COMPARISON OF THE EFFICACY OF INTRAVENOUS OXYCODONE VERSUS MORPHINE ON POSTOPERATIVE PAIN FOLLOWING ORTHOPAEDICS SURGERY UNDER GENERAL ANAESTHESIA

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Million thanks to Nurzulaikha Bt Mahd Ab. Lah from department of Biostatistics and Research Methodology for assisting me in the statistical analysis.

I also want to take this opportunity to convey many thanks to other lecturers, colleagues, operation theatre and general ward staffs of Hospital Universiti Sains Malaysia for making this study a success. Without their contribution and effort, it could not be completed effectively. Their effort and time spent during this period have been most valuable and priceless. Their abundance of experience and immense knowledge shared with me was my blessing. Without their passionate participation and input, this study could not have been successful.

Last but not least, I would like to extend my appreciation to my family for their infinite love and support.

Chua Boon Sim

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LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists
BMI	Body mass index
GA	General anesthesia
HUSM	Hospital Universiti Sains Malaysia
IV	Intravenous
JEPeM	Jawatankuasa Etika Penyelidikan Manusia USM
mcg/kg	Microgram per kilogram
mg/kg	Milligram per kilogram
min	Minute
OSA	Obstructive sleep apnoea
RCT	Randomized controlled trial
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
USM	Universiti Sains Malaysia
VAS	Visual Analogue Scale

ABSTRAK

Latar belakang Kesakitan yang akut dan teruk adalah perkara yang biasa selepas pembedahan ortopedik dan morphine adalah intravena opioid yang selalu digunakan. Pengenalan intravena (IV) oxycodone telah menggantikan morphine sebagai pilihan pertama opioid yang digunakan dalam rawatan kesakitan selepas pembedahan di beberapa negara. Tujuan kajian ini adalah untuk membandingkan keberkesanan antara intravena oxycodone dengan morphine pada tahap kesakitan selepas pembedahan ortopedik secara pembiusan am.

Kaedah Lima puluh lapan pesakit American Society of Anesthesiologists (ASA) fizikal I-II telah dibahagikan secara rawak untuk menerima IV oxycodone (Kumpulan O, n = 29) 0.08mg/kg atau IV morphine (Kumpulan M, n = 29) 0.08mg/kg semasa permulaan penutupan kulit. Kesakitan selepas pembedahan telah dinilai menggunakan skala analog visual (VAS) dari 0 min, setiap jam hingga 6 jam selepas pembedahan. Masa sehingga pemberian ubat tahan sakit tambahan pertama, keperluan ubat tahan sakit tambahan pertama dan kedua serta kesan-kesan sampingan dinilai.

Keputusan Kesakitan selepas pembedahan tidak berbeza secara signifikan dalam kumpulan O dan kumpulan M dari 0 min, setiap jam hingga 6 jam selepas pembedahan ($P > 0.950$). Tiada perbezaan significant dalam masa sehingga pemberian ubat tahan sakit tambahan pertama ($P = 0.721$), keperluan ubat tahan sakit tambahan pertama ($P = 0.594$) dan kedua ($P = 0.517$) serta kesan-kesan sampingan dalam kedua-dua kumpulan.

Kesimpulan Intravena oxycodone adalah sama berkesan seperti morphine dalam rawatan kesakitan yang akut selepas pembedahan ortopedik dan tidak dikaitkan dengan peningkatan risiko kesan-kesan sampingan opioid.

ABSTRACT

Background Acute, severe postoperative pain is common following orthopaedics surgery and morphine is the commonest used intravenous opioid. The introduction of intravenous (IV) oxycodone has replaced morphine as the first choice of opioid used in postoperative pain management in some countries. The aim of this study is to assess the efficacy of IV oxycodone versus morphine on postoperative pain following orthopaedics surgery under general anaesthesia.

Methods Fifty-eight American Society of Anesthesiologists (ASA) physical status I–II patients were randomly assigned to receive either 0.08 mg/kg IV oxycodone (Group O, n = 29) or 0.08 mg/kg morphine (Group M, n = 29) at the starting of skin closure. Postoperative pain was evaluated using a visual analogue scale (VAS) from at 0 min, hourly till 6th hour postoperatively. The time to first rescue analgesia, requirement of the first and second rescue analgesia and adverse effects were assessed.

