
- My loving wife, parents, parents in law and siblings.
- Lastly but not least for all the patients who participated in this study.

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LIST OF ABBREVATIONS

ASA	American Society Anaesthesiologists
AVF	Arteriovenous Fistula
BP	Blood Pressure
BPB	Brachial Plexus Block
ECG	Electrocardiography
ESRF	End- Stage Renal Failure
G	Gauge
HR	Heart rate
HUSM	Hospital University Sains Malaysia
IQR	interquartile range
Kg	kilogram
mA	milliampere
MAP	Mean Arterial Pressure
MHZ	Mega Hertz
mm	milimeter
mls	mililiters

mcg	microgram
NIBP	Non Invasive Blood Pressure
OT	Operation Theatre
SD	Standard Deviation
SpO2	Saturation of Oxygen
Bpm	beat per minute
VAS	Visual Analog Score

KESAN PENAMBAHAN DEXMEDETOMIDINE 100MCG DI DALAM 0.25 ROPIVACAINE DIBANDINGKAN DENGAN 0.5% ROPIVACAINE DALAM PEMBIUSAN SETEMPAT(SUPRAKLAVIKULAR) UNTUK PEMBEDAHAN ARTERIO-VENA FISTULA

ABSTRAK

Latar belakang

Pembiusan setempat brachial adalah kaedah anaesthesia pilihan untuk pembedahan fistula arteriovena (AVF) dalam pesakit yang mengalami kegagalan buah pinggang tahap akhir(ESRF). Dexmedetomidine digunakan untuk meningkatkan kualiti pembiusan ini. Objektif kajian ini adalah untuk mengkaji keberkesanan menambah dexmedetomidine 100mcg kepada ropivacaine 0.25% dalam blok supraclavicular.

Kaedah

68 pesakit ESRF yang dijadualkan untuk menjalani pembedahan AVF diteliti di dalam percubaan klinikal yang dikawal secara rawak. Mereka dibahagikan kepada 2 kumpulan; pesakit dalam kumpulan D menerima campuran 30 ml ropivacaine 0.25% dan 1 ml (100 mcg) dexmedetomidine manakala pesakit dalam kumpulan C menerima campuran 30 ml ropivacaine 0.5% dan 1 ml 0.9% saline normal. Hasil akhir kajian ialah permulaan dan tempoh masa blok deria dan motor dan membandingkan kepuasan pesakit dan pakar bedah.

Keputusan

Masa permulaan blok deria dalam kumpulan D [15.29 (3.24)] min lebih awal daripada kumpulan C [18.09 (3.26)] min dan statistik signifikan ($p < 0.001$) manakala masa permulaan blok motor terdahulu dalam kumpulan C berbanding dengan kumpulan D tetapi tidak signifikan secara statistic ($p = 0.76$). Kedua-dua tempoh sensor deria dan motor semakin lama dalam kumpulan D berbanding kumpulan C dengan signifikan secara statistik ($p < 0.001$). Dari segi skor kepuasan, kumpulan D mempunyai skor yang lebih baik dibandingkan dengan kumpulan C di kalangan kedua-dua pakar bedah dan pesakit ($p < 0.001$).

Kesimpulan

Penambahan dexmedetomidine 100mcg kepada ropivacaine 0.25% menyediakan anestesia yang mecukupi untuk pesakit ESRF menjalani pembedahan AVF.

THE EFFICACY OF DEXMEDETOMIDINE 100MCG AS AN ADJUVANT TO 0.25% ROPIVACAINE VERSUS 0.5% PLAIN ROPIVACAINE FOR SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK IN ARTERIOVENOUS FISTULA SURGERY

ABSTRACT

Background

Brachial plexus block is the preferred method of anaesthesia for Arteriovenous fistula (AVF) creation in End-Stage Renal Failure (ESRF) patients. Dexmedetomidine is an adjuvant used to improve the outcome of the block. The objective of this study was to investigate the efficacy of adding dexmedetomidine 100mcg to ropivacaine 0.25% in supraclavicular block.

Methods

68 ESRF patients scheduled for AVF surgery were studied in a prospective, randomized, double-blind controlled clinical trial. They were divided into 2 groups; patients in group D receive a mixture of 30 mls of ropivacaine 0.25% and 1 ml (100 mcg) dexmedetomidine whilst patient in group C receive mixture of 30 mls of ropivacaine 0.5% and 1 ml of 0.9% normal saline. The primary endpoint was the onset and duration of sensory and motor block while secondary endpoint was to score patient and surgeon satisfaction.

