COMPARISON OF THE PRE-EMPTIVE ANALGESIA OF LOW DOSE INTRAVENOUS KETAMINE IN COMBINATION WITH INTRAVENOUS PARECOXIB VERSUS INTRAVENOUS KETAMINE ALONE ON PATIENTS UNDERGOING LAPAROTOMY UNDER GENERAL ANAESTHESIA

DR RABIATUL AIDA BINTI RAMLI

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

(ANAESTHESIOLOGY)

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NOVEMBER 2019

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ACKNOWLEDGEMENT

"There is neither might nor power except with Allah's will" (Sahih Bukhari)

Producing this dissertation has been one of the difficult tests that Allah has put forward in order for me to become a competent anaesthetist. As a primary researcher, first and foremost, I would like to express my deepest gratitude to God who is my pillar of strength and wisdom. Indeed, Allah is always the Best Planner and Alhamdulillah this dissertation has finally made the cut.

To my teachers whom I am forever indebted to: Associate Professor Dr Wan Mohd Nazaruddin Wan Hassan, Associate Professor Dr Saedah Ali and Dr Abdul Karim Othman. Many thanks to my supervisor and co-supervisors who provided continuous support, insight and expertise that greatly assisted the research. AP Dr Wan Nazaruddin is always an avid teacher, giving me endless support especially when I was facing difficult time in my data collection. AP Dr Saedah is always been a great mother figure with her tough love and teaching. Dr Abdul Karim Othman has taught me that knowledge has no boundary and always guided me throughout the years in completing this dissertation.

My utmost gratitude also goes to my beloved husband and children who have been my pillars of strength throughout my entire life. To my parents as well as my siblings, thank you for your endless doa, love and support. Special thanks to Dr Sunna Saadan and Dr Noor Hidayah Zainol Abidin for their assistance in statistical analysis. Last but not least, to my colleagues, thank you for your comradeship. I wish nothing but success in this life and hereafter.

"SubhanAllah, Alhamdulillah, LailahaillAllah, Allahuakbar"

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologist
BMI	Body Mass Index
COX-2	Cyclo-oxygenase 2
ECG	Echocardiogram
HR	Heart Rate
ICU	Intensive Care Unit
IV	Intravenous
MAP	Mean Arterial Pressure
NIBP	Non Invasive Blood Pressure
NMDA	N-methyl-d-aspartate
NSAIDS	Non Steroidal Anti Inflammatory
OM	On Morning
ON	On Night
OT	Operation Theatre
PCAM	Patient-controlled Analgesia of Morphine
PONV	Post-operative Nausea Vomiting
RCT	Randomised Controlled Trial
RR	Respiratory Rate
SPO2	Saturation of Oxygen
USM	University Sains Malaysia
VAS	Visual Analogue Score

ABSTRAK

Latar belakang: Pam kawalan ubatan tahan sakit menggunakan ubatan tahan sakit kategori opioid adalah kaedah rutin bagi mengawal tahap kesakitan selepas pembedahan besar. Walau bagaimanapun, pengurusan kawalan kesakitan selepas pembedahan menjadi terhad dengan kesan sampingan ubatan tahan sakit kategori opioid ini. Tujuan kajian ini adalah untuk membandingkan keberkesanan antara penggunaan ubatan intravena ketamine dos rendah digabungkan bersama intravena parecoxib dengan ubatan intravena ketamine sahaja untuk pencegahan kesakitan bagi pesakit yang menjalani pembedahan laparotomi dengan pembiusan penuh.

