COMPARISON OF THE EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE ON DIFFERENT TARGET-CONTROLLED INFUSION PHARMACOKINETIC MODELS FOR PROPOFOL (MARSH VS SCHNIDER) DURING INDUCTION OF ANAESTHESIA

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

UNIVERSITI SAINS MALAYSIA

2017

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ACKNOWLEDEMENTS

I would like to thank all my lecturers from Department of Anaethesia and Intensive Care, Hospital Universiti Sains Malaysia for their support and encouragement, particularly to Dr W Mohd Nazaruddin bin W Hassan, as my supervisor who has been giving me lots of advice throughout the entire process of accomplishing this study.

Also thanks to Dr Laila as my academic supervisor who had give a lot of guidance throughout my training in HUSM.

I would also like to express my thanks to my fellow colleagues who has assisted me in giving anaesthesia in the recruited patients. Without them, it was impossible for me to complete this study.

I would also like to thanks the staff nurses in operation theatre for their willingness in helping me preparing the necessary equipment for my study.

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologist
DBP	Diastolic Blood Pressure
HR	Heart Rate
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
PVC	Polyvinyl Chloride
SBP	Systolic Blood Pressure
TCI	Target-controlled Infusion
TIVA	Total Intravenous Anaesthesia

Perbandingan Kesan Intravena Dexmedetomidine pada Cara Sasaran-Kawalan Infusi Propofol berbeza model (Marsh Vs Schneider) yang berbeza semasa Induksi Pembiusan

ABSTRAK

Latar belakang

Dexmedetomidine adalah alpha-2 selektif agonis, yang sering digunakan sebagai ubat pelali dan menjadi ubat tambahan semasa pembiusan am. Tujuan kajian ini adalah untuk menentukan kesan dexmedetomidine semasa induksi menggunakan dua teknik farmakokinetik infusi kawalan sasaran (IKS) propofol.

Tatacara

64 pesakit yang berumur 18-60 tahun , dalam klasifikasi ASA I dan II yang menjalani pembedahan elektif secara pembiusan umum telah dibahagikan secara rawak kepada dua kumpulan ;Kumpulan Marsh(n=32) dan Kumpulan Schnider(n=32).Kesemua pesakit menerima ubat permulaan intravena dexmedetomidine pada 1 mcg/kg selama 10 minit diikuti dengan IKS remifentanil 2ng/ml. Setelah kepekatan tempat sasaran (C_e) 2ng/ml remifentanil tercapai, induksi IKS propofol dimulakan. Kumpulan Marsh dimulakan dengan model Marsh dengan tahap kepekatan (C_pt) 2mcg/ml, manakala kumpulan Schnider dimulakan dengan model Schnider menggunakan tahap kepekatan (C_et) 2mcg/ml. Sekiranya induksi tidak berjaya selepas 3 minit, tahap kepekatan (Ct) akan dinakkan 0.5mcg/ml setiap 30 saat sehingga induksi berjaya.Keperluan tahap kepekatan propofol semasa berjaya induksi, masa induksi dan propofol C_e semasa berjaya induksi dan parameter hemodinamik direkod untuk analisis statistik

Keputusan

Keperluan propofol Ct untuk kejayaan induksi adalah rendah dengan signifikan di kumpulan Schnider berbanding kumpulan Marsh [3.48(0.90) vs 4.02(0.67)] μg/ml; *P* = 0.01]. Masa induksi pertengahan adalah lebih pendek di kumpulan Schnider berbanding kumpulan Marsh [134.96 (50.91) vs. 161.59 (39.64); *P* = 0.02] saat. Tidak terdapat perbezaan ketara antara C_e dan parameter hemodinamik semasa kejayaan induksi di antara dua kumpulan.

Kesimpulan

Dexmedetomidine sebagai ubat induksi bersama dengan TCI remifentanil dan TCI propofol mengurangkan keperluan Ct untuk induksi dan mengurangkan masa induksi untuk model Schnider berbanding model Marsh bagi TCI propofol. Bagaimanapun, kesan hemodinamik adalah stabil dalam kedua-dua kumpulan.

Kata-kata Kunci: Marsh,Schnider,propofol,dexmedetomidine, infusi kawalan sasaran

Comparison of the Effects of Intravenous Dexmedetomidine on Different Target-controlled Infusion Pharmacokinetic Models of Propofol (Marsh vs. Schnider) during Induction of Anaesthesia

ABSTRACT

Background: Dexmedetomidine is selective alpha 2-agonist which is commonly used for sedation and potential to be used as co-induction drug. The aim of this study was to determine the effects of dexmedetomidine on induction using different target-controlled infusion (TCI) pharmacokinetic models of propofol.

