Original Article

Comparison of the Effects of Dexmedetomidine on the Induction of Anaesthesia Using Marsh and Schnider Pharmacokinetic Models of Propofol Target-Controlled Infusion

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Abstract

Background: **The study aimed to determine the effects of dexmedetomidine on the induction of anaesthesia using different models (Marsh and Schnider) of propofol target-controlled infusion (TCI).**

Methods**: Sixty-four patients aged 18–60 years, American Society of Anaesthesiologists (ASA) class I-II who underwent elective surgery were randomised to a Marsh group (*n* = 32) or Schnider group (*n* = 32). All the patients received a 1 µg/kg loading dose of dexmedetomidine, followed by TCI anaesthesia with remifentanil at 2 ng/mL. After the effect-site concentration (Ce) of remifentanil reached 2 ng/mL, propofol TCI induction was started. Anaesthesia induction commenced in the Marsh group at a target plasma concentration (Cpt) of 2 µg/mL, whereas it started in the Schnider group at a target effect-site concentration (Cet) of 2 µg/mL. If induction was delayed after 3 min, the target concentration (Ct) was gradually increased to 0.5 µg/mL every 30 sec until successful induction. The Ct at successful induction, induction time, Ce at successful induction and haemodynamic parameters were recorded.**

Results**: The Ct for successful induction in the Schnider group was significantly lower than in the Marsh group (3.48 [0.90] versus 4.02 [0.67] µg/mL; *P* = 0.01). The induction time was also shorter in the Schnider group as compared with the Marsh group (134.96 [50.91] versus 161.59 [39.64]) sec; *P* = 0.02). There were no significant differences in haemodynamic parameters and Ce at successful induction.**

Conclusion**: In the between-group comparison, dexmedetomidine reduced the Ct requirement for induction and shortened the induction time in the Schnider group. The inclusion of baseline groups without dexmedetomidine in a four-arm comparison of the two models would enhance the validity of the findings.**

Keywords: *Marsh, remifentanil, propofol, dexmedetomidine, target-controlled infusion, pharmacokinetic*

Introduction

Dexmedetomidine is a highly selective alpha-2-adrenoreceptor agonist, which possesses sedative, hypnotic and analgesic effects (1). It is commonly used for conscious sedation in intensive care units and monitored anaesthesia care procedures, as well as an adjuvant drug for regional anaesthesia and peripheral nerve block. As compared with other sedative agents, one advantage of dexmedetomidine is its ability to provide more conscious sedation, without respiratory depression (2).

It also has an analgesic effect (2). The uses of dexmedetomidine have been extended to include general anaesthesia, where it is used as an adjuvant drug for pre-medication and co-induction in total intravenous anaesthesia (TIVA). Studies showed that dexmedetomidine was associated with better perioperative haemodynamic control, less intra-operative opioid consumption, fewer requests for post-operative antiemetics, reduced total propofol dose requirements and smooth emergence (3–5).

In TIVA, intravenous (IV) drugs rather than inhalational agents are administered. TIVA is associated with reduced post-operative nausea, in addition to decreased vomiting, antiemetic use, headaches and drowsiness, as compared with inhalational anaesthesia (6). TIVA can be administered using a manually-controlled infusion technique or via target-controlled infusion (TCI). The latter is a more advanced method IV drug infusion, which requires setting target plasma or target effect-site (brain) concentrations using a special infusion pump. Data on the pharmacokinetic parameters of the drug are programmed in the pump and the pump software. Only two drugs, propofol and remifentanil, can currently be administered using TCI. Furthermore, only two validated pharmacokinetic models for propofol are currently available for clinical usage in adults: Marsh and Schnider models. The Minto model is available for remifentanil TCI.

