

Original Research Article**Sedation with Dexmedetomidine versus Propofol during Regional Anaesthesia: Comparing Haemodynamic Parameters, Respiratory Rates and Offset Times**Nadia MN¹, Samsul Johari MA², Muhammad M¹, Raha AR¹, Nurlia Y¹¹Department of Anaesthesiology & Intensive Care, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000, Kuala Lumpur²Department of Anaesthesia and Intensive Care, Hospital Sultan Haji Ahmad Shah, Temerloh, 28000 Pahang**Abstract**

This study aimed to compare dexmedetomidine and propofol, in terms of haemodynamic parameters, respiratory rates and offset times, when used for sedation in patients undergoing elective orthopaedic and surgical procedures under regional anaesthesia. This was a prospective, randomised, single-blind study where 88 patients were recruited. Patients were randomised into two groups to receive either dexmedetomidine or propofol infusion. Central neuraxial blockade (spinal, epidural or combined spinal epidural) was performed. After ensuring an adequate block and stable haemodynamic parameters, dexmedetomidine was infused 15 minutes later at 0.4 µg/kg/hr, and propofol, at a target concentration of 2.5 µg/ml. Both drugs were titrated to achieve a bispectral index score of 70 before surgery commenced. Sedation level was monitored using the bispectral index score and assessed by the Observer Assessment of Alertness Scale score. Drug infusion was adjusted to maintain bispectral index scores ranging between 70-80 during surgery. Both groups showed reductions in mean arterial pressure and heart rate from baseline readings throughout the infusion time. However there was no significant reduction in the first 15 minutes from baseline ($p > 0.05$). Haemodynamic parameters and respiratory rate between both groups were not significantly different ($p > 0.05$). No patient demonstrated significant respiratory depression or $SpO_2 \leq 95\%$. Offset times were also not significantly different between both groups ($p = 0.594$). There were no significant differences in haemodynamic parameters, respiratory rates and offset times between dexmedetomidine and propofol used for sedation in patients undergoing elective orthopaedic and surgical procedures under regional anaesthesia.

Keywords: Dexmedetomidine, propofol, sedation, regional anaesthesia, bispectral index**Correspondence:**

Dr. Nadia Md Nor, Department of Anaesthesiology & Intensive Care, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia. Tel no: +60391455621 Fax: +60391456585 Email: nadiamn72@yahoo.com

Date of submission: 12 June, 2012

Date of acceptance: 25 July, 2012

Introduction

Sedation is given during regional anaesthesia to enhance patient comfort. Patients may feel uncomfortable and become restless especially if they need to remain immobile during a procedure. Sedation has been shown to increase patient satisfaction and acceptance of regional anaesthesia (1). The selection

of sedative agents depends on physician preference and the patient's pre-morbid status. Ideally, the sedated patient should be able to respond to physical and verbal stimuli, and also maintain their airway independently. A wide variety of centrally-acting drugs such as propofol, midazolam, clonidine and dexmedetomidine have been used to provide sedation and anxiolysis (1,2).

Propofol (2,6-diisopropylphenol) is an intravenous sedative-hypnotic agent used for induction and maintenance of general anaesthesia, as well as for sedation in patients undergoing surgery under regional anaesthesia. It acts by facilitating the inhibitory neurotransmission mediated by gamma amino butyric acid (1). The advantages of propofol are its rapid onset of action, easy titration, rapid emergence as well as antiemetic property (3-6). Propofol for intraoperative sedation can be delivered via target control infusion (TCI) with target plasma concentrations ranging between 1.0 - 3.0 µg/ml (2,4).

Dexmedetomidine is a selective α -2 receptor agonist, with potent sedative, anxiolytic and analgesic properties. Unlike propofol, it acts primarily on the postsynaptic α -2 receptor causing sedation and sympatholytic effects (1). Patients receiving dexmedetomidine at infusion rates ranging between 0.3 - 0.7 µg/kg/hour are effectively sedated, yet easily aroused with minimal respiratory depression (1,2). Its short half-life enables patients to have a rapid recovery with minimal hangover effect (2,7). It was licensed for use in the intensive care unit as a sedative for a maximum of 24 hours only (1,2,8). However, in 2008, the U.S Food and Drug Administration (FDA) approved the use of dexmedetomidine in non-intubated patients requiring sedation prior to and/or during surgical and other procedures. Studies have reported the use of dexmedetomidine for sedation in non-intubated patients during regional anaesthesia, radiological imaging and other procedures (7,9,10).