Kaedah: Seramai 48 pesakit yang dijadualkan untuk menjalani pembedahan laparotomi yang melibatkan bukaan di abdomen telah dipilih dan dibahagikan kepada dua kumpulan ubatan tahan sakit yang diberikan sebelum pembedahan secara rawak: kumpulan R menerima ubatan intravena ketamine dos rendah 0.3mg/kg digabungkan bersama intravena parecoxib 40mg (n= 24) dan kumpulan C menerima ubatan intravena ketamine sahaja (n= 24). Kesemua pesakit menjalani pembedahan dengan kaedah pembiusan penuh dan menggunakan pam kawalan ubatan tahan sakit menggunakan ubatan morfin selepas pembedahan. Jumlah keseluruhan penggunaan ubatan tahan sakit opioid semasa pembedahan, semasa di ruang pemulihan dan selepas pembedahan dicatatkan. Tahap kesakitan menggunakan skor visual analog (0-10) dicatatkan selama 24 jam. Masa penggunaan pam kawalan ubatan tahan sakit menggunakan ubatan morfin untuk kali pertama juga dicatatkan.

Keputusan: Kumpulan R menunjukkan pengurangan dalam penggunaan ubatan tahan sakit di ruang pemulihan [6.25 (16.9) vs. 20.8 (28) mg; p= 0.035], memanjangkan masa untuk penggunaan pam kawalan ubatan tahan sakit menggunakan ubatan morfin buat kali pertama [70.8 (40) vs. 22.2 (15.7) minit; p< 0.001], pengurangan jumlah keseluruhan penggunaan pam kawalan ubatan tahan sakit menggunakan ubatan morfin dalam 24 jam selepas

pembedahan [8.04 (4.6) vs. 16.8 (6.5); p< 0.001] dan pengurangan skor kesakitan (VAS) untuk jam pertama dan seterusnya setiap 4 jam sehingga 24 jam jika dibandingkan dengan Kumpulan C.

Kesimpulan: Penggunaan ubatan tahan sakit intravena ketamine dos rendah digabungkan bersama intravena parecoxib yang diberikan sebelum pembedahan adalah lebih berkesan jika dibandingkan dengan ubatan intravena parecoxib sahaja dalam menurunkan kadar kesakitan selepas pembedahan dan menunjukkan keputusan yang ketara dalam mengurangkan keperluan ubatan tahan sakit opioid selepas pembedahan.

ABSTRACT

Background: Pre-emptive analgesia is important for post-operative analgesia and reducing opioids requirement and their side effects after major surgery. The aim of this study is to compare the efficacy of low dose IV ketamine in combination with IV parecoxib versus IV ketamine alone as pre-emptive analgesia in patients undergoing laparotomy under general anaesthesia.

Methods: A total **of** 48 patients, scheduled for laparotomy under general anaesthesia were randomised into two different groups of pre-emptive analgesia: Group R: low dose IV ketamine 0.3mg/kg in combination with IV parecoxib 40 mg (n= 24) and Group C: IV ketamine 0.3mg/kg alone in combination with placebo (normal saline) (n= 24) and administered before induction of anaesthesia. Both groups received standardized technique of general anaesthesia and post-operative analgesia using patient-controlled analgesia of morphine (PCAM). Both groups were assessed for dosage of rescue analgesia requirement at the recovery bay, pain intensity using visual analogue scale (VAS) over 24 hours, time for the first PCAM demand and total dose requirement of intra-operative and post-operative opioids.

Results: Group R showed lower dose of rescue analgesia requirement at recovery bay [6.25 (16.9) vs 20.8 (28); p= 0.035], longer time for the first PCAM demand [70.8 (40) vs 22.2 (15.7); p< 0.001], less total requirement of PCAM within 24 hours post-operatively [-8.04 (4.6) vs -16.8 (6.46); p< 0.001] and less VAS at an hour and subsequently 4 hourly interval over 24 hours than Group C.

Conclusion: Combination of low dose IV ketamine and IV parecoxib was more effective as pre-emptive analgesia compared to IV ketamine alone for post laparotomy patients who were on PCAM as post-operative analgesia.