***Methods*:** 64 patients, aged 18-60 year-old, classified under ASA I and II, who underwent elective surgery under general anaesthesia, were randomised into two groups; Group Marsh (n=32) and Group Schnider (n=32). All patients received 1 mcg/kg loading dose of intravenous (IV) dexmedetomidine over 10 minutes and followed with TCI remifentanil at 2 ng /ml. After effect-site concentration (C_e) of remifentanil achieved 2 ng/ml, TCI propofol induction was started. Group Marsh was started with Marsh model at target plasma concentration (C_pt) of 2 mcg/ml, whereas Schnider group was started with Schnider model at target effect concentration (C_et) of 2 mcg/ml. If induction was unsuccessful after 3 min, target concentration (Ct) was gradually increased to 0.5 mcg/ ml every 30 seconds until succesful induction. Ct requirement of propofol at successful induction, induction time, C_e of propofol at successful induction and serial of haemodynamic parameters were recorded for statistical analysis.

***Results*:** Requirement of Ct of propofol for successful induction was significantly lower in Group Schnider than Group Marsh [3.48 (0.90) vs. 4.02 (0.67) μg/ml; *P* = 0.01]. Mean induction time was also shorter in Group Schnider than Group Marsh [134.96 (50.91) vs. 161.59 (39.64); *P* = 0.02] seconds. There were no significant differences in C_e at successful induction and haemodynamic parameters between the two groups.

***Conclusions*:** Dexmedetomidine as co-induction with TCI remifentanil and TCI propofol reduced Ct requirement for induction and shorter induction time in Schnider model than Marsh model of TCI propofol. However, haemodynamic effects were stable in both groups.

Keywords: Marsh model, Schnider model, propofol, dexmedetomidine, target-controlled infusion, induction time, target plasma concentration, target effect concentration.

SECTION 1

INTRODUCTION

1.0 Introduction

Dexmedetomidine is a highly selective alpha-2-adrenoreceptor agonist which has properties of sedation, hypnosis and analgesia (1). It has been used as conscious sedation in intensive care unit (ICU), during procedural sedation, and as an adjunct drug for regional anaesthesia as well as peripheral nerve block . Dexmedetomidine provide sedation and analgesia without respiratory depressant (2).

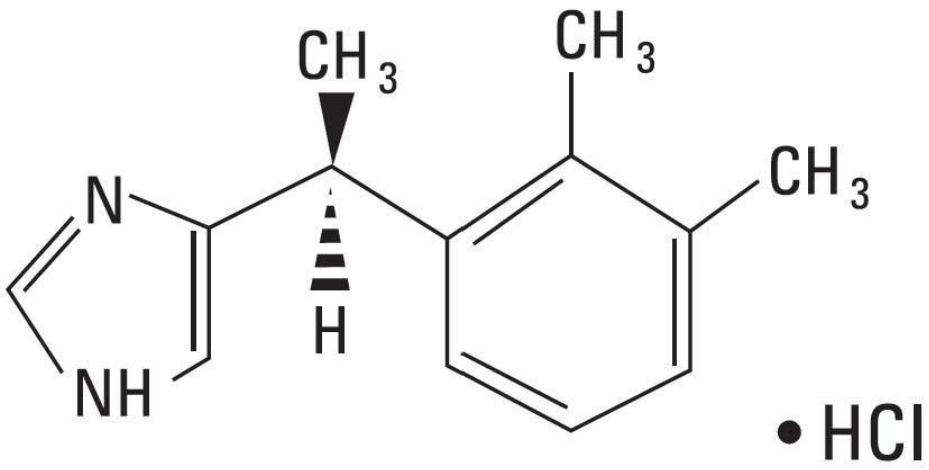

Figure 1 Molecular structure of dexmedetomidine (source: precedex full prescribing information, Hospira)

Dexmedetomidine is administered in adults with dosing of 1 micrograms/kg followed by 0.2-0.7 micrograms/kg/hour (3). Dexmedetomidine is 94% protein-bound in the plasma, distribution half-life is 6 minutes and undergoes extensive hepatic

metabolism to methyl and glucuronide conjugates (3). Dexmedetomidine elimination half life is 2 hours and 95% of metabolites are excreted in the urine (3).

Remifentanil is a selective mu opioid agonist(4). Remifentanil has a unique structure due to its ester linkage which is hydrolysed by nonspecific plasma and tissue esterases to inactive metabolites(4). Thus, remifentanil effect are fast, rapidly titratable due to its fast onset and offset, non cumulative and fast recovery after discontinuation (4).