Marsh and Schnider models utilise different pharmacokinetic and patient parameters, which can result in marked differences in the infusion rate on administration. The Marsh model, which was the first pharmacokinetic model developed for propofol TCI, calculates the target plasma concentration (Cpt) and takes account of the patient's weight and age. The Schnider model is a newer model, which uses the target effect-site concentration (Cet) and takes a patient's weight, height, age and gender into consideration (7). A modified Marsh model is also available that employs the Cet mode (8). Differences in infusion rates can result in different pharmacodynamic responses during anaesthesia. The effect of dexmedetomidine as a co-induction agent on different pharmacokinetic models of propofol TCI has not been investigated previously.

The aim of this study was to compare the effects of dexmedetomidine co-induction on the target concentration requirement for successful induction, in addition to the induction time, Cet at successful induction and haemodynamic changes, in Marsh and Schnider pharmacokinetic models of propofol TCI.

Materials and Methods

This was a prospective, double-blinded, randomised controlled trial, conducted in a single university hospital (Hospital Universiti Sains Malaysia) and approved by the university's ethics committee (USM/JEPeM/15040141).

After obtaining written informed consent from all the patients, 64 patients aged 18–60 years, American Society of Anaesthesiologists (ASA) class I-II who were scheduled to undergo elective surgery under general anaesthesia were randomised into two groups: a Marsh group (n = 32) and a Schnider group (n = 32). Patients with a history of allergies to the study drugs; pre-operative bradycardia (heart rate < 55 beats/min); cardiac dysrhythmia; pre-operative hypotension with mean arterial pressure < 60 mmHg; and a known history of difficult intubation, pregnancy, liver or renal disease, obesity and hypertension were excluded from the study. Patients with unanticipated difficult intubation and severe hypotension or bradycardia after infusion of the study drugs was started that required optimisation with rescue drugs (atropine/ephedrine) were withdrawn from the study.

All patients scheduled for elective surgery underwent a pre-operative assessment on the day prior to surgery, and patients who fulfilled the inclusion and exclusion criteria were selected. No sedative pre-medication was given to any of the patients. The recruited patients were randomly allocated to a Marsh group or a Schnider group (n = 32 in each) using a computer-generated table of random numbers and opaque sealed envelopes. The seal were broken by the attending anaesthetist to reveal the allocated group before proceeding with the induction of anaesthesia.

This was a double-blinded study, in which neither the patient nor the second medical officer who assessed the patient in the operation theatre knew which pharmacokinetic model of propofol TCI was going to be used. In all patients, a standard Alaris® PK TIVA/TCI pump (CareFusion, Hampshire, UK) was used for propofol and remifentanil. The drug preparation, TCI pump set-up and conduct of anaesthesia were performed according to the randomisation.

Prior to the induction of anaesthesia, standard non-invasive blood pressure, pulse oximetry, bispectral index (BIS), electrocardiogram and capnography monitoring was undertaken. Two 18-gauge IV cannulas were inserted, both of which were attached to a three-way stopcock. The first IV access was for infusion of propofol and remifentanil, and the second IV access was for infusion of Ringer's lactate solution and dexmedetomidine. A pre-loading dose of 10 mL/kg of Ringer's lactate solution was given to the patient before induction.

After administration of the pre-loading fluid, IV dexmedetomidine (1 µg/kg) was infused for 10 min. Subsequently, remifentanil TCI was started at 2 ng/mL using the target Cet of the Minto model, until the Ce of remifentanil reached the same concentration as that displayed on the monitor of the TCI pump. Induction with propofol TCI was subsequently started, depending on the randomisation group. In the Marsh group, induced was started according to the Marsh model at a Cpt of 2 µg/mL. In the Schnider group, induction was started according to the Schnider model at a Cet of 2 µg/mL. If induction was unsuccessful after 3 min, the target concentration was gradually increased to 0.5 mcg/mL every 30 second until successful induction. Successful induction was assessed based on loss of verbal responses and a BIS score < 55. The target concentration requirement of propofol upon successful induction, induction time and Ce of propofol upon successful induction were recorded, in addition to haemodynamic parameters at baseline (T1), 1 min after a loading dose of dexmedetomidine (T2), 1 min after remifentanil TCI (T3), 1 min after successful induction (T4), 1 min after intubation (T5) and 5 min after intubation (T6) were recorded. After successful induction, IV rocuronium (0.6 mg/kg) was given, followed by tracheal intubation 3 min later. IV titration of ephedrine in increments of 3 mg was given in cases where the arterial pressure was < 60 mmHg, and IV atropine (0.5 mg) was given in cases where the heart rate was < 50 beats/min. After tracheal intubation, maintenance of anaesthesia was continued with propofol (3–6 µg/mL) and remifentanil (2–8 ng/mL) TCI.