Results Postoperative pain score did not differ significantly in Group O and Group M from 0 min, hourly till 6th hour postoperatively (P > 0.950). There were no significant differences in the time to first rescue analgesia (P = 0.721), requirement of first (P = 0.594) and second rescue analgesia (P = 0.517) and adverse effects in both groups.

Conclusion Intravenous oxycodone is equipotent to morphine in treating acute postoperative pain following orthopaedics surgery, and it is not associated with an increased risk of opioid related adverse events.

CHAPTER 1: INTRODUCTION

1.1 Background

Acute, severe postoperative pain is common following orthopaedics surgery, and its safe and effective management can be challenging for everyone in the health care team (1). A good perioperative pain management helps in avoiding adverse physiological and psychological effects. It shortened the length of hospital stay, improve patients' satisfaction and achieve early mobilization after surgery (2).

Oxycodone and morphine are both strong opioids used for the treatment of moderate to severe pain. Both has similar mechanism of action which primarily bind to central mu-opioid receptor and have rapid onset of action. Oxycodone and morphine have the onset time of 5–8 min, with the peak effect of 20–30 min and are metabolised in the liver by CYP450 enzyme system with an elimination half-life of approximately 3-5 hours (3). Analgesic potency between intravenous oxycodone and intravenous morphine is 1:1 in ratio but more recent studies suggest that equianalgesic dose ratio of oxycodone and morphine is 2:3 (4). As a potent analgesia, it makes oxycodone useful in treating acute postoperative pain where pain is most intense immediately after surgery.

All opioids have significant side effects that limit their use such as nausea, vomiting, drowsiness, pruritus, hypotension and respiratory depression. With the introduction of oxycodone, it allows us to replace the use of morphine where study showed oxycodone provides postoperative analgesia faster and more effective with smaller doses required in compared to morphine. Oxycodone is also safer than morphine with lesser opioid induced adverse effects (5).

Up to date, most of the studies in comparing the effectiveness of IV oxycodone versus morphine in treating postoperative pain were conducted in intraabdominal surgery. None has been carried out in orthopaedics surgery. Furthermore, in our current practice, morphine is still the most popular intravenous opioid used in treating postoperative pain. In some countries, oxycodone has replaced morphine as the first choice of opioid used in perioperative pain management (6).

If single opioid is used in orthopaedics patient under general anaesthesia, we propose intravenous oxycodone has a better efficacy and safety profile compare to morphine.

1.2 Study Objective

1.2.1 General Objective

This study is carried out with the aim to assess the efficacy of intravenous oxycodone versus morphine on postoperative pain following orthopaedics surgery under general anaesthesia.

1.2.2 Specific Objective

1. To compare the pain score at 0 min, hourly till 6 hours postoperatively between intravenous oxycodone and morphine following orthopaedics surgery under general anaesthesia.
2. To determine the number of patients that require first rescue analgesia between intravenous oxycodone and morphine following orthopaedics surgery under general anaesthesia.
3. To determine the number of patients that require second rescue analgesia between intravenous oxycodone and morphine following orthopaedics surgery under general anaesthesia.
4. To determine the proportion of adverse effects between intravenous oxycodone and morphine following orthopaedics surgery under general anaesthesia.

1.3 Rationale of Study

Intravenous morphine is the commonest opioid used intraoperatively in orthopaedics surgery under general anaesthesia in HUSM. However, with the used of morphine, the incidence of opioid adverse effects is high. By conducting this study, we aim to prove that intravenous oxycodone is more effective than intravenous morphine in treating postoperative pain with lesser requirement of rescue analgesia and lesser incidence of opioid adverse effects.

1.4 Literature Review

Acute pain following orthopedic surgery is common and should be anticipated by every anaesthetist. A poorly managed acute postoperative pain is associated with long term morbidity and mortality (7). Oxycodone is safe and effective for general anaesthesia. It has been demonstrated that oxycodone is safe to be used as the sole opioid in orthopaedic surgery with good intra- and postoperative pain control (8).