Keywords Pre-emptive analgesia, ketamine, paracoxib, laparotomy, PCA morphine

CHAPTER 1

INTRODUCTION

Laparotomy is a surgical procedure involving a large incision through the abdominal wall to gain access into the abdominal cavity. Laparotomy that usually done under general anaesthesia is a major abdominal operation and associated with significant acute post-operative pain. Major abdominal surgeries can lead to severe abdominal pain, which if treated inadequately can cause shallow breathing, atelectasis, retention of secretions and lack of cooperation during physiotherapy. Severe pain can induce prolong hospital stay and poor patient's satisfaction. There are also associated with the development of chronic pain post-operatively. A cross sectional survey was performed in northern Norway regarding the persistent post-surgical pain in general population with questionnaire items:- survey, pain, sensory abnormalities in the area of surgery. Persistent post-operative pain incidence was 40.4% and about 18.5% experienced moderate to severe pain [1]. The pharmacological modalities during intra-operative and post-operative pain control is crucial and has many controversial issues due to its adverse effects. The commonly used drugs are opioids like intravenous morphine or fentanyl. Patient-controlled analgesia (PCA) with iv opioids is a well-established technique for post-operative pain control after major surgery. This technique adjusts the level of pain control better than iv bolus doses and also increases patient's satisfaction and cooperation. Post-operative pain management is often limited by adverse effects to opioid, including drowsiness, nausea, and vomiting. Sometimes, the post-operative pain was not fully relief with opioids. When used alone in large doses for an extensive period, opioids can lead to acute tolerance which further impairs pain control and, more seriously, respiratory and haemodynamic depression.

Ketamine hydrochloride is one of the iv anaesthetic agent, first used in 1965. Ketamine, a non-competitive NMDA antagonist, exerts at sub-anaesthetic doses a specific

NMDA blockade and modulates central sensitization and hence provides anti-hyperalgesic effect. Studies in animals have shown that concomitant administration of an NMDA antagonist and an opioid may result in synergistic or additive analgesic effects. Parecoxib is a potent non-steroidal anti-inflammatory drug, whose prodrug valdecoxib is a selective inhibitor of cyclo-oxygenase 2 (COX-2) that can reduce inflammation and pain by reducing the production of prostaglandin.

The pre-emptive analgesia had a role in treating post-operative pain by preventing the establishment of central sensitization [2]. Immediate post-operative pain, analgesic requirements can be reduced and the development of chronic pain may be prevented with pre-emptive analgesia. A few studies done to evaluate the effects of pre-emptive analgesia in terms of different doses, different drugs combinations, different modes and time of administration. A study done to investigate the significant adjunction of pre-emptive administration of IV ketamine for controlling post-operative acute post thoracotomy pain management and the results showed significant reduction of morphine consumption and higher satisfaction of pain relief as compared with placebo group [3]. Pre-emptive administration of low dose IV ketamine alone was proven to reduce the intra-operative opioids requirement in patients undergoing caesarean section under general anaesthesia [4]. A study done with administration of combination of pre-emptive low dose IV ketamine plus IV diclofenac sodium and it was proven to improved post-operative pain as compared to pre-emptive IV ketamine alone [8]. There was a study on the effect of pre-emptive analgesia in patients undergoing radical resection of lung cancer in that received IV parecoxib 40mg pre-operative compared with IV parecoxib 40mg post-operatively and the results showed significant reduction of acute post-operative pain in the pre-emptive group [12].

Studies on wether pre-emptive analgesia can improve the management of intra-operative pain and post-operative pain are relatively recent and few. The validity of pre-

emptive analgesia as a standard treatment needs more clinical trials. This study aimed to compare the efficacy between low dose iv ketamine in combination with iv parecoxib and iv ketamine alone as pre-emptive analgesia.

Problem statement and study rationale

Until now, there is no ideal or optimal medication that can fully act as pre-emptive analgesia especially for the major surgery such as abdominal laparotomy. By finding the close to ideal medication for pre-emptive analgesia, we can minimize the consumption of morphine in the post-operative period and indirectly can minimize the side effects of morphine to the post-operative patients. Second from epidural analgesia, Patient Control Analgesia (PCA) Morphine is routinely use to manage the post-operative pain especially for laparotomy surgery and can be used objectively as a guidance to assess the severity of pain among the post-operative patients.