The sample size calculation was based on the study by Viterbo et al. (9). PS Power and Sample Size Calculation software version 3.1.2 by William D. Dupont and Walton D. Plummer was used for sample size calculations. The sample size was estimated based on a mean difference of 14% between the groups in the time to the induction of anaesthesia, with a power of 0.8 and $\alpha = 0.05$. The calculated sample size was 32 per group.

Statistical Analysis

All measurement data were analysed for normal distribution and homogeneity variance. Data with a normal distribution were presented as mean (standard deviation). Data with a non-normal distribution were presented as median. Variables between groups were analysed with independent *t*-tests. A repeated measures analysis of variance test was conduced to compare haemodynamic parameters at different time intervals. All statistical analyses were performed using SPSS version 22 software, and $P < 0.05$ was taken to denote a statistically significant difference.

Results

The demographic data on the 64 patients in the Marsh group ($n = 32$) and Schnider group ($n = 32$) are presented in Table 1. The types of surgeries performed included general surgery (32.8%), gynaecological (6.3%), orthopaedic (48.4%), ear, nose and throat (18.6%), plastic (3.1%), ophthalmological (3.1%) and dental (3.1%). There were no significant differences in age, height and ASA health status of the two study groups. There were significant between-group differences in weight and sex.

The requirement of the target concentration of propofol for successful induction was significantly lower in the Schnider group than in the Marsh group (3.48 [0.90] versus 4.02 [0.67] µg/mL; $P = 0.01$). The mean induction time was also shorter in the Schnider group then the Marsh group (134.96 [50.91] versus 161.59 [39.64] sec; $P = 0.02$). There were no significant differences in Ce in cases of successful induction (Table 2). In terms of haemodynamic parameters, there were no significant differences between the two groups at different time intervals (Table 3).

Discussion

The use of dexmedetomidine as an adjuvant to general anaesthesia is becoming more popular because of its advantage in providing haemodynamic stability during sympathetic stimulation throughout anaesthesia and

Table 1. Demographic data

	Group Marsh (n = 32)	Group Schnider (n = 32)	P-value
Age	32.3 (11.2)	31.3 (10.9)	0.727
Height (m)	1.60 (0.05)	1.57 (0.07)	0.059
Weight (kg)	64.3 (11.2)	56.4 (9.8)	0.004*
ASA:			
I	28 (87.5%)	28 (87.5%)	1.000
II	4 (12.5%)	4 (12.5%)	
Sex:			
Male	11 (34.4%)	22 (68.8%)	0.006*
Female	21 (65.6%)	10 (31.3%)	
Type of Surgery:			
Gen. Surgery	8 (25.0%)	13 (40.6%)	0.157
Gynaecology	1 (3.1%)	3 (9.4%)	
Orthopaedics	21(65.6%)	11 (34.4%)	
ENT	1 (3.1%)	3 (9.4%)	
Plastic Surgery	1 (3.1%)	0	
Ophthalmology	0	1 (3.1%)	
Dental	0	1 (3.1%)	

All numerical data were expressed in mean (SD); all categorical data were expressed in n (%)

Table 2. Mean of target concentration, effect-site concentration and induction time

