COMPARISON OF DIFFERENT SUBANAESTHETIC KETAMINE DOSES ON PERIOPERATIVE OPIOID CONSUMPTION IN MAJOR GYNAECOLOGICAL SURGERY

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TABLE OF CONTENTS

	Pages
ACKNOWLEDGEMENTS	ii
TABLE OF CONTENTS	iii
ABBREVIATIONS	vi
ABSTRAK	viii
ABSTRACT	xi
CHAPTER 1: INTRODUCTION	1
1.1 Introduction	1
1.2 Study Objectives	4
CHAPTER 2: STUDY PROTOCOL AND ETHICAL APPROVAL	5
2.1 Study Protocol	5
2.2 Ethics Approval Letter	41
CHAPTER 3: MANUSCRIPT	45
3.1 Title Page	45
3.2 Abstract	47
3.3 Introduction	49
3.4 Materials and Method	50
3.5 Results	54
3.6 Discussion	57

3.7 Conclusion 59

3.8 Conflict of Interest 59

3.9 Correspondence 59

3.10 References 60

3.11 Tables and Figures 62

CHAPTER 4: The MALAYSIAN JOURNAL OF MEDICAL SCIENCES FORMAT (GUIDELINES FOR AUTHORS) 67

CHAPTER 5: APPENDICES 80

5.1 Data Collection Form 80

5.2 Good Clinical Practice (GCP) certificate 84

6.3 Raw Data on SPSS softcopy 85

LIST OF TABLES AND FIGURES

Table 1: Demographic characteristics of participants

Table 2 : Comparison of perioperative opioid consumption and first PCA time by groups

Table 3 : Comparison of pain score for each hour post operative by groups

Table 4 : Comparison of mean arterial pressure (MAP) and heart rate (HR) for each time of measurements by groups

ABBREVIATIONS

ANOVA - Analysis of variance

APS - acute pain service

ASA – American society of anaesthesiologists

BP – Blood pressure

CD – Compact Disc

CNS – Central Nervous System

ECG - electrocardiogram

etCO2 - End tidal carbon dioxide

GOT – General Operation Theatre

HUSM – Hospital University Sains Malaysia

HR – heart rate

IHD – Ischaemic Heart Disease

IV- Intravenous

Kg- kilogram

MAC – Minimum alveolar concentration

MAP – Mean Arterial Pressure

Mcg – microgram

mg – milligram

MREC - Medical Research and Ethics Committee

N_2O – Nitrous oxide

NIBP – Non Invasive Blood Pressure

NMDA - N-methyl-D-aspartate

NRS - mean numerical rating scale

OT- Operation theatre

PCAM - patient-controlled analgesia morphine

RCT – Randomised Control Trial

SAE - Serious Adverse Event

SD - Standard deviation

SPSS – Statistical analysis software package

TOF - train of four

VAS – visual analogue scale

ABSTRAK

Latar belakang: Ketamine, antagonis reseptor N-methyl-D-aspartate (NMDA) pada dos subanaestetik (dos yang lebih rendah) digunakan sebagai suplimentasi rawatan analgesik. Dalam kebanyakan kajian yang diterbitkan, dos subanaestetik bolus intraoperatif yang berkesan adalah di antara 0.15 mg / kg hingga 0.5 mg / kg dan dos infusi dalam julat 0.12-0.2 mg / kg / jam. Kesan sampingan ke atas sistem saraf cerebrum meningkat pada dos lebih dari 0.3 mg / kg, jadi ini boleh dianggap sebagai had maksimum untuk dos bolus tetapi had minimum tidak diketahui. Tujuan kajian ini adalah untuk menilai sama ada dos yang lebih rendah iaitu 0.075mg / kg bolus dan infusi 0.06mg / kg /jam (1mcg / kg / min) akan memberikan pengurangan penggunaan opioid dalam tempoh perioperatif berbanding dengan had minumum semasa 0.15mg / kg bolus dengan infusi 0.12mg / kg / jam (2mcg / kg / min), seterusnya mengurangkan kesan sampingan ketamine.

Kaedah: 80 pesakit wanita dewasa yang menjalani pembedahan elektif ginekologi major dengan insisi garis tengah di Hospital Universiti Sains Malaysia dan Hospital Sultanah Bahiyah, Alor Setar, Kedah dipilih secara rawak untuk menerima sama ada Kumpulan A: (ketamine 0.15mg/kg IV bolus + 0.12mg/kg /jam infusi (2mcg/kg/min)) atau Kumpulan B: (ketamine 0.075mg/kg IV bolus + 0.06mg/kg /jam infusi (1mcg/kg/min)). Keputusan yang diukur adalah 1. Untuk membandingkan jumlah penggunaan opioid semasa tempoh pembedahan, 2. Untuk membandingkan purata jumlah penggunaan opioid selepas 24 jam pembedahan, 3. Untuk membandingkan masa pertama untuk permintaan ubat tahan sakit melalui mesin PCA 4. Untuk membandingkan skala kesakitan selepas pembedahan pada 2 jam, 6 jam, 12 jam dan 24 jam selepas pembedahan. Keputusan lain yang dipantau termasuk status hemodinamik

intraoperatif dan kemunculan manifestasi ke atas sistem saraf cerebrum antara dua kumpulan.