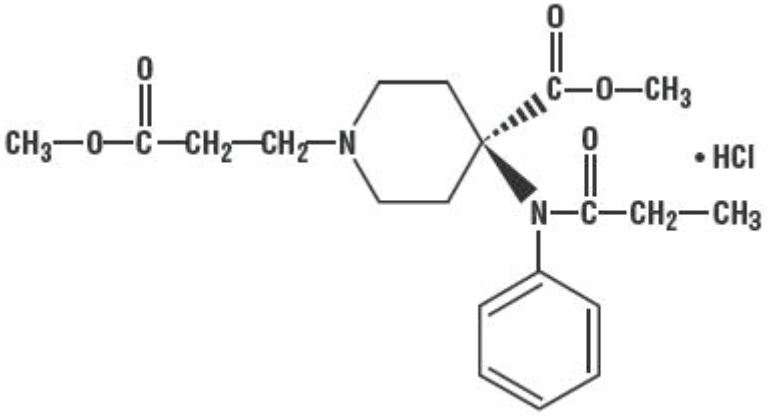

Figure 2 Molecular structure of Remifentanil (source: remifentanil prescribing info, Mylan)

With the availability of sophisticated drug delivery system such as target controlled infusion (TCI), Remifentanil can be delivered by precise titration to achieve narrow therapeutic margin (5). TCI Remifentanil can be delivered via Minto mode(6).

Propofol is a phenol derivative with chemical name 2,6-diisopropylphenol (3). Propofol is presumed to act on GABA-A receptor to produce anaesthesia effect (4). In healthy adults, the induction dose is 1.5-2.5mg/kg intravenous, with corresponding blood levels of 2-6 micrograms/ml to produce loss of consciousness (4).

The usage of Dexmedetomidine was further extended as adjunct in general anaesthesia which includes being used as adjunct in total intravenous anaesthesia (TIVA) and was shown to have several added advantages. During intracranial procedure, Dexmedetomidine as an anaesthetic adjunct leads to better perioperative hemodynamic control, less intraoperative opiod consumption, and fewer postoperative antiemetic requests (7). Dexmedetomidine as adjunct to Propofol and Remifentanil based anaesthesia reduced the total Propofol dose requirement and produce a more stable intraoperative haemodynamics (8). Intraoperative infusion of Dexmedetomidine leads to smooth and haemodynamically stable emergence (9).

Compared to inhalational technique, TIVA has less post operative nausea and vomiting, less usage of antiemetic, produce less headache and less drowsiness (10). TIVA can be used in any type of surgery unless contraindicated (6). TIVA can be delivered via a sophisticated system called TCI where Propofol and Remifentanil can be delivered via such methods using specific pharmacokinetic mode (6).TCI Propofol can be delivered via Marsh or Schnider mode. According to Malaysia TIVA/TCI pocket reference (2^{nd} edition), recommended initial target concentration for TCI Propofol is 4mcg/ml and for TCI Remifentanil is 2ng/ml (6). However, when BIS monitoring is used, a lower initial target concentration of TCI propofol at 2mcg/ml is used (6).

Early TCI machine was designed to produce target plasma concentration. Soon after that, it was noted that there is a delay between plasma concentration and clinical effect which is due to the time taken for equilibrium between plasma concentration and the site of action at central nervous system, known as effect-site (12). The rates of plasma/effect site equilibriums are determined by factors such as cardiac output,

cerebral blood flow and lipid solubility of the drug (13). Mathematically, this time course for plasma/effect site equilibration was described by a first order kinetic known as Keo (13). To achieve the effect-site targeting, the TCI machine will manipulate plama concentration to achieve the effect-site concentration by overshooting the plasma concentration or stopping the infusion (13). The degree of overshooting the plasma concentration or stopping the infusion will depend on the Keo and rate of plasma redistribution (13).Keo(min/1) for Marsh model is 0.26, modified Marsh is 1.21 and Schnider is 0.456. The time to peak effect for Marsh is 4.5minutes, for modified Marsh is 1.5 minutes and Schnider is 1.5minutes (12).

Marsh and Schnider model with different pharmacokinetic parameter when used can result in significantly different in infusion rate. This different in infusion rate will result in different pharmacodynamics response during anaesthesia. Previous study examined the effect of intravenous Dexmedetomidine on TCI Propofol in a single mode. The purpose of this study is to compare the effect of intravenous Dexmedetomidine on two different TCI mode of Propofol (Marsh vs Schnider) on haemodynamic changes, induction time and effect-site concentration of TCI Propofol. This study is important because haemodynamic stability and smoothness of induction is an important aspect to be achieved during induction of anaesthesia.