So far, there is lack of study conducted to assess the efficacy and safety of the use of pre-emptive analgesia by comparing the administration of low dose intravenous ketamine in combination with intravenous parecoxib and intravenous ketamine alone in patients undergoing laparotomy under general anaesthesia. If this study is found to be significant and the combination of ketamine with parecoxib are proven to be efficacious and safe to be used as pre-emptive analgesia in reducing the opioids requirement which has many adverse effects intra-operative and post-operatively in patients undergoing laparotomy under general analgesia, then it would provide an alternative treatment to current standard pain control peri-operatively.

Literature review

There are several studies on the topic of pre-emptive analgesia but limited studies were done on patients undergoing laparotomy comparing the efficacy of low dose iv ketamine in combination with parecoxib or with placebo. Few studies looked at the role of pre-emptive analgesia in comparison between pre- or postsurgical administrations of different forms of analgesics. The studies were conducted using multiple drugs with different groups and actions. Some studies looked at the efficacy of either by giving low dose ketamine alone, magnesium sulphate alone or in combination for both drugs can reduce the requirement of analgesia intra-operatively and post-operatively. Some studies were conducted via different route of administration, as intravenous bolus or infusion, given as adjunct to intravenous PCA of opioid, and administered as combination with local anaesthetic epidurally.

A randomized, double-blinded, placebo-controlled clinical trial was done to investigate the significant adjunction of pre-emptive administration of ketamine 1mg/kg to intravenous morphine analgesia for controlling post-operative acute post-thoracotomy pain management. The satisfaction of pain relief was significantly higher with a significant reduction of inflammatory response and morphine consumption compared in ketamine group with placebo group [3].

A study was done on the low dose ketamine versus magnesium sulfate on parturients undergoing caesarean section under general anaesthesia. They gave infusion ketamine 0.3mg/kg and compared with a group that received magnesium sulfate infusion 30mg/kg and a group that received only normal saline as placebo. The results were the placebo group required higher dose of opioid intra-operatively and the requirement for post-operative opioid was lower in group that received ketamine infusion as compared to magnesium sulfate infusion's group [4].

A study was done on pre-emptive analgesia with iv ketamine for laparoscopic cholecystectomy. They were divided into 4 groups of study with ketamine dose of 1 mg/kg (group 1), 0.75 mg/kg (group 2), 0.5 mg/kg (group 3), and placebo with normal saline (group 4). Group 1, 2, 3 showed significantly less post-operative analgesic consumption with the lower dose of 0.5mg/kg being devoid of any adverse effects and haemodynamic changes [5].

A systematic review done by Laskowski et al. found a reduction in total opioid consumption and increase in time to first analgesic request in groups receiving ketamine. The most benefit was observed in painful procedures including upper abdominal, thoracic and major orthopaedic surgeries [6].

There was a study which compared post-operative pain and analgesic requirement in patients undergoing appendicectomy under general anaesthesia with pre-emptive low dose iv ketamine (0.5mg/kg) administered 10 minutes prior to incision versus placebo. The results showed that the VAS score were significantly lower in ketamine group and the total dose of pethidine injections over the first 24 hours post-operatively was lower in the ketamine group [7].

A study was done on the pre-emptive analgesic effect of ketamine in patients undergoing elective cesarean section involving 60 patients. In the observation group, the patients received 0.5mg/kg ketamine, and in the control group, the patients received isotonic saline, 5 minutes before the induction of anaesthesia. The result showed significant lower amounts of morphine used in the observation group (4.8 mg +- 2.5 mg vs 8.1 mg +- 4.2mg) during the first 2 hours post-operative [8].

There was a prospective blinded study performed in patients undergoing abdominal hysterectomy with adnexectomy that comparing the efficacy of pre-emptive combination of iv morphine and ketamine given 10 minutes before induction with the administration of either iv ketamine 0.6mg/kg or iv morphine 0.1mg/kg separately 10 minutes before the induction.