	Group: Marsh (n = 32) Schnider (n = 32)	Mean (SD)	t	df	Mean Diff	P
Target concentration at successful induction (mcg/mL)	Marsh	4.02 (0.67)	2.68	62	0.53	0.01*
	Schnider	3.48 (0.90)				
Effect-site concentration at successful induction, (mcg/mL)	Marsh	3.57 (0.98)	1.69	62	0.39	0.10
	Schnider	3.18 (0.85)				
Induction time (sec)	Marsh	161.50 (39.64)	2.34	62	26.64	0.02*
	Schnider	134.96 (50.91)				

*Significant difference was found by Independent t-test, $P < 0.05$

surgery. The main aim of the present study was to investigate the effects of the loading dose of dexmedetomidine as co-induction on induction using Marsh and Schnider pharmacokinetic models of propofol TCI. To the best of our knowledge, there have been no studies of the effects of dexmedetomidine on different TCI pharmacokinetic models. In the present study, the loading dose of dexmedetomidine resulted in a lower target concentration requirement for successful induction and a shorter induction time in the Schnider model than Marsh model. In terms of haemodynamic changes, both groups were comparatively stable.

In the present study, the speed of induction using the Schnider model was most likely due to the use of Cet in this model. One advantage of Cet is the administration of a larger initial dosage of propofol, which speeds up the induction of anaesthesia. The dosage is determined by a combination of parameters, such as the target setting and blood-effect time-constant (keo) in

Table 3. Comparison of haemodynamic parameters

Time	Group: Marsh (n = 32) Schnider (n = 32)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (beats/ min)
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
T-baseline	Marsh	132.0 (123.1, 140.9)	78.7 (75.3, 82.1)	100.7 (96.4, 105.0)	80.3 (74.9, 85.7)
	Schnider	128.4 (123.4, 133.4)	75.3 (71.8, 78.7)	95.9 (92.0, 99.8)	82.1 (75.7, 88.6)
T-after IV Dex	Marsh	125.7 (119.1, 132.2)	72.3 (68.8, 75.9)	90.9 (86.0, 95.7)	64.2 (60.9, 67.4)
	Schnider	119.8 (113.7, 126.0)	72.0 (67.7, 76.3)	90.5 (85.7, 95.2)	63.2 (58.6, 67.8)
T-after TCI Remi	Marsh	119.8 (113.3, 126.2)	69.4 (66.1, 72.6)	87.9 (83.4, 92.4)	63.7 (60.3, 67.1)
	Schnider	112.7 (106.2, 119.2)	67.3 (63.1, 71.6)	85.3 (80.3, 90.2)	62.1 (56.9, 67.2)
T-after LOC	Marsh	109.4 (102.9, 116.0)	61.9 (58.5, 65.3)	80.2 (75.6, 84.7)	60.7 (57.8, 63.5)
	Schnider	105.3 (99.9, 110.8)	62.8 (59.1, 66.6)	79.4 (75.2, 83.6)	59.8 (56.2, 63.4)
T-baseline before intubation	Marsh	108.5 (98.6, 118.4)	63.1 (59.0, 67.2)	81.5 (75.8, 87.1)	63.2 (69.8, 66.6)
	Schnider	109.9 (103.5, 116.4)	68.6 (64.2, 72.9)	84.0 (79.4, 88.6)	61.0 (57.1, 64.8)
T-1 min after intubation	Marsh	113.0 (106.8, 119.1)	65.8 (62.3, 69.3)	84.4 (79.9, 88.9)	70.5 (67.6, 73.3)
	Schnider	115.2 (109.6, 120.7)	69.2 (65.4, 72.9)	86.8 (82.6, 91.0)	68.3 (64.3, 72.4)
T-5 min after intubation	Marsh	105.8 (99.2, 112.5)	60.3 (56.6, 64.0)	77.6 (72.6, 82.7)	68.2 (65.2, 71.2)
	Schnider	108.0 (104.6, 111.4)	63.7 (60.7, 66.6)	81.0 (77.9, 84.1)	69.4 (64.9, 74.0)
P-value		0.570	0.604	0.985	0.780