Keputusan: Penggunaan sub anestetik IV ketamine bolus 0.075mg / kg dan infusi 0.06mg / kg / jam (1mcg / kg / min) dalam kumpulan B tidak mempunyai perbezaan berbanding kumpulan A: IV ketamine bolus 0.15mg / kg dan infusi 0.12mg / kg / jam (2mcg / kg / min) kepada jumlah penggunaan opioid (morfin) 24 jam selepas pembedahan (p = 0.477), masa pertama untuk permintaan ubat tahan sakit melalui mesin PCA (p= 0.22) dan skala kesakitan pada 2 jam (p = 0.182), 6 jam (p = 0.58), 12 jam (0.149) dan 24 jam (p = 0.521) selepas pembedahan. Walau bagaimanapun terdapat perbezaan yang signifikan dalam penggunaan fentanyl intraoperatif dimana kumpulan A mempunyai penggunaan fentanyl yang lebih rendah iaitu 26.25ug ± 49.3 berbanding kumpulan B, 50ug ± 55.7 dengan nilai p = 0.047. Infusi ketamine pada 2 jam, mendapati MAP lebih rendah dalam Kumpulan A (min = 89.52mmHg, SD = 11.03) berbanding dengan Kumpulan B (min = 97.07mmHg, SD = 5.19) sebanyak 7.55 (perbezaan min = -7.55, 95% CI: -12.96, -2.13, t-statistik (df) = - 2.84 (33.42), p = 0.008). Walau bagaimanapun tidak terdapat perbezaan yang signifikan dalam MAP pada garis dasar, 10 minit dan 1 jam. Tidak ada subjek yang melaporkan kemunculan manifestasi ke atas sistem saraf cerebrum antara dua kumpulan walaupun kumpulan A menerima rejimen ketamine yang lebih tinggi.

Kesimpulan: Kami mengesyorkan untuk menggunakan dos iv ketamin bolus 0.15mg / kg dan infusi 0.12mg / kg / h (2mcg / kg / min) kerana pada dos ini terdapat pengurangan di dalam penggunaan opioid semasa pembedahan dan pada dos ini, tidak ada kesan sampingan pada hemodinamik atau psikotomimetik. Walau bagaimanapun, dos bolus 0.075mg / kg dan infusi 0.06mg / kg / jam (1mcg / kg / min) mungkin berpotensi untuk menjadi dos subanestetik yang berkesan kerana walaupun pada dos

yang sangat rendah, ia menunjukkan keputusan yang serupa dengan dos standard dari segi jumlah penggunaan opioid selepas 24 jam pembedahan, masa pertama untuk permintaan ubat tahan sakit dan skala kesakitan selepas pembedahan pada 2 jam, 6 jam, 12 jam dan 24 jam.

ABSTRACT

Background: Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, at a subanaesthetic dose (lower dose), has been used preemptively as an adjuvant to analgesic treatment. In majority of studies, the effective intraoperative bolus doses used are from 0.15 mg/kg to 0.5 mg/kg and infusions in the range of 0.12-0.2 mg/kg/h. CNS manifestation incidence is higher at doses above 0.3 mg/kg, thus this is considered as the upper limit for bolus doses, but the lower limit has not been studied. The aim of this study is to evaluate whether a lower dose of ketamine 0.075mg/kg bolus with infusion of 0.06mg/kg/h (1mcg/kg/min) will offer the same reduction in perioperative opioid consumption as compared to the current lower limit of 0.15mg/kg bolus with infusion of 0.12mg/kg/h (2mcg/kg/min).

Methods: 80 adult female patients who underwent elective major gynaecology surgery in Hospital Universiti Sains Malaysia and Hospital Sultanah Bahiyah, Alor Setar, Kedah were randomly assigned to receive either Group A: (ketamine 0.15mg/kg IV bolus + 0.12mg/kg /h infusion (2mcg/kg/min)) or Group B: (ketamine 0.075mg/kg IV bolus + 0.06mg/kg /h infusion (1mcg/kg/min)). The measured outcomes were: 1. The mean total opioid consumption during the intraoperative period, 2. The mean total opioid consumption within 24 hours after surgery, 3. The mean time for first patient-controlled analgesia (PCA) demand between the two groups and 4. The mean numerical rating scale (NRS) of pain score at 2 hours, 6 hours, 12 hours and 24 hours post-surgery. Other outcomes monitored include the intraoperative hemodynamic status and presences of CNS manifestation (vivid dreams, hallucinations, confusion and irrational behaviour)**.**

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Results: There were no significant statistical difference between group A and B in terms of total opioid consumption (morphine) 24 hours postoperatively (p= 0.477), meantime for first patient-controlled analgesia (PCA) demand (p=0.22) and mean numerical rating scale (NRS) at 2 hour (p=0.182), 6 hour (p=0.58), 12 hour (0.149) and 24 hour (p=0.521). However, there was a significant statistical difference in the mean intraoperative fentanyl consumption, where group A had lower mean fentanyl consumption of 26.25 ug ± 49.3 compared to group B of 50ug ± 55.7 with a p-value 0.047. With prolong ketamine infusion at 2 hours, there was a lower mean MAP in ketamine Group A (mean=89.52mmHg, SD=11.03) compared to Group B (mean=97.07mmHg, SD=5.19) and a p=0.008. However, there was no significant statistical difference in the mean MAP at baseline, 10 min and 1 hour. Both groups had no reported CNS manifestation.