Oxycodone is effective in relieving acute postoperative pain and well tolerated irrespective of type of surgery. A prospective study was undertaken by Kloub *et al* 2015 where a 15-item survey was given to 263 post-operative patients undergoing major surgery, ear nose and throat, general, local sedation, obstetrics and gynaecology, ophthalmic, orthopaedic, plastic and urological surgery with a documented history of moderate or severe non-malignant pain that required continual parenteral oxycodone equivalent of ≥20 mg/day and ≤80 mg/day. Results showed 83.7% patients had no pain and only 7.6% patients reported a pain score of ≥5. Although obstetrics, gynecology and

orthopedic surgeries were associated with a higher pain score, it still proved that oxycodone is as potent as morphine and can be used in all types of surgery and none of the patients reported adverse effects (9).

In comparison to intravenous morphine, intravenous oxycodone showed a significant lower pain score both at rest and during coughing at 30 minutes and 1 hour after laparoscopic hysterectomy where both groups received 0.07 mg/kg of morphine or oxycodone 10 to 15 minutes before surgery ended (10). The study also found that significantly longer time to the first PCA oxycodone requirement in oxycodone group. This indicated that oxycodone is more potent than morphine which is also proved by Kalso *et al* that equianalgesic dose ratio of IV oxycodone and IV morphine was 2:3 and the first state of pain relief was faster and lasted longer in oxycodone group (5).

However, there are also some study showed that both intravenous oxycodone and morphine are equipotent. In a comparative study of oxycodone and morphine in a multi-modal, tissue-differentiated experimental pain model, it demonstrated that both opioids attenuated the sensory response mainly to painful stimulations. Oxycodone has greater analgesic profile than morphine in treating visceral pain but both opioids showed an equipotent profile in pain stimulation on skin and muscle (11). Oxycodone bind at the central mu-opioid receptor as morphine. However, some study proposed that intrinsic antinociceptive effects of oxycodone in visceral pain is mediated by its activity at κ-opioid receptors done in rodent experiments (12, 13).

In a study of 50 patients underwent plastic reconstruction of the breast or a major spinal surgery, patients were randomized to receive PCA morphine or PCA oxycodone after surgery. The study showed similar amount of oxycodone and morphine requirement in recovery room and in the ward at 3, 9 and 24 hours postoperatively. Both opioids appeared equipotent and no difference in incidence of side effects, such as nausea, vomiting, pruritus and urinary retention. No respiratory depression was reported in the study (14).

Opioids-related adverse effects are commonly seen following opioids administration including central nervous system, cardiovascular, respiratory depression and gastrointestinal problem. Poorly manage opioids-related adverse effects significantly impact quality of life and prolonged the recovery postoperatively (15). A review article conducted by Pergolizzi *et al* in 2016 (4) revealed that oxycodone results opioid-related adverse effects as does other opioids, but some studies have found fewer or lesser severe adverse events with oxycodone at equianalgesic doses as compared to morphine. Oxycodone showed less nausea, hallucination, pruritus and sedation compared to morphine, but no difference in vomiting, respiratory depression, and dizziness (10, 16-18). Oxycodone appears to be safe and effective for postoperative pain control.

1.5 Reference for Introduction and Literature Review

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CHAPTER 2: STUDY PROTOCOL

2.1 Study Protocol Submitted For Ethical Approval

Study design

A prospective, double blinded randomised control trial study will be performed from October 2018 to October 2020 to assess the efficacy of intravenous oxycodone compared to intravenous morphine on postoperative pain following orthopaedics surgery under general anaesthesia.

Study area

The study will be carried out in general operation theatre and trauma operation theatre Hospital Universiti Sains Malaysia (HUSM).

Study population

Patients scheduled for elective or emergency orthopedic surgery in HUSM under general anaesthesia and fulfilling the inclusion criteria will be enrolled for the study.

Subject criteria

Inclusion criteria

- Patient undergoing orthopaedics surgery under general anaesthesia
- Patient is ASA I or II (American Society of Anesthesiologists physical status classification system)
- Age 18 till 60 years old
- Fixation of opened or closed fracture in single bone with implantation

Exclusion criteria

- Patient undergoing orthopaedics surgery under regional anaesthesia or with epidural catheter
- Refusal to involve in study
- Documented known allergy to opioids
- Patient with history of chronic use of opioids or analgesics
- Patient with underlying heart, liver or renal impairment
- Pregnant patients
- Orthopaedic surgery involving joint replacement
- Patient with BMI >40
- Patient with peripheral neuropathy

Withdrawal criteria

- Patients who has critical incidence perioperatively that impairs patients' outcome

Sample size calculation and estimation

The sample size is calculated using G power software 3.1.9.2.