Repeated Measures ANOVA between group analysis with regard to time; $P < 0.05$ is considered significantly different

the pharmacokinetic model. With the help of a computer simulation, Glen et al. (10) determined the ke0 values required to deliver a range of initial doses using three pharmacokinetic models for propofol. With an Cet of 4 µg/ mL, in a 35-year-old, 170-cm tall, 70-kg male subject, the ke0 values delivering a dose of 1.75 mg/kg with the Marsh, Schnider and Eleveld models were 0.59 min^{-1}, 0.20 min^{-1} and 0.26 min^{-1}, respectively (10). Thus, in terms of the Cet, the Schnider model had a faster ke0, even without the dexmedetomidine effect (10). Ramos Luengo et al. (11) examined the performance of two propofol pharmacokinetic models, the modified Marsh model and Schnider model, to determine the best model in terms of patient requirements and major haemodynamic side effects during induction and intubation. They failed to detect any haemodynamic differences between the two groups, despite the use of Cet in the modified Marsh model and the Marsh group receiving a larger dose of propofol. In the current study of the effects of dexmedetomidine on remifentanil TCI, we found no haemodynamic differences

between the two groups. Yang et al. (12) also studied haemodynamic changes during the induction of anaesthesia using Marsh and Schnider different models. The initial target concentration was 4 μg/mL in both groups. They found that when target concentrations were titrated according to the narcotrend index during the induction of anaesthesia, the Marsh model induced sedation faster than the Schnider model, although there were no differences in haemodynamic parameters. The same study reported that the time to loss of responsiveness and time for the narcotrend index to decrease to 64 was significantly faster using the Marsh than Schnider model (1.51 [0.8] versus 2.8 [1.2] min; 3.3 [2.0] versus 5.2 [2.3] min), respectively. Yang et al. also showed that hypotension induced by plasma propofol TCI was mainly attributed to a decreased stroke volume instead of vascular dilation (12). Thomson et al. (13) studied the use of a new ke0 value (0.6 min^{-1}) for the Marsh pharmacokinetic model for propofol. In their study, the median (interquartile range) induction times were significantly shorter using the Marsh model in the Cet control mode, with a ke0 of either 0.6 min^{-1} (81 [61–101] [49–302] sec) or 1.2 min^{-1} (78 [68–208] [51–325] sec) than using the Marsh model in Cpt mode (132 [90–246] [57–435] sec). Using the Cet control mode in the Schnider model resulted in significantly longer induction times than using Cpt mode (298 [282–398] [58–513]) sec). The induction times were longer than those observed using the Marsh model in either mode. In the same study, there were no differences in the magnitude of blood pressure changes or frequency of apnoea. In contrast, in the present study, the induction time was faster using the Schnider model. Kim et al. (14) also showed that when both models used the Cpt, the induction time using the Marsh model was faster than that using the Schnider model, with no significant difference in the Ce upon loss of responsiveness.

Issues of predictive performance and bias affect different pharmacokinetic models of TCI. Soehle et al. (15) examined the predictive performances of the Marsh and Schnider models during awake craniotomy. They determined that the Marsh model was associated with significantly higher inaccuracy than the Schnider model, with the former showing a tendency towards higher bias. The prediction probability of the two models was comparable. However, after adjusting the models to each individual patient, the prediction probability of the Schnider model was significantly better than that of the Marsh model. Soehle et al. advocated using the Schnider model when using the 'asleep-awake-asleep' anaesthetic technique during awake craniotomy, together with additional monitoring of the anaesthetic depth due to considerable inter-individual variation (15). In a subsequent study, Soehle et al. (16) examined the Cp and Ce of propofol, as well as the related BIS required for intra-operative return of consciousness and beginning of neurological testing in awake craniotomy. They showed that propofol concentrations estimated using the Schnider model were significantly more accurate than those determined using the Marsh model at neurologically crucial time points (16).