Conclusion: We recommend to adhere to the current dose of IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) as at this dose, intraoperative opioid consumption is lower. Nevertheless, a bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) may hold promise as even at this very low dose, this regime showed similar results to standard dose in terms of postoperative opioid requirement, first analgesic request and pain score. However, further research is needed to confirm the current findings.

CHAPTER 1: INTRODUCTION

1.1 Introduction

Gynaecological abdominal surgery is associated with moderate to severe postoperative pain. (1) Multiple analgesic techniques have been developed to treat postoperative pain after open gynaecological surgery. Options include epidural analgesia and patient-controlled analgesia (PCA) morphine, both of which are effective therapies for managing pain after major abdominal surgeries.(2)

Major gynecologic surgery, especially radical pelvic dissection, upper abdominal exploration and tumour reduction are associated with a high risk of thromboembolic events, making surgeons opt for PCA morphine over epidural for early initiation of thromboembolism prophylaxis (3). Proper timing of epidural catheter removal can be affected, and there is a potential risk of an epidural haematoma. Epidural analgesia is a more invasive technique requiring the placement of a catheter in the epidural space. However placing an epidural may be time-consuming, carries failure possibility and is contraindicated in patients with coagulopathy.

Opioids are widely used during the perioperative period because of their good analgesic effect. However, this drug is associated with respiratory depression, hypotension, sedation, nausea and vomiting, urinary retention and postoperative ileus. Side effects related to opioid analgesia in surgical patients can lead to increased institutional costs and longer hospital length of stay (4).

Recent studies have pointed out that peripheral and central neuronal sensitisation play a vital role in the development of hyperalgesia and allodynia at the postoperative site in the acute setting. If uncontrolled, it may lead to subsequent persistent

postoperative pain or chronic pain thus it is vital to control pain intraoperatively (5). Given various of mechanisms involved in pain pathophysiology, it is suggested to employ a multimodal analgesia regime that uses a combination of opioids and other groups of analgesic drugs, in turn reducing the quantity of opioids used.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist at the dose of 1 mg per kg IV has routinely been used as an induction agent, in hemodynamically unstable patients as it has minimal negative effects on the cardiorespiratory system. Ketamine has effects in the central nervous system that cause a dissociative anaesthetic state. However, emergence hallucinations and nightmares have hindered the use of large-dose ketamine (6). At subanaesthetic dose (lower dose) it has been used preemptively as an adjuvant to analgesic treatment.

The NMDA receptor exerts its pain processing effect in the dorsal horn of the spinal cord. In response to tissue injury or trauma, the primary nociceptive neuron triggers a release of glutamate in the dorsal horn of the spinal cord, which binds to NMDA receptors on second-order neurons (7). By blocking the NMDA receptor, ketamine attenuates these centrally mediated pain processes, reducing acute pain and potentially preventing chronic pain (8). Ketamine has been shown to be useful via variable routes in reducing acute postoperative pain and analgesic requirement in various types of surgery. (9)

At subanaesthetic dose, it avoids unfavourable central nervous system (CNS) side effects and also avoids its direct effect on the sympathetic nervous system. Many studies have extensively studied subanaesthetic ketamine, but it is uncertain of what is considered the ideal dose of subanesthetic ketamine. In the majority of the published studies, effective intraoperative bolus dose used are from 0.15 mg/kg to 0.5 mg/kg, and

infusions of 0.12-0.2 mg/kg/h (8). CNS manifestation incidence is higher at doses above 0.3 mg/kg, thus this is considered as the upper limit for bolus doses, but the lower limit has not been studied (8).

Many studies done in the Asian population also proves that subanaesthetic ketamine provides reduction in perioperative opioid consumption and pain scores. (10-12) However given the difference in the pharmacogenetics of the Asian population, we postulate that a lower dose of ketamine may be as effective in terms of analgesic properties and there are also no similar study performed in Malaysia and this study may thus provide vital information in improving current anaesthetic practice in Malaysia

The aim of this study was to evaluate whether a lower dose of 0.075mg/kg bolus with infusion of 0.06mg/kg/h (1mcg/kg/min) will offer the same reduction in perioperative opioid consumption as compared to the current lower limit of 0.15mg/kg bolus with infusion of 0.12mg/kg/h (2mcg/kg/min), thus further reducing the side effects of ketamine.

1.2 : Study Objectives:

1.2.1 General Objective:

To evaluate the effect of lower dose of subanaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) on perioperative opioid consumption in major gynaecological surgery compared to IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min).

1.2.2 Specific Objectives

1. To compare mean total opioid consumption during the intraoperative period between the two groups.
2. To compare mean total opioid consumption within 24 hours after surgery between the two groups.
3. To compare the mean time for first PCA demand between the two groups
4. To compare the mean numerical rating scale (NRS) for pain at 2 hours, 6 hours, 12 hours and 24 hours post-surgery between the two groups

1.2.3 Secondary Objectives

1. To compare intraoperative hemodynamic status of both groups
2. To compare incidence of CNS manifestation (vivid dreams, hallucinations, confusion, irrational behaviour) between two groups

CHAPTER 2: STUDY PROTOCOL AND ETHICAL APPROVAL

2.1 Literature Review

Ketamine has been widely used at subanaesthetic dose in various types of operation for perioperative pain management as shown by Laskowski et al. (20) in 2011 who published a systematic review of 70 studies from 1966 to 2010 that looked at only IV ketamine for perioperative analgesia. Laskowski observed that there was a reduction in total opioid consumption and an increase in time for the first analgesia request seen across all studies ($p<0.001$) which was profound especially in painful procedures such as upper abdominal and thoracic procedures.