1. To compare the pain score at 0 min, hourly till 6 hours postoperatively between intravenous oxycodone and morphine following orthopaedics surgery under general anaesthesia.

   To compare between oxycodone and morphine group, calculation of sample size using F test, ANOVA Repeated measure, between factors.

Effect size f	= 0.25
α err prob	= 0.05
Power (1-β err prob)	= 0.8
Number of groups	= 2
Number of measurements	= 7
Corr among rep measures	= 0.3

   The calculation revealed that about 54 total candidates needed as sample size. Considering the drop out of 10%, total sample size required is 60 patients.

   To compare within oxycodone or morphine group, calculation of sample size using F test, ANOVA Repeated measure, within factors.

Effect size f	= 0.25
α err prob	= 0.05
Power (1-β err prob)	= 0.8
Number of groups	= 2

Number of measurements = 7

Corr among rep measures = 0.3

Nonsphericity correction ε = 1

The calculation revealed that about 24 total candidates needed as sample size. Considering the drop out of 10%, total sample size required is 27 patients.

The calculation revealed that the biggest sample size required is 60 patients. Therefore, 60 patients will be enrolled into the study with 30 candidates per arm.

Methodology and data collection method

The study requires approval from Ethics Committee of Universiti Sains Malaysia (USM) prior to the enrolment of the patients. Eligibility of the patients will be screened during preoperative assessment in the ward one day prior to surgery and patients who fulfil the inclusion criteria will be selected. Procedure will be explained in detail to the patients and confidentiality will be reassured. Informed written consent will be taken.

Patients need to be fasted for at least 6 hours before surgery. In operating room, routine haemodynamic monitoring (non-invasive blood pressure, pulse oximetry and electrocardiography) will be recorded.

Patients who met the criteria for the study will be randomly divided into two groups. One group receives intravenous oxycodone and another group receives intravenous morphine. Randomization will be done by closed envelope method. Drug to be used is decided by a computer-generated randomization sequence (available at http://www.randomization.com). Anaesthetist not involved in this study will pick up the envelope and according to the drug chosen, prepare the study drug in identical syringes. Each syringe is labeled with the patients' number and the initials, and neither the treatment assignment nor the content of the syringe is known by the anesthesia staff involve in the patient management and data recording.

To prepare the drug, in Group O, 10mg of oxycodone will be diluted in 10 ml saline to make the concentration of 1mg/ml, whereas in Group M, 10mg of morphine will be diluted in 10 ml saline to make the concentration 1mg/ml.

Patient will be induced with intravenous fentanyl 1-2mcg/kg, intravenous propofol 1.5-2mg/kg, intravenous rocuronium 0.6mg/kg and endotracheal intubation will be performed. Post induction, preemptive intravenous paracetamol 1g and intravenous dexamethasone 4mg will be administered to the patients. During the surgery, bolus intravenous fentanyl 25mcg will be given if patient in pain. Intravenous oxycodone or morphine 0.08mg/kg will be administered at the starting of skin closure by attending anaesthetist to the group allotted. Intravenous ondansetron 4mg will also be given as prophylaxis for postoperative nausea and vomiting. Patient will be reverse with intravenous neostigmine 2.5mg and intravenous atropine 1mg.

Postoperative pain will be assessed using a visual analogue score (VAS) on arrival in the recovery room at 0min, and hourly up to 6 hours in the ward by blinded trained nurses. First rescue analgesia intravenous parecoxib 40mg will be given if VAS scores > 4 or requested by patient. In subsequent assessment, if VAS scores still > 4 or requested by patient, intravenous tramadol 50mg will be given as second rescue analgesia. The time and the requirement of rescue analgesia will be recorded. Adverse effect (respiratory depression, nausea, vomiting, pruritus, sedation) will be observed and recorded till 6 hours postoperative.