Results

The onset time of sensory block in group D [15.29(3.24)] min was earlier than group C [18.09(3.26)] min and statistically significant ($p < 0.001$) while the onset time of motor block earlier in group C compare to group D but not statistically significant ($p= 0.71$). Both sensory and motor block durations were significantly longer in group D then group C with statistically significant ($p< 0.001$). In terms of satisfaction scoring group D has better scoring compare to group C among both surgeons and patients ($p < 0.001$).

Conclusion:

Low dose ropivacaine 0.25% with adjuvant of dexmedetomidine 100mcg is non inferior to the control group in providing anaesthesia for ESRF patients in AVF surgery.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

The number of end-stage renal failure (ESRF) cases rising worldwide. There are many treatment options for this disease but hemodialysis is preferred among others while waiting for renal transplant. Hemodialysis via arteriovenous fistula (AVF) is the procedure of choice because of less complication.

Creation of arteriovenous fistula can be performed under general anaesthesia, regional blocks or by local anaesthesia infiltration at the site of the procedure. Regional blocks are the technique of choice because of its sympatholytic effects that improve the success of vascular access. Brachial plexus block (BPB) significantly dilates the vessel and increase blood flow (Shyam M, Virendra A et al. 2015). BPB firstly performed in year 1889 by William S. Halsted. He injected cocaine into each roots of brachial plexus under direct visualization. In 1911 Hirshel first described the percutaneous technique for brachial plexus. Kulemkampff first described the classical supraclavicular approach to the brachial plexus. This technique is highly efficient because block performed at a point where three trunks present in compact form, hovewer it is associated with serious complications like pneumothorax, hemi diaphragmatic paralysis, intravascular injection and hematoma. These complications reduce the popularity of brachial plexus blockade. Introduction of nerve stimulator and ultrasound guidance increases the success rate of the block and reduces the complications. Ultrasound guidance aids the view of nerve bundle, visualizes the

spreading of local anaesthesia along the targeted nerves and helps avoiding key structures like blood vessels and pleura during needle advancement.

Different types of local anaesthesia used to perform peripheral nerve block. In current year ropivacaine is drug of choice compared to bupivacaine. Ropivacaine is an amino- amide local anaesthetic drug with long duration of action and with less cardiac and central nervous system toxicity. It's a pure "S" enantiomer. Various additives added to local anaesthesia to fasten the onset of block, prolong the duration of block and to improve postoperative pain management (Murphy, McCartney et al. 2000). Currently alpha- 2 adrenergic agonists are popular because of their sedative (Kwon, Hwang et al. 2015), analgesic (Patki, Bengali et al. 2015), antihypertensive, antiemetic action in addition to reducing the anaesthetic drug requirements.

Clonidine and dexmedetomidine are two well-known drugs from alpha-2 adrenergic groups. Dexmedetomidine has 8 times high specificity for alpha 2 receptor compared to clonidine. Adding Dexmedetomidine to local anaesthesia shown to fasten the onset of the block, prolong the duration of block, provide postoperative analgesia and reduce requirement of local anaesthesia (Das, Majumdar et al. 2014, Harshavardhana 2014, Patki, Bengali et al. 2015)

1.2 STUDY RATIONALE

Many studies conducted on dexmedetomidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block in upper limb surgery but patients involved in these studies mostly consist of ASA I, II. Patients involved in AVF procedures are mostly from ASA III. Using the same dosage of local anaesthesia for ESRF patients

might increase the risk of toxicity due to their altered pharmacokinetics. By conducting this study, we would like to prove that adding dexmedetomidine perineurally can further reduce the dose of local anaesthesia for brachial plexus block and still provide adequate block for AVF procedure.