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A single bolus dose IV ketamine of 0.15mg/kg prior to surgical incision was used by Roytblat et al. (13) and Menigaux et al. (14) resulted prolonged time for first request for analgesic drugs and enhanced postoperative analgesia. A study in Hong Kong by Kwok et al. 2004 also showed similar results of subanaesthetic ketamine dose of 0.15mg/kg reduces the perioperative opioid requirement and pain scores even in Asian populations.

However, in major gynaecological surgeries, two studies done in 2008 by Aubrun (17) and 2016 by Garcia –Navia et al. (18), showed that a single bolus dose of subanaesthetic ketamine only, did not reduce the perioperative opioid requirement. Thus by adding an infusion of ketamine to this regime may offer a reduction in perioperative opioid consumption.

Andrew W Gorlin et al. (8) who conducted a systematic review regarding intravenous subanesthetic ketamine for perioperative analgesia stated at subanesthetic ketamine doses of iv bolus < 0.3mg/kg or infusion of 0.1-0.2mg/kg/hour, has minimal physiologic

impact and low incidence of mild psychomimetic symptoms. Subanesthetic ketamine improves pain scores and reduces perioperative opioid consumption in various surgical procedures. In the majority of the published studies, effective intraoperative bolus dose used are from 0.15 mg/kg to 0.5 mg/kg, and infusions of 0.12-0.2 mg/kg/h (8) CNS manifestation incidence is higher at doses above 0.3 mg/kg, thus this is considered as the upper limit for bolus doses, but the lower limit has not been studied.

Even though the current lower limit of ketamine bolus dose of 0.15mg/kg and infusions of 0.12-0.2mg/kg/h has proven to provide effective analgesia with minimal side effects, we postulate that an even lower dose of 0.075mg/kg bolus with infusion of 0.06mg/kg/h (1mcg/kg/min) may offer similar analgesic effect. Given the difference in the pharmacogenetics of the Asian population, a lower dose of ketamine may be adequate in terms of analgesic properties. Furthermore, no similar study has been performed in Malaysia.

2.2 Research Objectives

2.2.1 General Objectives

To evaluate the effect of a lower dose of sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/hour (1mcg/kg/min) on perioperative opioid consumption in major gynaecological surgery compared to IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/hour (2mcg/kg/min)

2.2.2 Primary Objective

1. To compare mean total opioid consumption during the intraoperative period between the two groups.
2. To compare mean total opioid consumption within 24 hours after surgery between the two groups.
3. To compare the mean time for first PCA demand between the two groups
4. To compare the mean numerical rating scale (NRS) for pain at 2 hours, 6 hours, 12 hours and 24 hours post-surgery between the two groups

2.2.3 Secondary Objectives

1. To compare intraoperative hemodynamic status of both groups
2. To compare incidence of CNS manifestation (vivid dreams, hallucinations, confusion, irrational behaviour) between two groups

2.3 Research Hypotheses

1. There is no difference between sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) and IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) on total opioid consumption during intraoperative period
2. There is no difference between sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) and IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) on total opioid

consumption 24 hours postoperatively

3. There is no difference between sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) and IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) on the mean time for first patient-controlled analgesia (PCA) demand
4. There is no difference between sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) and IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) on the mean numerical rating scale (NRS) at 2 hour, 6 hour, 12 hour and 24 hour post surgery
5. There is no difference between sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) and IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) on the intraoperative hemodynamic status of both groups
6. There is no difference between sub anaesthetic IV ketamine bolus of 0.075mg/kg and infusion of 0.06mg/kg/h (1mcg/kg/min) and IV ketamine bolus of 0.15mg/kg and infusion of 0.12mg/kg/h (2mcg/kg/min) on the incidence of CNS manifestation (vivid dreams, hallucinations, confusion, irrational behaviour) between two groups

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Comment [p4]: Addition of hypothesis for secondary objective

2.4 Research Methodology

2.4.1 Study design

This was a randomised, double-blinded clinical trial, with a 1:1 allocation ratio.

2.4.2 Study period

December 2017 – December 2019

2.4.3 Study population

Elective surgical patients who were planned for general anaesthesia in Hospital Sultanah Bahiyah Alor Setar and Hospital Universiti Sains Malaysia (HUSM)

2.4.4 Study setting

General Operation Theatre Hospital Sultanah Bahiyah, Alor Setar, Kedah and General Operation Theater HUSM

2.4.5 Sampling method

Purposive sampling

2.4.6 Interventions

Patient were randomly assigned to 2 groups (by computer-generated randomisation):

Group A: (ketamine 0.15mg/kg IV bolus + 0.12mg/kg /h infusion (2mcg/kg/min))

Group B: (ketamine 0.075mg/kg IV bolus + 0.06mg/kg /h infusion (1mcg/kg/min))

2.4.7 Blinding

Both the study subjects and assessors were blinded for the allocation arms

2.4.8 Eligibility Criteria

Inclusion criteria

1. Age 18 -65 years old
2. American Society of Anaesthesia (ASA) I – II

3. Elective major gynaecology surgery with midline incision under general anaesthesia

Exclusion criteria

1. Patient with chronic pain or drug and alcohol abuse
2. Patient with known heart disease: IHD or uncontrolled hypertension
3. Patients with a history of psychiatric disorder
4. Patients with renal or hepatic dysfunction
5. Known allergic to study drugs
6. Pfannenstiel incision or pubic incision excluded as the level of pain between these two incisions are different, lesser in Pfannenstiel incision
7. Pregnant patients
8. Emergency surgery

Withdrawal criteria:

1. The patient decided to withdraw from the study.
2. If an adverse event occurs
3. Death not related to study conducted which occurs during the study period
4. Withdrawn subjects are not replaced as the sample size is calculated to counter patient withdrawal with a dropout rate of 20%.