Few studies had been done to examine Dexmedetomidine as an anaesthetic adjunct which can provide some insight to lead our research further on this aspect. Ke Peng et al. studied the efficacy and safety of Dex as an anaesthetic adjunct for patients undergoing intracranial surgery (7). It was a meta-analysis study where systemic literature search of randomized controlled trials was done to compare Dex with placebo

or opioids in these patients. Eight RCT were included in the study. The study showed that patients treated with Dexmedetomidine required less intraoperative treatment for hypertension and hypotension (RR= 0.48, 95% CI 0.31-0.75, p=0.001; and RR=0.66, 95% CI 0.43-1.01, p=0.05, respectively) and less postoperative treatment for hypertension and tachycardia (RR=0.37, 95% CI 0.17-0.79, P=0.01; and RR=0.14, 95% CI 0.03-0.59, p=0.007, respectively) compared with placebo. Patients also had lower mean arterial pressure and heart rate when extubated (MD=-9.7mmHg, 95% CI -12.35 to -7.12, p<0.00001; and MD= -16.35 beats/minute, 95% CI -20.00 to -12.70, p<0.00001, respectively), a lower intraoperative additional fentanyl consumption (MD=-0.78mcg/kg/min, 95% CI -1.51 to -0.05, p=0.04), and a lower postoperative antiemetic requests (RR=0.51, 95% CI 0.33-0.80, P=0.003).

Kang W S et al. studied the effect of dexmedetomidine on the adjuvant propofol requirement and intraoperative hemodynamics during remifentanil-based anaesthesia in twenty patients undergoing breast surgery (8). Patients were randomly allocated to receive dexmedetomidine (group dex) or placebo (group c). It was concluded that group dex require lesser propofol infusion rate than group c (63.9 +/-16.2 vs 96.4 +/-10mcg/kg/min, respectively p<0.001) and also produce a more stable intraoperative hemodynamics).

Viterbo J F et al. compared Marsh and Schnider model during induction of anaesthesia in elective cardiac surgery (11). It was shown that marsh model produce lower predicted effect-site concentration (2.3+/-0.4 vs 2.7 +/-0.6mcg/ml, p=0.006) and a shorter time to induction (296+/-59 vs 338+/-87s, p=0.024).

Naaz S et al. stated that frequently observed adverse effects with dex use include hypotension, hypertension, bradycardia, dry mouth and nausea (14). Other reported adverse effects include fever, rigors, cyanosis, muscle weakness. It may also lead to arrhythmia, AV block, cardiac arrest, T-wave inversion, tachycardia, angina pectoris, pulmonary edema, bronchospasm, respiratory depression, syncope, neuropathy, paresthesia, paresis, hyperkalemia, lactic acidosis and hyperglycemia. In healthy subjects, tolerability of dex was noted in subjects who achieved plasma concentrations from 1.8 up to 13 times the upper boundary of therapeutic range. Dex when coadminister with other anaesthetics, sedatives, hypnotics or opiods will lead to enhancement of it effects, thus a reduce dosage with these agents is required.

Ghodki PS et al. study the effect of dex as an anaesthetic adjuvant in laparascopic surgery (15). 30 patients were loaded with dex at 1mcg/kg followed by routine induction with propofol and fentanyl. There is a statistically significant reduction in heart rate, however is not clinically significant. The mean heart rate on starting was 85(17) reduce to lowest mean of 72(13). Mean systolic blood pressure was 125(22) at beginning fell to 113(20). Mean diastolic blood pressure fell at statistically insignificant value, 68(12) to 56(10). From this literature, using dexmedetomidine with propofol together will lead to risk of reduction in blood pressure and heart rate, however, this risk is tolerable to the patient.

1.1 Rationale of Study

This study was to to compare the effect of IV dexmedetomidine on different TCI mode of propofol (Marsh vs Schnider) on haemodynamic changes, induction time and effect-site concentration of TCI propofol during general anaesthesia. Previous study which was done by Viterbo J F et al. compared this two TCI propofol mode without IV dexmedetomidine preloading. This research is necessary because haemodynamic stability and smoothness of induction is an important aspect to be achieved during induction of anaesthesia. Thus the aim of this study is to determine the clinical effect of IV dexmedetomidine between two different TCI propofol modes.

1.2 Objective of the Study

Primary objective:

- To compare the effect of intravenous Dex on the hemodynamic changes (decrease in mean blood pressure) during induction and after endotracheal intubation between marsh and schnider models of TCI propofol

Secondary objective:

- To compare the effect of intravenous Dex on induction time between Marsh and Schnider models of TCI propofol
- To compare the effect of intravenous Dex on the effect site concentration of propofol at successful induction between Marsh and Schnider models of TCI propofol

SECTION 2

STUDY PROTOCOL

2.1 Study Protocol

Study design : prospective, randomized control trial, double-blinded

Study period : 1/6/2015-1/6/2016

Study population : patient in Hospital University Sains Malysia(HUSM) undergone elective surgery, requiring general anaesthesia, requiring intubation. The tracheal tube used for endotracheal intubation was the standard polyvinylchloride (PVC) type.