Research tools

1. Drugs used during this study: oxycodone 1mg/ml and morphine 1mg/ml.
2. Standard monitoring devices in operative theatre which includes pulse oximetry, non-invasive blood pressure monitoring, continuous electrocardiogram monitoring.
3. Devices used in general anaesthesia: Direct laryngoscope, endotracheal tube or laryngeal mask airway.
4. Drugs used for induction of anaesthesia: Fentanyl 10mcg/ml, Propofol 10mg/ml, Rocuronim10mg/ml.
5. Ephedrine 6mg/ml diluted in 5cc syringe with normal saline or phenylephrine 100mcg/ml diluted in a 10cc syringe with normal saline in the event of hypotensive episode.
6. Atropine 0.2mg/ml diluted in 5cc syringe with normal saline in the event of symptomatic bradycardia.
7. Analgesia use: Intravenous paracetamol 1g and intravenous fentanyl 25mcg bolus for intraoperative pain.
8. Antiemetic: intravenous dexamethasone 4mg and intravenous ondansetron 4mg.
9. Intravenous parecoxib 40mg as first rescue analgesia and intravenous tramadol 50mg as second rescue analgesia postoperative.
10. Visual analogue scale for assessment of postoperative pain score.
11. The University of Michigan sedation scale for assessment of the degree of sedation.

Operation definition

Orthopaedics surgery:

- Operation which includes fixation of fractures with implantation under general anaesthesia

Intravenous oxycodone:

- Opioid.
- Clear, colourless solution for injection containing 10mg/ml of oxycodone
- Analgesia potency intravenous oxycodone: intravenous morphine = 1:1

Intravenous morphine:

- Opioid.
- Clear, colourless solution for injection containing 10mg/ml of morphine
- Analgesia potency intravenous morphine: intravenous oxycodone = 1:1

First rescue analgesia

- Intravenous parecoxib 40mg
- Nonsteroidal anti-inflammatory drug
- Given postoperatively as first rescue analgesia if VAS scores > 4 or requested by patient.

Second rescue analgesia

- Intravenous tramadol 50mg
- Opioid
- Analgesia potency intravenous morphine: intravenous tramadol = 1:10
- Given postoperatively as second rescue analgesia if VAS scores > 4 or requested by patient.

American Society of Anesthesiologists physical status classification system

- A system to assess the fitness of patients before surgery
- Scale from 1 to 6
- ASA 1 – A normal healthy patient
- ASA II – A patient with mild systemic disease
- ASA III – A patient with severe systemic disease.

  BMI >40 which carrying risk of potential difficult intubation and severe OSA is consider ASA III
- ASA IV – A patient with severe systemic disease that is a constant threat to life
- ASA V – A moribund patient who is not expected to survive without the operation
- ASA VI – A declared brain-death patient whose organs are being removed for donor purposes.

Visual analogue scale for pain

- VAS is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured in this case the measurement of pain
- VAS is a unidimensional measure of pain intensity
- Allows the scoring of 0 to 10
- In which 0 is non existence of pain, while 10 is severe, excruciating pain