2.5 Sample Size Estimation

The formulae for calculation for sample size are as follows:

$$n = \frac{2\sigma^2}{\Delta^2} (Z\alpha+Z\beta)^2$$

$\alpha = 0.05$ σ = standard deviation Δ = estimated detectable mean difference $Z\alpha = 1.96$, when $\alpha = 0.05$ $Z\beta=0.84$ (when power 80%)

For objective 1, we need 33 participants in each group to detect the difference of 0.07ug/kg/min in mean total opioid consumption during intraoperative period between ketamine group and placebo (SD was estimated as 0.1 (15) with 80% power and alpha 0.05 (using Power & Sample Size Calculations, Version 3.0.10, Dupont and Plummer, 1997). 20% is added for the drop out participants. Therefore sample size, n = 33 + 0.2(33) = 39.6 approximately 40 patients for each group.

For objective 2, we need 21 participants in each group to detect the difference of 14 mg in mean total opioid consumption within 24 hours after surgery between ketamine group and placebo group (SD was estimated as 16 (14) with 80% power and alpha 0.05 (using Power & Sample Size Calculations, Version 3.0.10, Dupont and Plummer, 1997). 20%

is added for the drop out participants. Therefore sample size, n = 21 + 0.2(21) = 25.2 approximately 26 patients for each group.

For objective 3, we need 4 participants in each group to detect the difference of 1.1hours in meantime for first patient-controlled analgesia (PCA) demand between ketamine and placebo group (SD was estimated as 0.5 hours (12) with 80% power and alpha 0.05 (using Power & Sample Size Calculations, Version 3.0.10, Dupont and Plummer, 1997). 20% is added for the drop out participants. Therefore sample size, n = 4+ 0.2(4) = 4.8 approximately 5 patients for each group.

For objective 4, we need 8 participants in each group to detect the difference of 1.3 in mean numerical rating scale (NRS) at 12 hours post-surgery between ketamine and placebo group (SD was estimated as 0.9 (16) with 80% power and alpha 0.05 (using Power & Sample Size Calculations, Version 3.0.10, Dupont and Plummer, 1997). 20% is added for the drop out participants. Therefore sample size, n = 8+ 0.2(8) = 9.6 approximately 10 patients for each group.

Thus, a total of 80 participants is needed with 40 patients per each group.

2.6 Methodology

- Approval from the Ethics Committee will be taken before enrollment of the patients. Eligibility of the patients will be screened by principal investigator during preoperative assessment round which

is usually done at least a day before the scheduled surgery

- Written consent will be obtained by the principal investigator from all selected patients who fulfil the inclusion and the exclusion criteria.
- Consented Patients will be randomized into two arms using computer-generated randomisation.

  Group A:

  ketamine 0.15mg/kg IV bolus + 0.12mg/kg /h infusion (2mcg/kg/min)

  Group B:

  ketamine 0.075mg/kg IV bolus + 0.06mg/kg /h infusion (1mcg/kg/min)
- On the day of surgery, an indistinguishable 10ml syringe was prepared by nurses who are not involved in this study, in the post anaesthesia care unit: where group A received ketamine (dilution 5mg/ml) and group B received (2.5mg/ml). The anesthesiologist, the surgeons, other nursing staff and patients were blind to the group assignment until the end of the study.
- In OT, the monitoring was identical for all women. The patient will be monitored using non-invasive setup (Marquette VE10b® GE Monitor) 3 leads ECG, NIBP using appropriate cuff and SPO2 and capnography monitoring.
- BP and HR are recorded at the starting of induction, at 10 minutes then at 30 minutes intervals until completion of the operation.
- The anaesthetic management of all patients will be standardised. For all patients, they will induce with IV propofol 2 mg/kg, IV fentanyl 2mcg/kg,

IV rocuronium 0.6mg/kg. Proper size endotracheal tube (PVC, IDEALCARE, Malaysia, 2018) will be used for tracheal intubation. Anaesthesia will be maintained with sevoflurane in a 50% oxygen; air mixture with minimal flow ventilation of 2 liters/ minute, keeping MAC 1.0

- IV morphine of 0.1mg/kg was given post induction for postoperative analgesia.

Group A will receive:

IV ketamine 0.15mg/kg bolus after induction, followed by 0.12mg/kg /h infusion (2mcg/kg/min) using infusion pump (Injectomat MC Agilla, Fresenius Kabi, France, 2016), stopping 30 minutes before completion of operation.

Group B will receive:

IV ketamine 0.075mg/kg bolus after induction, followed by 0.06mg /kg /h infusion (1mcg/kg/min) using infusion pump (Injectomat MC Agilla, Fresenius Kabi, France, 2016), stopping 30 minutes before completion of operation.