Study setting : Operation theatre (OT), HUSM

Sample Recruitment Criteria:

a) Inclusion criteria :
   - Patients with age 18-60
   - ASA 1-2

b) Exclusion criteria:
   - Any allergic to study drugs
   - Preoperative bradycardia, heart rate (HR) <55/minute or cardiac dysrhytmia
   - Preoperative hypotension mean arterial pressure(MAP) <60mmhg
   - Known difficult intubation
   - Pregnancy
   - Liver or renal disease
   - Obesity
   - Hypertension

c) Withdrawal criteria:
   - Unanticipated difficult intubation (requiring more than 30 sec for intubation , or more than 1 attempt for intubation)

- Severe hypotension or bradycardia after starting infusion of study drug requiring rescue drugs (ephedrine/atropine) that was given up to the time of 5 minutes post intubation.

Methodology:

- Obtained approval from ethics committee HUSM and Medical Research & Ethics Comittee.
- Patients scheduled for elective surgery was seen two or more days earlier and selection of patient based on criteria.
- Written consent was obtained from the patient.
- No sedative premedication was given.
- Study numbers ranged from 01 to 80 were prepared. These numbers would either be labelled as group M (marsh) or group S (schnider). This randomization was done through internet, at the website of www.randomization.com. 80 subjects were randomised into 20 blocks. Thus, those study numbers would be divided into 2 groups equally, group M (marsh) and group S (schnider).
- This was a double blinded study. The person (MO in charge) who assessed the patient in the OT and the patients would not know which mode of TCI propofol was used.
- Non invasive monitoring such as pulse oximetry, electrocardiogram (ECG) ,bispectral index (BIS) and non invasive blood pressure (NIBP) were attached to patient once admitted to OT.
- Two 18G IV branulla was setted to the patient. Both were attached to a three way stopcock.One was dedicated for infusion of TCI propofol and remifentanil.
- The second IV access was dedicated for infusion of ringer lactate and dex
- IV ringer lactate 10ml/kg preloading was infused to the patient
- This was followed by IV Dex 1mcg/kg was infused over 10 minutes. The dosing was based on Precedex full prescribing information, last revised September 2014, downloaded from internet at http://www.precedex.com/wp-content/uploads/Precedex_PI.PDF.
- TCI remifentanil was started at 2ng/ml, using Minto model.

- Once the target concentration of remifentanil was achieved (which will be shown in the display monitor of the TCI machine), TCI propofol was started at 2mcg/ml, which was either using Marsh or Schnider model, based on randomisation.
- When using Marsh model, plasma concentration mode was used. When using Schnider model, effect-site concentration mode was used.
- Successful of induction is monitored via loss of verbal response and BIS score <55. If after 1 minutes and successful of induction is not achieved, propofol is titrated up by 0.5mcg/ml every 30 sec until loss of verbal response and BIS score<55 is achieved.
- Effect site concentration and BIS value were recorded at the time of successful induction. Effect site concentration was obtained from the display monitor of TCI machine.
- Once successful induction, rocuronium 0.6mg/kg is given followed by tracheal intubation 3 minutes later.
- Intravenous ephedrine 6mg will be given whenever MAP<60mmhg and intravenous atropine 0.5mg will be given when HR<50/minutes. The dose of atropine is based on Bradycardia ACLS algorithm. Patients who were administered atropine or ephedrine within the time frame of starting iv dex infusion up to the time of 5 minutes post intubation were excluded from the study.
- Patients with unanticipated difficult intubation and develop severe hypotension and bradycardia requiring rescue drugs (atropine/ephedrine) after infusion of study drugs will be withdrawn. This patients will be observed for two hours in recovery bay and will only be discharged to ward once all the haemodynamic parameters are stable. The withdrawn patients will not be replaced.
- The following data will be recorded:

  -induction time taken (secondary end points)

  -blood pressure and heart rate during induction of anaesthesia at four time interval (T-baseline, T-after loading, T-after TCI remifentanil and T-after successful TCI propofol induction) (primary end points).

  -effect site concentration of TCI-propofol after successful induction of TCI propofol (secondary end points).