1.3 LITERATURE REVIEW

Dexmedetomidine in supraclavicular plexus block

There are several studies that have demonstrated the usage of dexemedetomidine as adjuvant to ropivacaine in brachial plexus block. Kwon, Hwang et al. (2015) conducted a randomized, double blinded study included 60 patients undergoing wrist and hand surgery under ultrasound- guided supraclavicular brachial plexus block. Patient divided in two group: Group R (n = 30) 40 mls of ropivacaine 0.5% with 1 mcg/kg dexmedetomidine and Group RD (n = 30) 40 mls of ropivacaine 0.5% with 0.01ml/kg normal saline. Secondary objective of this study measure the onset and duration of the sensory and motor block, changes in mean arterial pressure(MAP) and heart rate. Onset time is shorter for sensory and motor block in Group RD ($P < 0.05$), duration of sensory and motor block in Group RD is increased compared Group R ($P < 0.05$). MAP and heart rate were unchanged in Group R, while in in Group RD MAP reduce continuously till 30 min after the block (88.9 ± 10.4, $P<0.001$) and heart rate decrease continuously till 20 minutes after the block (62.2 ± 10.9, $P< 0.001$) and remains relatively constant after that.

Anjan das et al. (2014) and Patki, Bengali et al. (2015) conducted similar studies with usage of dexmedetomidine and ropivacaine in supraclavicular plexus block. Results of this studies shows shorter onset of sensory and motor block while prolonged duration of sensory and motor block in intervention group. Postoperative analgesic requirement also delayed in Group RD in both studies.

Ultrasound and nerve stimulator usage in supraclavicular plexus block

Clinical usefulness of ultrasound technology for supraclavicular plexus block was studied by Chan, Wincent w. Sa et al (2003). Total of 40 healthy outpatients planned for elective upper limb surgery involved in this study. Ultrasound imaging was used to identify the brachial plexus prior to block, guide the needle to reach target nerves and visualize the pattern of local anaesthesia spread. Nerve stimulator used to further confirm needle placement. The block performed by 5 anaesthesiologists and successful in 95% (38 of 40) of cases after one attempt, even though only 2 investigators had prior ultrasound experience. The procedure took 9.0 ± 4.4 min. Postoperative complications included one case of Horner's syndrome and one transient paraesthesia (<48 h), but no pneumothorax. Ultrasound increase accuracy of needle placement for nerve localization and view local anaesthesia spread.

Xioming Liu, Xuan Zhao et al (2012) conducted a randomized control trial include 150 patients who scheduled for elective forearm surgery, using multiple nerve stimulation technique. Patient injected with ropivacaine 0.25% after obtaining a visible motor response at a current output of less than 0.5 mA and negative response lower than 0.2 mA. This study concluded that usage of nerve stimulator reduces further the

concentration of local anaesthesia from usual dosage of 0.5% or 0.75% to 0.25% with success rate higher than 90%.

Dexmedetomidine in severe renal disease patient

De Wolf, Fragen et al (2001) conducted a study to compare pharmacokinetics of dexmedetomidine in humans with impaired renal function and healthy volunteers. Six volunteers with severe renal disease (RD) (creatinine clearance < 30 ml/min) and six volunteers with normal renal function (C) (creatinine clearance > 80ml/min). Both group received demedetomidine infusion 0.6 µg/ kg over 10 min. venous blood drawn and plasma dexmedetomidine concentrations measured before, during and up to 12 hours after the infusion. The pharmacokinetics of dexmedetomidine in volunteers with severe renal disease were similar to healthy volunteers except for the elimination half-life which is shortened in renal disease group (RD 113.4_11.3 vs C 136.5_13.0 min; P_0.05). findings consistent with the observations in animal models that dexmedetomidine is cleared primarily by the liver.

CHAPTER 2: STUDY OBJECTIVES

2.1 GENERAL OBJECTIVES

To compare efficacy of adding dexmedetomidine 100mcg as adjuvant to ropivacaine 0.25% versus plain ropivacaine 0.5% for ultrasound guided supraclavicular brachial plexus block in arteriovenous fistula procedure.