- Fentanyl boluses of 1mcg/kg will be used as rescue analgesia during anaesthesia with an increase of 20% in blood pressure or if the heart rate was higher than 100 beats per minute. The total amount of fentanyl used was recorded at the end of the procedure.

- Rocuronium 0.2mg /kg boluses were given for intraoperative muscle relaxation to maintain moderate neuromuscular block to train of four stimulation 1-3 (TOF)

- Neuromuscular blockade was antagonised using IV neostigmine 0.05mg/kg

and IV atropine 0.015mg/kg after the reappearance of T4 in TOF.

- Both groups will be prepared; IV PCA morphine pump of lockout time 5minutes, dilution 1mg/ml with no background infusion using PCA pump Bbraun, Germany, 2016. No other analgesics are used.
- In the ward, the Numerical rating scale (NRS) scores for pain were recorded at 2, 6, 12, and 24 h postoperatively by trained acute pain service (APS) nurses
- The incidence of CNS manifestation of ketamine was recorded postoperatively by qualified APS nurses at 2, 6, 12, and 24 hours postoperatively
- Patients are asked regarding the presence of vivid dreams and hallucinations which is recorded as yes or no
- Ward nurses in charge of patients were asked regarding the existence of confusion and irrational behaviour which is recorded as yes or no
- Patient's outcome and patient satisfaction regarding pain management will be evaluated.

2.7 Adverse Event

Adverse effects reported from drug product information for ketamine are listed below:

- Emergence reactions (e.g. vivid dreams, hallucinations, confusion, irrational behaviour)
- Increased muscle tone sometimes resembling seizures

- Temporary hypertension and tachycardia, hypotension, bradycardia and arrhythmias
- Apnoea, laryngospasm
- Respiratory depression
- Diplopia or nystagmus
- Nausea and vomiting
- Hypersalivation

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

2.7.1 Reporting Adverse Event

The following will be notified as adverse events:

- Adverse effects due to ketamine administration
- Medical conditions or signs or symptoms that were absent before starting study treatment
- Medical conditions or signs or symptoms that were present before starting study treatment and worsen (increasing severity or frequency) after starting study treatment
- Abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy
- Any doubtful event should be treated as an Adverse Event
- Serious Adverse Event (SAE) is defined as any adverse event resulting in death

or any life-threatening that places the subject at immediate risk of death from the reaction as it occurred.

2.7.2 Detecting and Documenting Adverse Events

Information about all adverse effects, whether volunteered by the patient, discovered by the investigator during questioning or detected through physical examination, laboratory test or other means, would be recorded and followed up as appropriate.

All events documented as SAE will be reported within 24hours to the Medical Research and Ethics Committee (MREC). The investigator should not wait to receive additional information to document the SAE before notifying MREC fully. A fax SAE form detailing relevant aspects of the SAE in question should follow telephone report of SAE. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious drug reactions to the regulatory authorities.

2.7.3 Treatment and Follow Up of SAE

Should any adverse reaction occur, the symptoms will be managed accordingly, and the patient will not be discharged from the ward and followed up until symptoms resolve. Referral to psychiatry team/ medical and ophthalmology team if indicated

Regularly scheduled visits until satisfactory clinical resolution of adverse effects are achieved.

After discharged from the ward, subjects will be followed up for safety evaluation during the two weeks in the anaesthetic clinic.

2.8 Study Visits and Procedures

The total duration of patient involvement is the day of surgery until 24 hours postoperatively.

Intraoperatively total fentanyl consumption will be recorded: from starting of operation until finish operation.

Patient's intraoperative haemodynamic status is monitored by systolic blood pressure, diastolic blood pressure and heart rate at starting of induction, at 10 minutes then at 30 minutes intervals until completion of the operation.

Postoperative time for first patient-controlled analgesia morphine (PCAM) demand is recorded.

Pain score using Numerical rating scale (NRS) and incidence of CNS manifestation - vivid dreams, hallucinations, confusion, irrational behaviour: (yes/no) in both groups at 2,6,12, 24 hours postoperatively is recorded.

The total morphine consumption over 24 hours via PCAM is recorded postoperatively

2.9 Statistical Analysis

All analysis will be using SPSS software version 24. Results were presented as mean and standard deviation (SD). The data from 2 groups were analysed using independent t-test for numerical data and chi-square for categorical data. Additionally, one way and two-way analysis of variance with repeated measures (ANOVA) were used to determine the effects of group, time and group-time interaction. Differences were considered statistically significant when the P-value < 0.05. If there were statistical significant findings within group analysis, further analysis with multiple paired t-test with Bonferroni correction (p-value =0.05/55=0.0009) was applied.

2.10 Risk and Benefit to Study Participants

As stated in the literature above, there are no serious side effects known to be caused by ketamine at the dose given. The study procedures are all routine procedures for the surgery done. There is thus a minimal risk for the subjects. This study does not present any direct benefit to the participants. However, the study does provide a better understanding of the drug ketamine.

2.11 Ethics of This Study

The study will be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

2.11.1 Informed Consent/Assent Process

Routine preoperative assessment will be done by an anaesthetist (other than principal investigator/ study team). Patients that fit inclusion criteria will be alerted to the

principal investigator and team. Patients are then approached by the principal investigator/ study team to be informed regarding the study. If they are interested, a patient information sheet will be given and explained to them. If they are willing to participate, the consent forms will be signed and dated.