The results showed that the combination of morphine and ketamine as pre-emptive analgesia significantly reduced the requirement of PCA morphine as compared when the drugs are used separately [9].

A study was done to assess the post-operative pain score of pre-emptive ketamine at a dosage 0.15mg/kg in patients undergoing gynaecologic laparoscopic surgery and the results showed significant reduction of pain score within the first 6 hours post-operatively [10].

A randomised, double-blinded control of a study on the effects of ketamine pre-emptive analgesia on post-operative pain in patients undergoing a hysterectomy showed results of reduction in total opioids PCA requirement and less VAS pain score. From this study, 60 patients undergoing hysterectomy under general anaesthesia divided into 2 groups with experimental group received 0.3mg/kg of ketamine after induction of anaesthesia, approximately 5 minutes before surgery started and control group did not receive ketamine [11].

There was a study on the effect of pre-emptive analgesia in patients undergoing radical resection of lung cancer in comparing experimental group that received IV parecoxib 40mg pre-operative + normal saline 2mls post-operative compared with control group received 2mls normal saline pre-operatively and IV parecoxib 40mg post-operatively. The results showed that pre-emptive analgesia with iv parecoxib sodium can significantly reduce the acute pain and also can reduce the incidence of emergence agitation [12].

A study was done on pre-emptive use of diclofenac sodium in combination with ketamine in patients undergoing laparoscopic cholecystectomy and the results showed the combination of both drugs significantly improved post-operative pain as compared to groups that received either ketamine or diclofenac sodium alone [13].

Another randomised double blinded study investigated the efficacy co-administration of magnesium gluconate during cardiac surgery. Magnesium prevents the induction of central

sensitization from peripheral nociceptive stimulation and the results showed reduced opioids requirement (remifentanil) after cardiac surgery [14].

A study was done on pre-emptive analgesia with parecoxib sodium on the post-operative pain for gynaecological laparoscopy. About 100 patients were recruited. The patients in the observation group were given injections of iv parecoxib sodium 40mg 30 minutes before operation and fentanyl citrate injections 1mcg/kg 30 minutes before the end of the surgery, while the patients in the control group received parecoxib sodium injections 40mg and fentanyl citrate injections 30 minutes before the end of surgery. The result showed the postoperative VAS score and the total dosage of fentanyl in the observation group were significantly lower than the patients in the control group [15].

CHAPTER 2

OBJECTIVES

General objective

To determine the efficacy of low dose intravenous ketamine in combination with intravenous parecoxib as pre-emptive analgesia in patients undergoing elective laparotomy under general anaesthesia.

Specific objectives

a) To compare the intra-operative requirement of opioids between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.
b) To compare the requirement of PCA Morphine within 24hours post-operatively between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.
c) To compare the time for first PCA demand between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.
d) To compare the trend of pain score based on visual analogue score (VAS) after 1 hour, 4 hour, 8 hour, 12 hour, 16 hour, 20 hour and 24 hour post-operative between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.

Null hypotheses

a) There is no significant difference in the requirement of intra-operative opioids in both groups.
b) There is no significant difference in the requirement of PCA morphine over 24 hours post-operatively in both groups.

c) There is no significant difference in the time for the first PCA demand in both groups.

d) There is no significant difference in the intensity of VAS in both groups.

Alternative hypothesis

a) There is a difference in the requirement of intra-operative opioids. The requirement of intra-operative opioids is less in pre-emptive low dose iv ketamine + iv parecoxib group.

b) There is a difference in the requirement of PCA morphine over 24hours post-operatively. Total morphine consumption is less in pre-emptive low dose iv ketamine + iv parecoxib group.

c) Time for the first PCA demand is earlier in pre-emptive low dose iv ketamine alone.

d) Intensity of VAS is less in pre-emptive low dose iv ketamine + iv parecoxib group.

CHAPTER 3

STUDY PROTOCOL

Research title

COMPARISON OF THE PRE-EMPTIVE ANALGESIA OF LOW DOSE INTRAVENOUS KETAMINE IN COMBINATION WITH INTRAVENOUS PARECOXIB VERSUS INTRAVENOUS KETAMINE ALONE ON PATIENTS UNDERGOING LAPAROTOMY UNDER GENERAL ANAESTHESIA.