2.1 SPECIFIC OBJECTIVES

a. To compare mean onset time of the sensory and motor block between 100mcg of dexmedetomidine in 0.25% ropivacaine and plain 0.5% ropivacaine
b. To compare mean duration time of the sensory and motor block between 100mcg of dexmedetomidine in 0.25% ropivacaine and plain 0.5% ropivacaine

Secondary objectives

a. To compare patient and surgeon satisfactory in between the two groups

2.3 RESEARCH HYPOTHESIS (NULL HYPOTHESES)

a. There is no difference in the onset of the sensory and motor block between 100mcg of dexmedetomidine in 0.25% ropivacaine and plain 0.5% ropivacaine
b. There is no difference in duration of the sensory and motor block between 100mcg of dexmedetomidine in 0.25% ropivacaine and plain 0.5% ropivacaine

CHAPTER 3: STUDY PROTOCOL & ETHICAL APPROVAL

3.1 STUDY PROTOCOL

Sampling method

Study design: Prospective, randomized, double blind controlled clinical trial

Study area: Operation theatre (OT) HUSM Kubang Kerian

Study period: 24 months

Study population:

End Stage Renal Failure (ASA III) patients scheduled for arteriovenous fistula procedure in Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian.

Subject criteria:

- Inclusion criteria:
    - Adult, age 18 to 65 years
    - End stage renal disease patients
- Exclusion criteria
    - Refusal for brachial plexus block
    - Allergy to dexmedetomidine or local anesthesia
    - Pregnancy
    - History of previous brachial plexus injury
    - Coagulopathy
    - Local skin site infection
    - Known neuropathy involving the arm undergoing surgery
    - Pre-existing severe bradycardia (heart rate < 50 bpm) or heart block of any degree

- Withdrawal criteria
    - Patient developed local anaesthetic toxicity (seizure)
    - Patient developed hemodynamically instability (bradycardia /hypotension)
    - Patient developed anaphylaxis reaction

Sample size estimation

Sample size calculated using "PS: Power and Sample Size Calculations" software version 3.0.10. The α value is set at 0.05 and power of study at 80%. The sample size is calculated using t-test. Calculation is derived from the study by (Kwon *et al.*, 2015)

1. Onset of sensory block

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 4.4. If the true difference in the experimental and control means is 3.2, we will need to study 31 experimental subjects and 31 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.

2. Onset of motor block

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 5.6. If the true difference in the experimental and control means is 4.1, we

will need to study 30 experimental subjects and 30 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.

3. Duration of sensory block

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 145.2. If the true difference in the experimental and control means is 214.3, we will need to study 8 experimental subjects and 8 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.

4. Duration of motor block

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 153.7. If the true difference in the experimental and control means is 162.4, we will need to study 15 experimental subjects and 15 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 sample study required is 31 for each group, with additional 10% for dropout rate, this study would require 34 patients in each group, giving a total of 68 patients.

Subject recruitments

Elective arteriovenous fistula procedure patients who meet the study criteria will be approached during their visit to plastic and reconstructive clinic and invite them to participate in this study. Each patient will be explained about the study along with a copy of the Patient information sheet. All their question will be answered.

Research tool:

- Dexmedetomidine 2mls vial with concentration 100mcg/ml,
- Ropivacaine 20mls vial with 7.5mg/ml
- 50 mm 22G insulated pencil point needle Stimuplex D Plus
- Nerve stimulator- Stimuplex HNS 12
- Ultra Sonographic machine Samsung Version HM70A, Manufactured in Korea with high frequency (10-15 MHZ) linear probe
- Lignocaine 2% 5 mls- for skin infiltration
- 2% chlorhexidine in 70% isopropyl alcohol solution for skin cleaning

Methodology

- Approval from Ethics Committee of Universiti Sains Malaysia (USM) will be taken before enrolment of the patients.
- Eligibility of the patients will be screened during patient visit to plastic and reconstructive clinic.
- Patients who fulfil the inclusion and the exclusion criteria selected.
- Procedure will be explained in details as well as patient is reassured of the privacy and confidentiality of the data obtained.
- Patient will be reassessed again one day prior to procedure and written consent will be obtained from the patient.
- All the patients were fasted for at least 6 hours
- No premedication given prior to operation for both groups of patients. Patients anti- hypertensive medication will be served as usual in the morning with sips of clear fluid
- Upon arrival in recovery bay, all patient will be monitored based on standard anaesthesia monitoring (non-invasive BP (NIBP), pulse oximetry (Sp02), electrocardiography (ECG) and baseline BP, HR will be documented before procedure
- Intravenous acess at least 20G will be inserted in non-operated hand
- Supraclavicular brachial plexus block will be performed at the recovery bay
- All selected patients will be randomized using software from website: www.randomizer.com
- Study drug will be prepared by general anaesthetic nurse

- Drug regime for supraclavicular brachial plexus will be prepared, which is
    - 30mls of Ropivacaine 0.25% + 100mcg dexmedetomidine (1mls) --- Group D
    - 30mls of Ropivacaine 0.5% + 0.9% normal saline (1mls) --- Group C
- Both patient and the researcher will be double- blinded, hence minimize assessment bias.
- Block will be performed by reasearcher.
- Patient will be monitored in operation theatre post procedure by the medical officer in charge of respective operation theatre.