2.11.2 Privacy and Confidentiality

Subject's name will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient's identifiers will be used on subject datasheets. All data will be entered into a computer that is password protected. On completion of the study, data will be copied to CDs and the data in the computer erased. CDs and any hardcopy data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after the period of storage. Subjects will not be allowed to view their study data, as the data will be consolidated into a database. Subjects can write to the investigators to request access to study findings.

2.12 Conflict of Interest

The investigators declare they have no conflict of interest

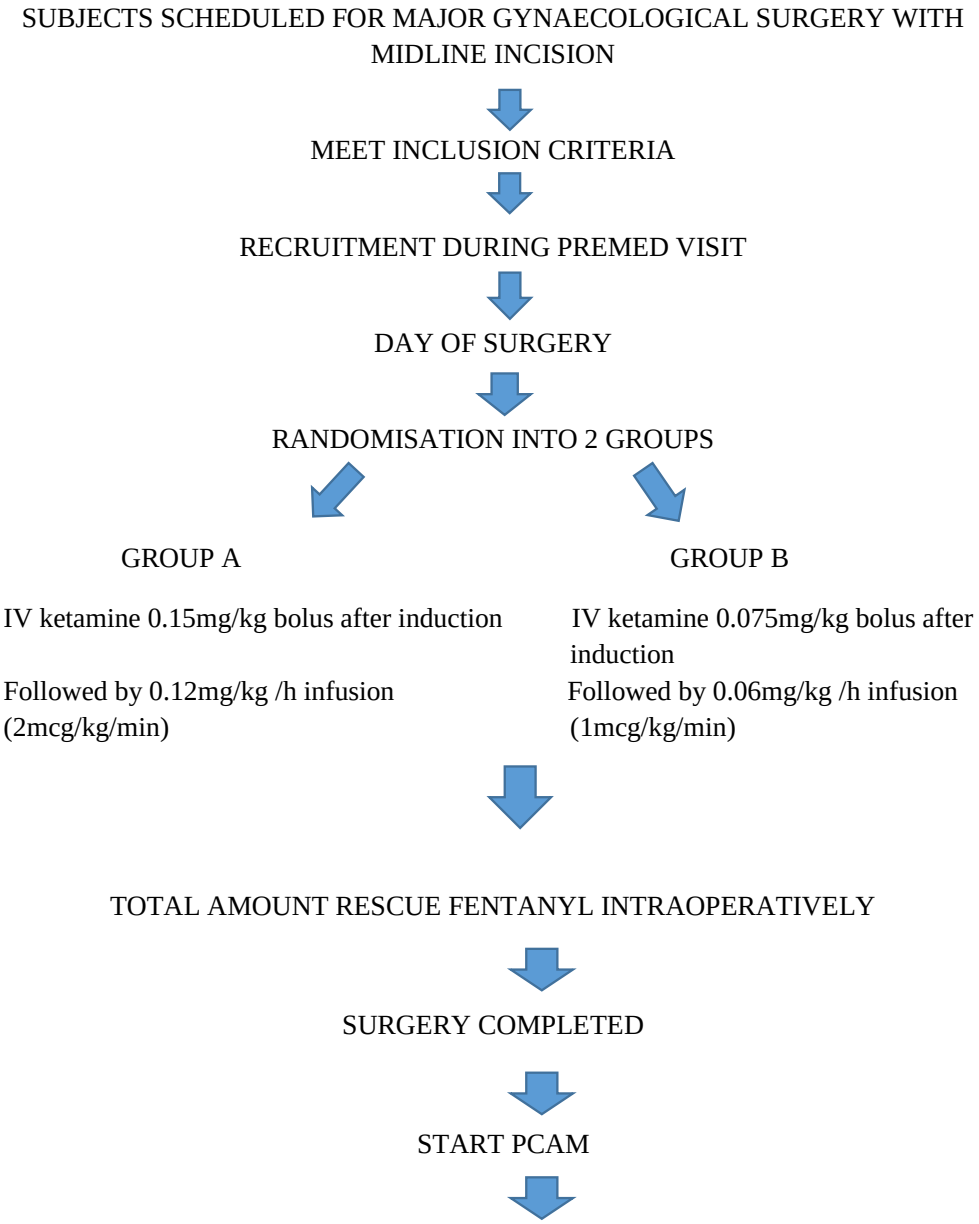
2.13 Publication Policy

No personal information will be disclosed, and subjects will not be identified when the findings of the survey are published

2.14 Termination of Study

The sponsor may decide to terminate the study at any time. Subjects will be informed if the study is terminated and follow up visits will be arranged if needed.

2.15 Study Flow Chart



ASSESSMENT OF PAIN SCORE AND CNS MANIFESTATION IN BOTH GROUP

AT 2,6,12, 24 HOURS POST OPERATIVELY

TOTAL MORPHINE CONSUMPTION VIA PCAM OVER 24 HOURS RECORDED

2.16 Patient information and consent form

MAKLUMAT KAJIAN

Tajuk Kajian : ***PERBANDINGAN DI ANTARA DUA DOS SUB ANESTETIK KETAMINE TERHADAP JUMLAH OPIOID YANG DIGUNAKAN SEMASA DAN SELEPAS PEMBEDAHAN GINEKOLOGI MAJOR***

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PENGENALAN

Anda adalah dipelawa untuk menyertai satu kajian penyelidikan secara sukarela. Kajian ini adalah berkaitan dengan ubat Ketamine yang diberi sebagai ubat tahan sakit semasa pembedahan. Kajian ini bertujuan untuk membandingkan dua dos ketamine yang berbeza terhadap jumlah ubat tahan sakit opioid yang digunakan semasa dan selepas pembedahan.