Some recent studies investigated the effects of dexmedetomidine on anaesthesia using the TCI technique. Park et al. (17) studied the effects of low-dose dexmedetomidine in a placebo controlled study on haemodynamic and anaesthetic requirements during propofol and remifentanil anaesthesia for laparoscopic cholecystectomy. Dexmedetomidine infusion of 0.3 μg/kg/h or placebo was administered, together with propofol and remifentanil TCI used for induction and maintenance, respectively. They demonstrated that low-dose dexmedetomidine (0.3 μg/kg/h) reduced propofol and remifentanil requirements by 16% and 23%, respectively, as well as haemodynamic changes in the pneumoperitoneum, without delayed recovery. This study did not state the loading dose of dexmedetomidine and did not assess the Ct, Ce or induction time. Wang et al. (18) examined the effects of different loading doses of dexmedetomidine on the BIS using stepwise propofol TCI, in which dexmedetomidine at doses of 1.0, 0.5, 0.25 or 0 mcg/kg was infused over 10 min, followed by 0.5 mcg/kg/h. The stepwise propofol TCI protocol was a Cet of 0.5 mcg/mL, which was increased by 1.0 mcg/mL 5 min after reaching the target Ce until 2.5 mcg/mL. Their results showed that only a loading dose of dexmedetomidine of 1.0 mcg/kg over 10 min, followed by 0.5 mcg/kg/h definitely decreased the BIS using stepwise propofol TCI, with clinically stable blood pressure and without respiration depression. However, Wang et al. noted that attention should be paid to a decreased heart rate using this protocol. Kang et al. (4) investigated the effects of dexmedetomidine TCI as an adjuvant to remifentanil-based TCI propofol-supplemented anaesthesia in breast surgery

patients. They compared either 1 μg/kg loading dose of dexmedetomidine or placebo before anaesthesia induction, followed by infusion of 0.6 μg/kg/h during surgery. Their results showed that dexmedetomidine reduced the propofol requirement for remifentanil-based anaesthesia while producing more stable intra-operative haemodynamics (4).

The present study has some limitations. The main limitation was the difference in the weight and sex of the participants. The mean weight of the patients in the Marsh group was significantly higher than that of the patents in the Schnider group (64.3 [11.2] versus 56.4 [9.8] kg). However, as the between-group difference in weight was not great, this may not have a major effect on the results. The percentage of females was higher in the Marsh group, whereas the percentage of males was higher in the Schnider group. Although sex is not a required parameter for input data in the Marsh model, it is required by the Schnider model. The differences in these two parameters (sex and weight) could be confounding factors in the present study. The inclusion of comparable demographic groups would have improved the validity of the results. Thus, the results should be interpreted with caution. Another limitation of our study was that it was not possible to differentiate whether the induction speed was influenced by dexmedetomidine or the type of pharmacokinetic model applied. A four-arm study of the two models, with and without dexmedetomidine could help to clarify the effect of dexmedetomidine on the speed of induction and the propofol target-sparing effect during induction.

Conclusion

In conclusion, the use of dexmedetomidine in co-induction of anaesthesia with remifentanil TCI and propofol TCI reduced the Ct requirement for induction and resulted in a shorter induction time in the Schnider model than the Marsh model of propofol TCI. Haemodynamic parameters and CE at successful induction were comparable in both groups. The validity of the findings could be improved by the inclusion of baseline groups without dexmedetomidine in a four arm-comparison of the two models. It is possible that both models would show a propofol-sparing effect under this scenario.

Authors' Contributions

Conception and design: THS, WMNWH
Analysis and interpretation of the data: THS, WMNWH
Drafting of the article: THS, WMNWH, RHMZ
Critical revision of the article for important intellectual content: THS, WMNWH, RHMZ
Final approval of the article: THS, WMNWH, RHMZ
Provision of study materials or patients: THS, WMNWH, RHMZ
Statistical expertise: THS, WMNWH
Administrative, technical, or logistic support: WMNWH, RHMZ
Collection and assembly of data: THS

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