-blood pressure and heart rate after endotracheal intubation at three time interval (T-before intubation, T-1 min after intubation, T-5 min after intubation) between two groups (primary end points)

-BIS score at five time interval (T-baseline, T-after loading, T-after TCI remifentanil ,T-after successful TCI propofol induction, and T-5min after intubation)

- Dex infusion will be given loading dose at 1mcg/kg over 10 minutes, assuming the maximum weight of patient enrol in this study is 100kg, he will require 100mcg of Dex. Each vial of Dex contain 200mcg of dex in 2ml solution. 2 ml Dex will be diluted with 48ml 0.9% sodium chloride to achieve concentration of 4mcg/ml.The required amount will be calculated and the exact amount will be drawn up for him. The total dose of propofol and remifentanil will depend on patient parameters (gender, age, weight, and height), haemodynamic responses and the length of surgery. Infusion of propofol and remifentanil is done through individual TCI machine using 50ml syringes, which will alert the user when to volume of the infuse drug is reaching the end. By this time the infused drugs will be topped up manually. The combination medication will cover the required period.

Sample size calculation:

- The sample size calculation is based on the study by Viterbo J F et al (2012) for all the three objective in this study .We use power and sample size calculations software version 3.1.2 using independent t-test. For the first objective, sample size was estimated to detect a 10% difference between groups in decrease in mean blood pressure, with a power of 0.8 and α=0.05. Calculated sample size is 28 per group.
- For the second objective, sample size was estimated based on mean difference of 14% between group in time to induction, with a power of 0.8 and α=0.05. Calculated sample size is 32 per group.
- For the third objective, sample size was estimated based on mean difference of 17% between group in predicted effect-site concentration, with a power of 0.8 and α=0.05. Calculated sample size is 17 per group.

- The highest sample size calculated was based on the second objective, different in group in induction time. Calculated sample size is 64. Taking into account at 20% sample drop out rate, the total number of patient required will be 80.

Statistical analysis:

Objective parameter	**Statistical analysis**
• To compare induction time between two groups	Independent t-test
• To compare haemodynamic changes (MAP and HR) during induction of anaesthesia at four time interval (T-baseline, T-after dexmedetomidine loading, T-after TCI remifentanil, T-after successful propofol induction)	Repeated measures ANOVA and paired t-test
• To compare haemodynamic changes (MAP and HR) after endotracheal intubation at three time intervals (T-before intubation, T-1 min after intubation, T-5 min after intubation) between two groups	Repeated measures ANOVA and paired t-test
• To compare effect site concentration of propofol at successful induction	Independent t-test

Concurrent medications:

The following medications are not permitted during their study:

- Any sedative premedication (eg:midazolam, morphine)

The following medications are permitted during their study:

- Steroids (eg:dexamethasone, hydrocortisone)
- Non steroidal anti-inflammatory drugs (eg: brufen, celecoxib, paracetamol)
- Antibiotics (eg: cefuroxime, augmentin, metronidazole, ceftriaxone)
- Antiepileptics (eg: gabapentin, carbamazepine)
- Antiyhroids (eg ; carbimazole, prophylthiouracil)
- Tramadol

Flow chart of Study

Approval from ethics committee HUSM and NMRR.

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Selection of patients based on criteria being determined.

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Obtain written consent from patients.

↓

Premedication is omitted from the patient. 2 dedicated intravenous access is applied, one for TCI propofol and TCI remifentanil infusion. The other for intravenous Dex and ringer's lactate.

↓

Standard monitoring of baseline saturation, ECG ,blood pressure and BIS is applied.

↓

IV ringer's lactate 10ml/kg preloading is given

↓

Patient is randomized into two groups, marsh (M) and schnider (S)

↓

Marsh (M) group (n=40)	Schnider (S) group (n=40)
• Iv Dex 1mcg/kg over 10 minutes • TCI remifentanil using Minto model with target concentration of 2ng/ml • TCI propofol using Marsh model with target concentration of 2mcg/ml, titrating upward to loss of verbal response and BIS<55	• Iv Dex 1mcg/kg over 10 minutes • TCI remifentanil using Minto model with target concentration of 2ng/ml • TCI propofol using Schnider model with target concentration of 2mcg/ml, titrating upward to loss of verbal response and BIS<55

↓

IV rocuronium 0.6mg/kg followed by intubation after 3 minutes

↓

Following data will be recorded

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- Induction time taken for successful induction
- Haemodynamic changes (MAP and heart rate) at four time interval (T-baseline, T-after Dex loading, T-after TCI remifentanil, T-after successful propofol induction)
- Effect site concentration of TCI-propofol after successful induction
- Haemodynamic changes (MAP and heart rate) at three time interval (T-before intubation, T-1 min after intubation, T-5 min after intubation)
- BIS score at five time interval (T-baseline, T-after Dex loading, T-after TCI remifentanil, T-after successful propofol induction and T-5 mins after intubation