Adalah penting bagi anda membaca dan memahami maklumat kajian sebelum anda bersetuju untuk menyertai kajian penyelidikan ini. Sekiranya anda menyertai kajian ini, anda akan menerima satu salinan borang ini untuk simpanan anda.

Penyertaan anda di dalam kajian ini dijangka mengambil masa dari mula pembedahan sehingga 24 jam selepas pembedahan. Seramai 80 orang dijangka akan menyertai kajian ini.

TUJUAN KAJIAN

Kajian ini bertujuan untuk membandingkan dua dos ketamine yang berbeza terhadap jumlah penggunaan ubat tahan sakit semasa dan 24 jam selepas pembedahan. Kajian ini juga akan membandingkan masa untuk permintaan pertama ubat tahan sakit selepas pembedahan dan membandingkan tahap kesakitan pada 2,6,12 dan 24 jam selepas pembedahan.

KELAYAKAN PENYERTAAN

Salah seorang kakitangan kajian akan membincangkan kelayakan anda untuk menyertai kajian ini. Adalah penting anda berterus terang kakitangan tersebut.

Kajian ini akan melibatkan

1. Individu sihat atau hanya mengalami penyakit yang tidak serius yang akan menjalani pembedahan ginekologi major secara elektif dibawah pembiusan penuh dimana insision yang dilakukan adalah secara midline
2. Berumur 18 hingga 65 tahun

Kajian ini tidak akan melibatkan

1. Individu ada sakit yang kronik atau masalah penggunaan dadah dan arak
2. Pesakit yang ada sakit jantung
3. Pesakit yang ada masalah psikiatrik
4. Pesakit yang ada kerosakan buah pinggang atau hati
5. Pesakit yang ada alahan terhadap ubat kajian

Kriteria pengeluaran dari kajian :

1. Pesakit menarik diri dari kajian
2. Jika pesakit mengalami kesan sampingan yang serius
3. Kematian yang tidak berkaitan dengan kajian yang dijalankan semasa tempoh kajian

PROSEDUR KAJIAN

Penyelidikan ini mendapat kelulusan dari pihak Lembaga Etika dan CRC unit Hospital Sultanah Bahiyah. Pesakit yang dipilih mengikut kriteria yang ditetapkan akan diterangkan mengenai penyelidikan ini dan jika bersetuju perlu menandatangani borang keizinan peserta.

Peserta kajian akan dibahagikan kepada dua kumpulan A dan B secara rawak. Selepas pembiusan penuh kumpulan A akan menerima ubat ketamine secara bolus (diberi secara cepat melalui vena) 0.15mg/kg IV diikuti infusi ketamine 0.12mg/kg/h (2mcg/kg/min) dan kumpulan B akan menerima ubat ketamine secara bolus 0.075mg/kg bolus diikuti oleh infusi ketamine 0.06mg/kg/h (1mcg/kg/min)

Peserta dan pengamal perubatan yang bertugas memberi bius tidak akan mengetahui pembahagian kumpulan tersebut. Pada hari pembedahan ubat ketamine akan disediakan oleh jururawat post anaesthesia care unit yang tidak terlibat semasa proses kajian dijalankan dalam dewan bedah.

Semua peserta akan menerima bius penuh dan pemantauan yang sama mengikut standard yang ditetapkan. Ubat fentanyl sejenis ubat tahan sakit opioid akan digunakan sebagai ubat tahan sakit tambahan jika pesakit menunjukkan tanda- tanda sakit and jumlah fentanyl yang digunakan akan direkod di akhir pembedahan. Kedua –dua kumpulan akan diberi IV Patient controlled analgesia morphine (PCAM) untuk ubat tahan sakit selepas pembedahan.

Di wad, jururawat terlatih acute pain service (APS) akan merekod tahap kesakitan dan kewujudan mimpi/halusinaasi/ kekeliruan atau tingkah laku yang tidak rasional pada 2,6,12 dan 24 jam lepas pembedahan. Jumlah ubat PCAM akan direkod 24 jam selepas pembedahan.

KESAN SAMPINGAN

Ubat ini mungkin boleh menyebabkan mimpi yang nyata, halusinasi, kekeliruan, tingkah laku tidak rasional, tona otot meningkat, darah tinggi atau rendah, dengupan jantung laju atau perlahan, dengupan jantung tidak sekata, apnea, laryngospasm, pernafasan perlahan, diplopia, nystagmus, mual dan muntah, hypersalivasi. Namun kesan tersebut jarang berlaku pada dose yang digunakan dalam kajian ini.

Sila maklumkan kepada kakitangan kajian sekiranya anda menghadapi sebarang masalah atau mempunyai sebarang maklumat penting yang mungkin mengubah persetujuan anda untuk terus menyertai kajian ini.

MELAPORKAN PENGALAMAN KESIHATAN

Sila hubungi kakitangan berikut pada bila-bila masa sekiranya anda mengalami sebarang masalah kesihatan, samada berkaitan atau tidak berkaitan dengan kajian ini.

Dr. Puteri Nadia binti Kamaruzamar secepat mungkin.