Procedure

- The Supraclavicular area will be clean using clorohexidine and draped. The ultrasound probe also will be draped for the procedure.
- Patients were laid supine position and head turned away from the side that received the block.
- The ultrasound probe was placed in coronal oblique plane in supraclavicular fossa to visualize the subclavian artery.
- Once the subclavian artery visualised, the area lateral and superficial to it was explored until the plexus is seen. A caudad- cephalad rocking motion was used to find the ‘honeycomb’ appearance (hypoechoic).
- Skin will be infiltrated with 2% lignocaine 2-3 mls on the targeted needle insertion side.

- 22-G 50mm insulated block needle inserted in plane toward the brachial plexus, in a lateral to medial approach.
- Needle advancement observed in real time. Once reach the brachial plexus cluster, a nerve stimulator (stimuplex) was turned on and present of flexion of the fingers at current < 0.5 and >0.3 confirm proper placement of needle.
- After negative aspiration, 20 mls of the local anaesthesia will be injected at the point where the subclavian artery meets the first rib. The remaining 10mls will be injected to a point approximately level with the superior aspect of the subclavian artery, but not further then 1cm lateral to artery.

Intraoperative and post operative assessment

Sensory block assessment

- Sensory block was assessed by pinprick (23G needle) test in respective dermatomal distribution of nerves using 3- point scale: 0 = Normal sensation, 1 = Loss of sensation to pinprick , 2 = Loss of sensation to touch
- Onset of sensory block was defined by completion of the local anaesthetic infiltration to development of score 2.
- Sensory blockage is assessed every 5 minutes within the first 45 minutes following completion drug administration and hourly after the end of surgery till the regression of the sensory block.
- Duration of sensory block was defined as the time interval between onset of sensory block till complete recovery of sensation (score 0).

Motor block assessment

- Motor block was assessed using Bromage three- point scale: 0 = normal motor function with full flexion and extension of elbow, wrist and fingers, 1 = decreased motor strength with ability to move the fingers only, 2 = complete motor block with inability to move fingers
- Onset of motor block is defined by completion of local anaesthesia infiltration to development of score 2
- Duration of motor block is defined as the time interval between the onset of motor block and complete recovery of motor functions (score 0).

- Vital sings monitoring was recorded every 10 minutes intraoperatively.
- After period of 45 minutes in view of unsatisfactory blockade or failed blockade, the surgery proceeded under local infiltration of anaesthesia and the patient is excluded from study.
- At the end of the procedure the patients were asked to rate their satisfaction with the operative experience on 5 point satisfaction scale. 0 = extremely dissatisfied, 1 = dissatisfied, 2 = neither satisfied nor dissatisfied, 3 = satisfied, 4 = extremely satisfied
- The surgeon asked to rate satisfaction and patient cooperation during surgery on 5 point scale. 0 = extremely poor, 1 = poor, 2 = fair, 3 = good, 4 = excellent.
- Pain was assessed using Visual Analog Scale (VAS) hourly post operation. Visual analog scale evaluated as ; 0-2 no pain, 3-4 mild pain, 5-6 moderate pain, 7-8 severe pain, 9-10 excruciating pain.
- Upon score more then 4, patient given rescue analgesic iv tramal 50 mg.

- Any complication rises during intraoperative or postoperative period will be treated accordingly and will be documented.
- Any additional requirements of local anaesthesia during procedure due to pain by surgeon is recorded.