↓

Maintenance of subsequent anaesthesia according to respective TCI model

↓

Data collection

↓

Statistical analysis

↓

Dissertation report writing

↓

Submission of dissertation

Gantt Chart

	FEB 2015	June 2015	July-Dec 2015	Jan 2016	Feb 2016	June 2016	July 2016
Proposal presentation to Dissertation Committee, HUSM							
Proposal submission to Research & Ethics Committee, HUSM							
Data collection							
Data analysis and interpretation							
Presentation and submission of report							
Report writing							
Submission of research paper							

2.2 Ethical Approval Letter

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

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9th November 2015

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JEPeM Code : USM/JEPeM/15040141
Protocol Title : Comparison the Effect of Intravenous Dexmedetomidine (Dex) on Different Target-Controlled (TCI) Mode of Propofol (Marsh vs Schnider) for Induction of 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/15040141**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **November 2015** until **October 2016.**

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

1. Research Proposal

In addition to the above-mentioned 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

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) 2014: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2014: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2014: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2014: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2014.**
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) 2014: Final Report Form.**

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

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

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,

PROF. DR. MOHD SHUKRI OTHMAN
Deputy Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
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Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
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Date of meeting : 13 August 2015
Venue : Meeting Room, Centre for Research Initiatives, Clinical and Health Sciences, USM Kampus Kesihatan.
Time : 9.00 a.m – 1.00 p.m
Meeting No : 314

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

	Member (Title and Name)	Occupation (Designation)	Male/ Female (M/F)	Tick (✓) if present when above items, were reviewed
Deputy Chairperson :	Professor Dr. Mohd Shukri Othman	Deputy Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	M	✓ (Deputy Chairperson)
Secretariat:	Miss Siti Fatihah Ariffin	Research Officer	F	✓
Members :				
1.	Professor Dr. Zeehaida Mohamed	Lecturer, School of Medical Sciences	F	✓
2.	Associate Professor Dr. Lee Yeong Yeh	Lecturer, School of Medical Sciences	M	✓
3.	Dr. Teguh Haryo Sasongko	Lecturer, Human Genome Center	M	✓
4.	Dr. Azlan Husin	Lecturer, School of Medical Sciences	M	✓
5.	Dr. Haslina Taib	Lecturer, School of Dental Sciences	F	✓
6.	Mrs. Zawiah Abu Bakar	Community Representative	F	✓

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SECTION 3

BODY CONTENT

3.1 Title page

Title:

Comparison of the Effect of Intravenous Dexmedetomidine on Different Target-controlled Infusion Pharmackinetic Models for Propofol (Marsh vs. Schnider) during Induction of Anaesthesia

Short title:

The Effects of Dexmedetomidine on Marsh and Schnider Models of Target-controlled Infusion Propofol

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Conflict of interest: None

Acknowledgement:

I would like to acknowledge Wong Weng Kin for his help on statistical analysis

3.2 Main document

Title:

Comparison of the Effects of Intravenous Dexmedetomidine on Different Target-controlled Infusion Pharmacokinetic Models of Propofol (Marsh vs. Schnider) during Induction of Anaesthesia

Abstract

Background: Dexmedetomidine is selective alpha 2-agonist which is commonly used for sedation and potential to be used as co-induction drug. The aim of this study was to determine the effects of dexmedetomidine on induction using different target-controlled infusion (TCI) pharmacokinetic models of propofol.

Methods: 64 patients, aged 18-60 year-old, classified under ASA I and II, who underwent elective surgery under general anaesthesia, were randomised into two groups; Group Marsh (n=32) and Group Schnider (n=32). All patients received 1 mcg/kg loading dose of intravenous (IV) dexmedetomidine over 10 minutes and followed with TCI remifentanil at 2 ng /ml. After effect-site concentration (C_e) of remifentanil achieved 2 ng/ml, TCI propofol induction was started. Group Marsh was started with Marsh model at target plasma concentration ($C_p t$) of 2 mcg/ml, whereas Schnider group was started with Schnider model at target effect concentration ($C_e t$) of 2 mcg/ml. If induction was unsuccessful after 3 min, target concentration (Ct) was gradually increased to 0.5 mcg/ ml every 30 seconds until succesful induction. Ct requirement of propofol at successful induction, induction time, C_e of propofol at successful induction and serial of haemodynamic parameters were recorded for statistical analysis.

Results: Requirement of Ct of propofol for successful induction was significantly lower in Group Schnider than Group Marsh [3.48 (0.90) vs. 4.02 (0.67) μg/ml; *P* = 0.01]. Mean induction time was also shorter in Group Schnider than Group Marsh [134.96 (50.91) vs. 161.59 (39.64); *P* = 0.02] seconds. There were no significant differences in C_e at successful induction and haemodynamic parameters between the two groups.