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Date of re-submission:

Version:

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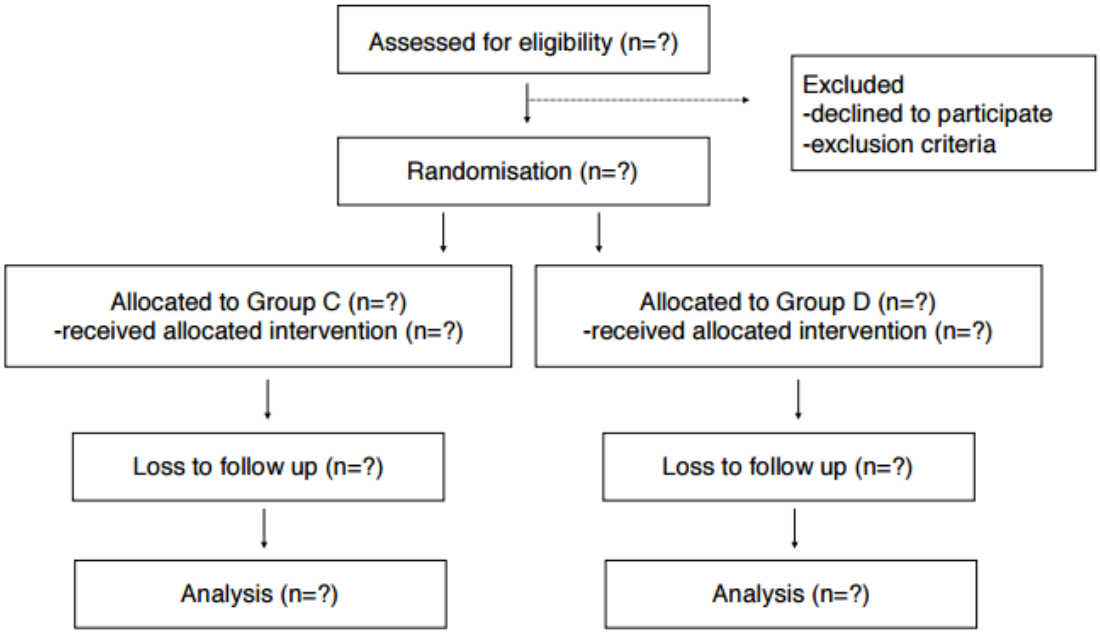
analgesia as compared to groups that received either ketamine or diclofenac sodium alone [13].

Another randomised double blinded study investigated the efficacy co-administration of magnesium gluconate during cardiac surgery. Magnesium prevents the induction of central sensitization from peripheral nociceptive stimulation and the results showed reduced opioids requirement (remifentanil) after cardiac surgery [14].

A study was done on pre-emptive analgesia with intravenous parecoxib sodium on the post-operative pain for gynaecological laparoscopy. About 100 patients were recruited. The patients in the observation group were given injections of parecoxib sodium 40mg 30 minutes before operation and fentanyl citrate injections 1mcg/kg 30 minutes before the end of the surgery, while the patients in the control group received parecoxib sodium injections 40mg and fentanyl citrate injections 30 minutes before the end of surgery. The result showed the postoperative VAS score and the total dosage of fentanyl in the observation group were significantly lower than the patients in the control group [15].

Conceptual framework



Objective

General objective

To determine the efficacy of low dose intravenous ketamine in combination with intravenous parecoxib as pre-emptive analgesia in patients undergoing elective laparotomy under general anaesthesia.

Specific objectives

a) To compare the intra-operative requirement of opioids between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.
b) To compare the requirement of PCA Morphine within 24 hours post-operatively between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.
c) To compare the time for first PCA demand between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.
d) To compare the trend of pain score based on visual analogue score (VAS) after 1 hour, 4 hour, 8 hour, 12 hour, 16 hour, 20 hour and 24 hour post-operative between pre-emptive low dose iv ketamine + iv parecoxib and pre-emptive low dose iv ketamine alone.