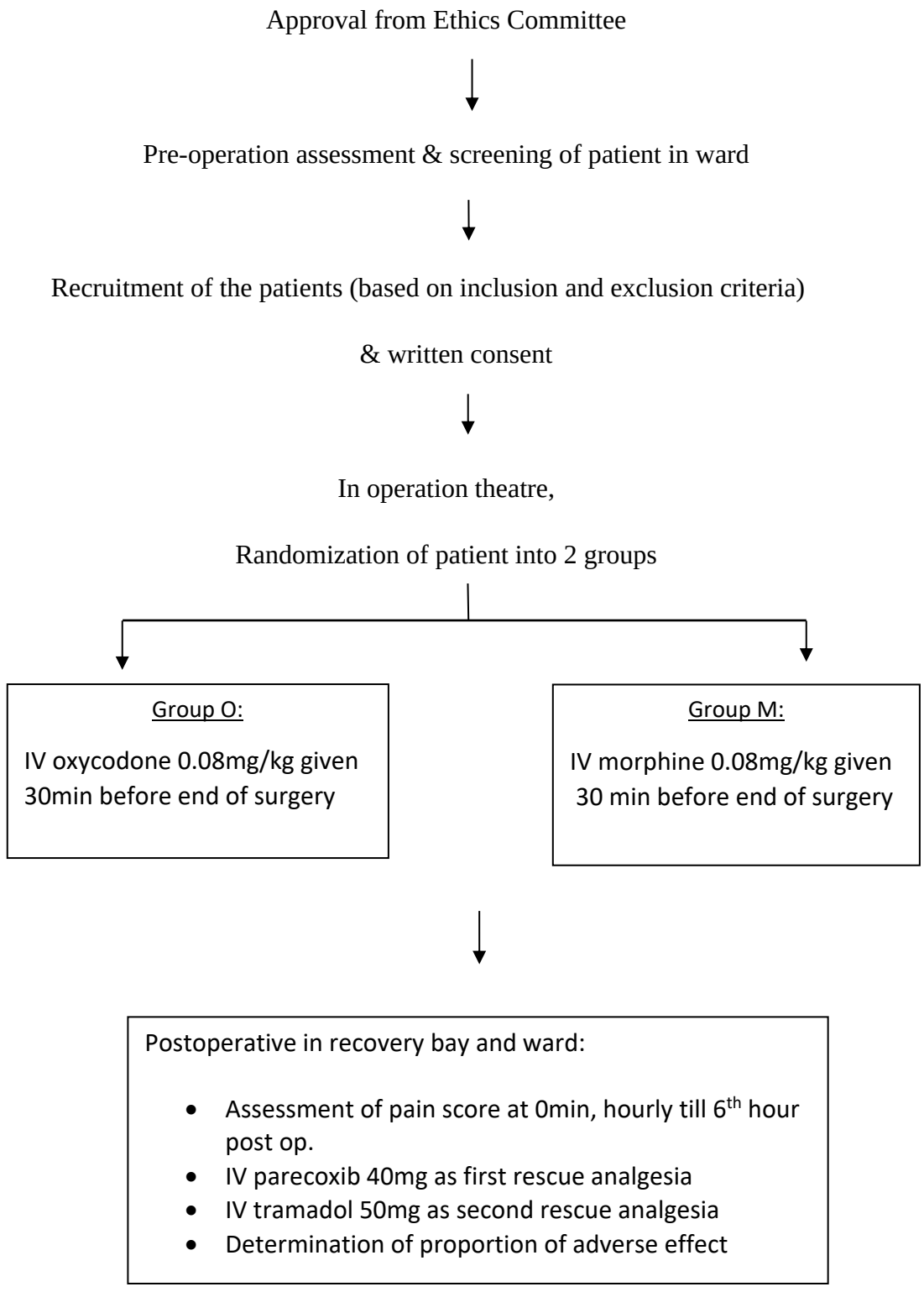
The University of Michigan sedation scale:

- This scale is used to access the degree of sedation that is present in the patient
- Scale from 0 to 4
- O-awake and alert
- 1-minimally sedated
- 2-moderately sedated
- 3-deeply sedated
- 4-unarousable

Respiratory depression:

- Respiratory rate less than 8 breath per minute

STUDY FLOWCHART



DATA ANALYSIS

Data will be entered and analysed by using SPSS software version 24. Data will be tested for normal distribution. Demographic and clinical data were compared by means of independent samples Student's t-test, or chi-square test if appropriate. Repetitive measurement data analysed using ANOVA.

Differences were considered as significant with $P < 0.050$.

ETHICAL CONSIDERATIONS

1) **Subject vulnerability**

   The subject who is a patient under my care as a doctor will be given full freedom to decide to participate in this study with the knowledge that his or her medical condition, management and care would be provided with utmost care.

2) **Declaration of conflict of interest**

   There is no conflict of interest during the conduct of this study

3) **Privacy and confidentiality**

   All forms are anonymous and will be entered into spss software. Only research team members which is me as the primary investigator and my supervisor will have access to the collected data.

   The collected data will be presented as grouped data and will not identify the responders individually