Conclusions: Dexmedetomidine as co-induction with TCI remifentanil and TCI propofol reduced Ct requirement for induction and shorter induction time in Schnider model than Marsh model of TCI propofol. However, haemodynamic effects were stable in both groups.

Keywords: Marsh model, Schnider model, propofol, dexmedetomidine, target-controlled infusion, induction time, target plasma concentration, target effect concentration.

Introduction

Dexmedetomidine is highly selective alpha-2-adrenoreceptor agonists which possess sedative, hypnotive and some analgesic effects. (1) It is commonly used for conscious sedation in intensive care unit (ICU) and monitored anaesthesia care procedures, and also as an adjunct drug for regional anaesthesia as well as peripheral nerve block. If it is compared to other sedative agents, one of the advantage of dexmedetomidine is its ability to provide more conscious sedation without respiratory depression effect and at the same time is able to provide some analgesic effect (2).

The usage of dexmedetomidine is currently further extended to an adjuvant drug during general anaesthesia which include being used for pre-medication, co-induction and adjuvant in total intravenous anaesthesia (TIVA) technique. It has been shown to provide better perioperative haemodynamic control, less intraoperative opioid consumption, and fewer postoperative antiemetic requests during intracranial procedure (3). Its effect as as adjuvant to propofol and remifentanil based anaesthesia also has been shown to reduce total propofol dose requirement and produced more stable intraoperative haemodynamics (4). The emergence from anaesthesia was also smooth and stable haemodynamically with intraoperative infusion of dexmedetomidine (5).

TIVA is a technique of anesthesia that conventionally using all intravenous drugs without using inhalational agents. This technique has less post operative nausea and vomiting, less usage of antiemetic, produce less headache and less drowsiness than inhalational anaesthesia technique (6). TIVA can be provided either using mannually-controlled infusion technique or more advanced technique, which is target-controlled infusion (TCI) technique. TCI is a method of administrating certain intravenous drugs

based on setting of target plasma or target effect-site (brain) concentration using special infusion pump, which is incorporated with software of algorithm of pharmacokinetic parameters of that drugs. Two drugs that are currently capable to be administered using TCI are propofol and remifentanil. There are only two validated pharmacokinetic models of propofol available for clinical usage in adult, which are Marsh and Schnider models whereas only Minto model is available for TCI remifentanil.

Marsh and Schnider model are derived from different pharmacokinetic parameters from different population pharmacokinetic, which can result in significantly different in infusion rate on adminitration. This different in infusion rate might result in different pharmacodynamics response during anaesthesia. The Marsh model was the first model developed for TCI propofol that commonly used target plasma concentration (C_pt) mode by taking into account of the patient's weight and age. On the other hand, Schnider model is a newer developed model that commonly used target effect-site concentration (C_et) mode by taking into account of patient's weight, height, age and gender to derive the lean body mass (7). There is also Marsh model with effect site concentration mode in some TCI pumps and were also being called as modified Marsh model (8).

The aim of this study was to compare the effects of loading intravenous (IV) dexmedetomidine co-induction on target concentration requirement for succesful induction, induction time, effect-site concentration at successful induction and haemodynamic changes between TCI propofol induction using Marsh and Schnider models.

Materials and Methods

This was a prospective, double-blinded, randomised controlled trial, conducted in the university hospital (Hospital Universiti Sains Malaysia).

After approval from university ethics committee and written inform consent from all patients, 62 patients undergoing elective surgery under general anaesthesia, with aged between 18-60 year-old and American Society of Anaesthesiologists (ASA) class I-II, were randomized into two groups; Group Marsh (n=32) and Group Schnider (n=32). Those patients with history of allergies to study drugs, preoperative bradycardia with heart rate (HR) < 55 beats/minute, cardiac dysrhythmia, preoperative hypotension with mean arterial pressure (MAP) <60 mmHg, known history of difficult intubation, pregnancy, liver or renal disease, obesity and hypertension were excluded from the study. Patients were withdrawn from study in the event of unanticipated difficult intubation, severe hypotension or bradycardia after starting infusion of study drugs that required optimisation with rescue drugs (atropine/ ephedrine).

Randomisation

A study number of 01 to 80 was prepared. These numbers was labelled as Group M (Marsh) or Group S (Schnider) and the randomization was done through internet, at the website of www.randomization.com. 80 subjects were randomised into 20 blocks and these study numbers were divided into 2 groups equally, Group M (Marsh) and Group S (Schnider). The study was completed after 64 patients successfully recruited. Initial 80 subjects for randomisation were based on calculation of 20 % drop out rate.