Null hypotheses

a) There is no significant difference in the requirement of intra-operative opioids in both groups.
b) There is no significant difference in the requirement of PCA morphine over 24 hours post-operatively in both groups.
c) There is no significant difference in the time for the first PCA demand in both groups.
d) There is no significant difference in the intensity of VAS in both groups.

Alternative hypothesis

a) There is a difference in the requirement of intraoperative opioids. The requirement of intraoperative opioids is less in pre-emptive low dose iv ketamine + iv parecoxib group.

b) There is a difference in the requirement of PCA morphine over 24hours post-operatively. Total morphine consumption is less in pre-emptive low dose iv ketamine + iv parecoxib group.

c) Time for the first PCA demand is earlier in pre-emptive low dose iv ketamine alone.

d) Intensity of VAS is less in pre-emptive low dose iv ketamine + iv parecoxib group.

Research design

This is a prospective, randomised, double-blinded, controlled clinical trial to be conducted at Hospital University Sains Malaysia, Kubang Kerian. The targeted study participants are patients undergoing laparotomy under general anaesthesia. The research group is pre-emptive analgesia with low dose intravenous ketamine in combination with intravenous parecoxib and the control group is pre-emptive analgesia with intravenous ketamine alone. Subject will be randomised based on computer-generated randomisation.

Sample size estimation

We use Power and Sample Size software version 3.1.2 and G*Power 3.1.9.2 software for sample size calculation.

1st Objective

Significance level, α= 0.05

Power of study 0.8

Based on previous study Nadia Helmy et al. (2014), means +- standard deviation of ketamine group (110 +- 20) versus control group (140 +- 41) for the intraoperative opioid requirement and the means difference are 30.

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 20. If the true difference in the experimental and control means is 30, 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 1 error probability associated with this test of this null hypothesis is 0.05.

If we consider 10% dropped out, the additional samples will be 1.6 (=2). Therefore, the total samples will be 18, which are 9 patients per group.

2nd Objective

Significance level, α= 0.05

Power of study 0.8

Based on previous study Nadia Helmy et al. (2014), means +- standard deviation of ketamine group (82 +- 33) versus control group (140 +- 38) for the postoperative opioid requirement and the means difference are 58.

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 33. If the true difference in the experimental and control means is 58, we will need to study 6 experimental subjects and 6 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.

If we consider 10% dropped out, the additional samples will be 1.2 (=2). Therefore, the total samples will be 14, which are 7 patients per group.

3rd Objective

Significance level, α= 0.05

Power of study 0.8

Based on study previous study Nadia Helmy et al. (2014), means +- standard deviation of ketamine group (82 +- 12) versus control group (33 +- 7) for the time for first analgesic demand post-operative and the means difference are 49.

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 12. If the true difference in the experimental and control means is 49, we will need to study 2 experimental subjects and 2 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.
If we consider 10% dropped out, the additional samples will be 0.4 (=2). Therefore the total samples will be 6, which are 3 patients per group.

4th Objective

Significance level, α= 0.05

Power of study 0.8

Based on previous study Akbar Behdad et al. (2011), means +- standard deviation of ketamine group (1.3 +- 0.5) versus control group (1.8 +- 0.6) for the VAS score during 24 hours post operative and the means difference are 0.5.

We are planning a study of a variable response from repeated measures ANOVA. By using G*Power 3.1.9.2 software version, with the number of two groups (control and experimental) and number of measurement of 7 (at 1 hour, 4 hour, 8 hour, 12 hour, 16 hour, 20 hour and 24 hour interval), we will need to study 22 experimental subjects and 22 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.

If we consider 10% dropped out, the additional samples will be 4.4 (=4). Therefore the total samples will be 48, which are 24 patients per group.

As conclusion, 24 participants will be recruit in each arm (n=24), with total 48 participants.