Data Analysis

Data will be entered and analysed using SPSS version 24. 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 1

Table 3.1:Intended statistical analysis

Objective Parameters	Statistical Analysis
Onset of sensory block	Independent t- test
Onset of motor block	Independent t- test
Duration of sensory block	Independent t- test
Duration of motor block	Independent t- test
Surgeons satisfaction score	Independent t- test
Patients satisfaction score	Independent t- test

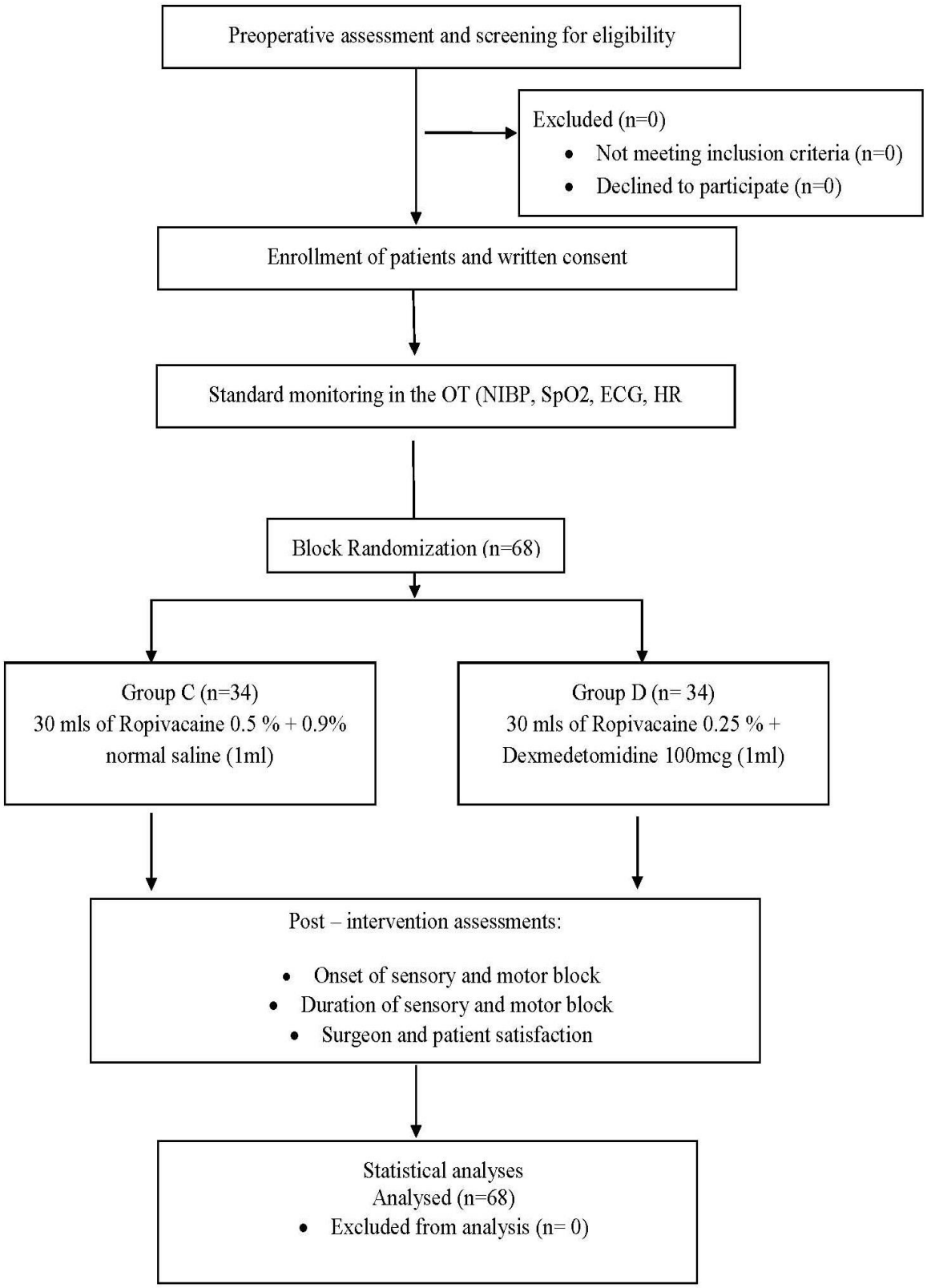

Figure 3.1: Study flow chart (prepared according to CONSORT 2010 Guidelines)

Gantt Chart

Project Activities	2017	2018			
	JULY - DEC	JAN- JULY	AUG-SEPT	OCT- NOV	DEC
Research activities					
Subject recruitments					
Data collection					
Data analysis					
Report writing					
Submission research					

Figure 3.2: Gantt Chart

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3.2 ETHICAL APPROVAL LETTER

UNIVERSITI SAINS MALAYSIA

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

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

19th March 2018

Dr. Prakash Seelan Mutthusamy
Department of Anaesthesiology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

Protocol Title : The Efficacy of Dexmedeitomidine 100 MCG as an Adjuvant to 0.25% Ropivacaine Versus 0.5% Plain Ropivacaine for Supraclavicular Brachial Plexus Block in Arteriovenous Fistula Surgery.