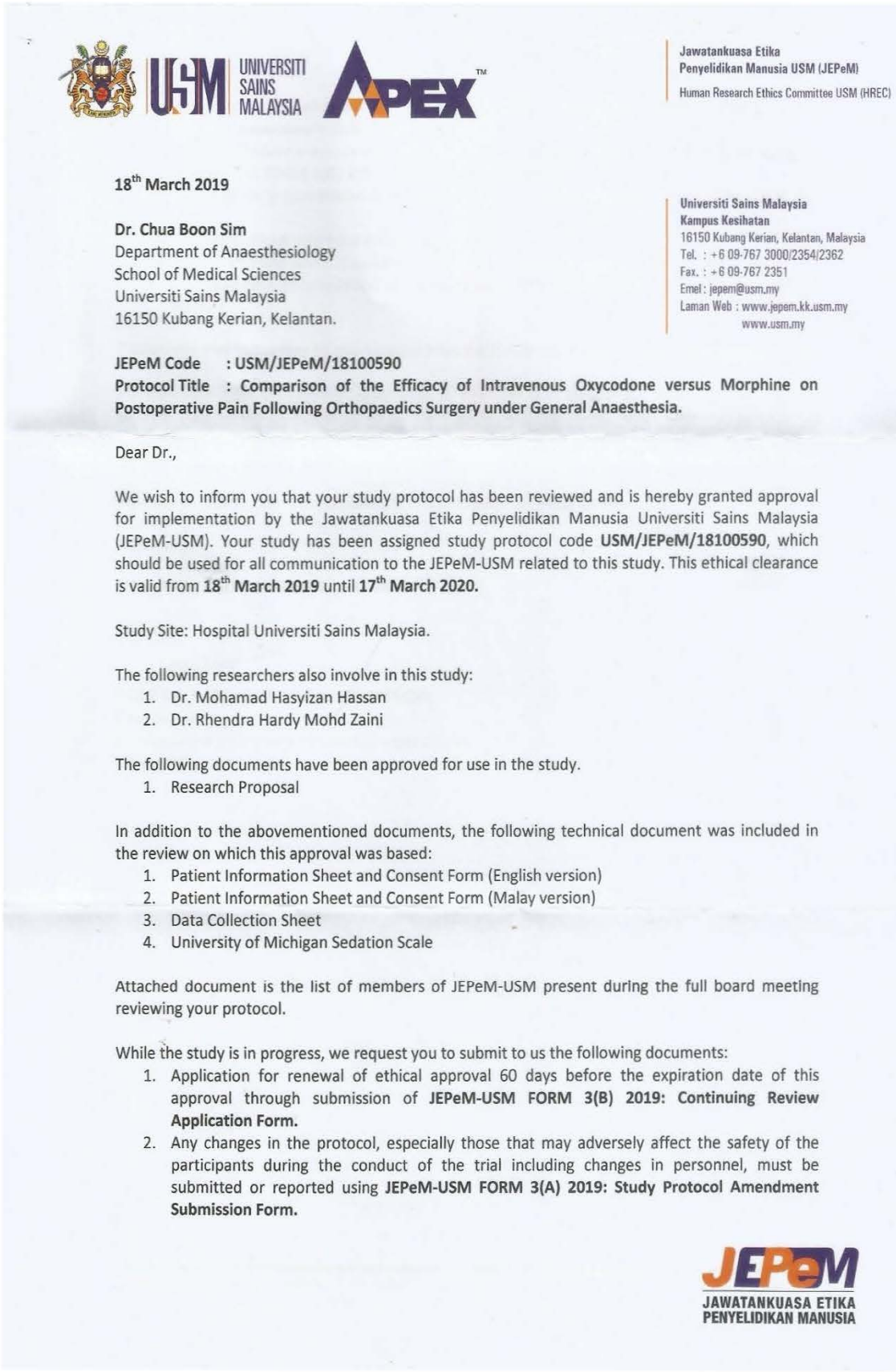
4) **Communities sensitivities and benefits**

   This study will benefit those patients going for general anaesthesia. It will allow us anaesthetists to decide upon the best opioid of choice to be given intravenously for better analgesia with the least complication and adverse effects.

5) **Honorarium and incentives**

   No incentives will be given to the participants

2.2 Ethical Aprroval Letter



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

18th March 2019

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JEPeM Code : USM/JEPeM/18100590
Protocol Title : Comparison of the Efficacy of Intravenous Oxycodone versus Morphine on Postoperative Pain Following Orthopaedics Surgery under General Anaesthesia.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/18100590**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **18th March 2019** until **17th March 2020.**

Study Site: Hospital Universiti Sains Malaysia.

The following researchers also involve in this study:
1. Dr. Mohamad Hasyizan Hassan
2. Dr. Rhendra Hardy Mohd Zaini

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

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:
1. Patient Information Sheet and Consent Form (English version)
2. Patient Information Sheet and Consent Form (Malay version)
3. Data Collection Sheet
4. University of Michigan Sedation Scale

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) 2019: Continuing Review Application Form.**
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) 2019: Study Protocol Amendment Submission Form.**

JEPeM
JAWATANKUASA ETIKA
PENYELIDIKAN MANUSIA

3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**
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) 2019: 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.