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 Man[illegible]alaysia (JEPeM-USM). Your study has been assigned study protocol code [illegible] which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **19th March 2018** until **18th March 2019.**

Study Site: Selected districts in Kelantan.

The following researchers also involve in this study:

1. Dr. Mohd Erham Mat Hassan
2. Dr. Wan 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. Patient & Data Collection Sheet

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

3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2017: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2017.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2017: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,

ASSOC. PROF. DR. AZLAN HUSIN
Deputy Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

UNIVERSITI SAINS MALAYSIA

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

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

Date of meeting : 18th January 2018
Venue : Meeting Room, Division of Research & Innovation, USM Kampus Kesihatan.
Time : 9.30 a.m – 2.00 p.m
Meeting No : 378

Members of Committee of the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM Universiti Sains Malaysia who reviewed the protocol/documents are as follows:

	Member (Title and Name)	Occupation (Designation)	Male/ Female (M/F)	Tick (✓) if present when above items, were reviewed
Deputy Chairperson:	Associate Professor Dr. Azlan Husin	Deputy Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	M	✓ (Deputy Chairperson)
Secretary:	Mr. Mohd Bazlan Hafidz Mukrim	Science Officer	M	✓
Members :				
1.	Mr. Harry Mulder	Community Representative	M	✓
2.	Professor Dr. Nik Hazlina Nik Hussain	Lecturer, School of Medical Sciences	F	✓
3.	Associate Professor Dr. Nor Azwany Yaacob	Lecturer, School of Medical Sciences	F	✓
4.	Mr. Sadasivam Ramiah	Community Representative	M	✓
5.	Associate Professor Dr. Sarimah Abdullah	Lecturer, School of Medical Sciences	F	✓
6.	Professor Dr. Zeehaida Mohamed	Lecturer, School of Medical Sciences	F	✓

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures 'SOPs), and Local Regulations and Standards in Ethical Review.

ASSOCIATE PROFESSOR DR. AZLAN HUSIN
Deputy Chairperson
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Universiti Sains Malaysia

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

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

25th February 2019

Dr. Prakash Seelan Mutthusamy
Department of Anesthesiology
School of Medical Sciences
Universiti Sains Malaysia
16150, Kubang Kerian, Kelantan.

Study Protocol Title: The Efficacy of Dexmedetomidine 100 MCG as an Adjuvant to 0.25% Ropivacaine versus 0.5% Plain Ropivacaine for Supraclavicular Brachial Plexus Block in Arteriovenous Fistula Surgery.

Dear Dr:

We wish to inform you that the Jawatankuasa Etika Penyelidikan Manusia, Universiti Sains Malaysia (JEPeM-USM) approved the proposed amendments in your study entitled, **"The Efficacy of Dexmedetomidine 100 MCG as an Adjuvant to 0.25% Ropivacaine versus 0.5% Plain Ropivacaine for Supraclavicular Brachial Plexus Block in Arteriovenous Fistula Surgery" [USM/JEPeM/17110575].**

Upon review of JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form, the following amendments have been approved:

1. Change in Supervisor – Dr Erham Mat Hassan replaced by Dr. Ariffin Marzuki Mokhtar.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

(PROF. DR. HANS AMIN VAN ROSTENBERGHE)
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

c.c Secretary
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

CHAPTER 4: MANUSCRIPT

4.1 TITLE PAGE

Title:

The Efficacy of Dexmedetomidine 100mcg as an Adjuvant to 0.25% Ropivacaine Versus 0.5% Plain Ropivacaine for Supraclavicular Brachial Plexus Block in Arteriovenous Fistula Surgery

Running head:

Dexmedetomidine as adjuvant to ropivacaine for supraclavicular brachial plexus block in arteriovenous fistula surgery

Authors:

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No conflict of interest between the authors and other research parties should be declared.

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