Both drugs provide effective sedation, but have slightly different cardiorespiratory effects, especially if a rapid loading dose was given (7-9). Propofol may be associated with cardiovascular depression, resulting in hypotension due to a reduction in systemic vascular resistance and cardiac contractility, and respiratory depression leading to apnoea (2,9,10). Although dexmedetomidine causes cardiovascular depression due to decreases in sympathetic outflow, it has only minimal effects on respiration (2,9). However, studies have shown that there were no significant haemodynamic effects when dexmedetomidine was used for sedation without a loading dose (11,12).

The aim of this study was to compare dexmedetomidine versus propofol, in terms of haemodynamic parameters, respiratory rates and offset times, when used for sedation in patients undergoing elective orthopaedic and surgical procedures under regional anaesthesia.

Materials and Methods

Subjects

This was a prospective, randomised, single-blind study. After obtaining institutional ethics committee approval and informed consent, patients of American Society of Anesthesiologists (ASA) physical status I or II, aged 18-70 years, planned for orthopaedic or surgical procedures requiring central neuraxial blockade were recruited into the study. Patients with allergies to the study drugs, potential airway difficulties, body mass index (BMI) ≥ 35 kg/m², on sedative medications and with conditions associated with low cardiac output, bradyarrhythmias, conduction defects and renal impairment were excluded from the study.

Methodology

Patients were fasted from midnight and given oral midazolam 3.75 mg the night before surgery. In the operating theatre, the patients were randomised into two groups using computerised generated randomised numbers. Group A patients received dexmedetomidine (Precedex™, Abbott Laboratories) infusion, and Group B patients received propofol (Diprivan™, Astra Zeneca) infusion. An 18G cannula was inserted and standard anaesthetic monitoring (electrocardiograph, pulse oximeter and non invasive blood pressure monitor) was applied. The bispectral index (BIS™) monitor (model A-2000, Aspect Medical Systems Inc.) was also used to monitor the level of sedation. The BIS is an index of depth of sedation, where completely awake patients scored 90 to 100; consciously sedated patients, 70 to 89; patients under general anaesthesia, 50 to 69; and deeply sedated and comatose patients, 0 to 50. The Observer Assessment of Alertness Scale (OAAS) was used together with the BIS score to monitor the depth of sedation, where the scores and corresponding responses were as follows: 6-Agitated; 5- Responds readily to name spoken in normal tone (alert); 4-Lethargic response to name spoken in normal tone; 3 - Responds only after name is called loudly and/or repeatedly; 2-Responds only after mild prodding or shaking ; 1-Does not respond to mild prodding or shaking ; 0-Does not respond to deep stimulus.

Haemodynamic parameters prior to the administration of regional anaesthesia were recorded. Regional anaesthesia (spinal, epidural or combined spinal epidural anaesthesia) was performed under full aseptic technique following standard protocols. Once an adequate level of anaesthesia was established,

supplemental oxygen at 5 L/min was given to all patients via face mask. The patients were monitored for blood pressure changes secondary to central neuraxial blockade. A reduction of 20% from the initial mean arterial pressure (MAP) was treated according to the study protocol. Infusion of the study drugs was started 15 minutes after, when the MAP was within 20% of initial readings. The drugs were infused using the Terufusion Syringe Pump TE-331 and baseline parameters were recorded before commencing drug infusion. In Group A, the infusion was started at an initial rate of 0.4 µg/kg/hour and increased in increments of 0.1 µg/kg/hour every five minutes, up to a maximum rate of 0.7 µg/kg/hour, to reach a target BIS score of 70. In Group B, TCI with a Graseby™ 3400 Syringe Pump was used, starting at a target concentration of 2.5 µg/ml and increased in increments of 0.2 µg/ml every three minutes, up to a maximum of 3 µg/ml, to reach a target BIS score of 70. Surgery was then allowed to proceed and the infusion rate or target concentration was adjusted as necessary to maintain a BIS score of between 70- 80 throughout the

Table 1: Demographic data, ASA class and duration of surgery. Values are expressed in mean ± SD and numbers (percentage) where appropriate

	Group A (n=43)	Group B (n=42)
Age (years)	57.5 ± 14.9	57.4 ± 15.2
Weight (kg)	68.0 ± 5.1	68.1 ± 4.7
Gender		
Male	28 (65.1%)	20 (47.6%)
Female	15 (34.9%)	22 (52.4%)
Race		
Malay	16 (37.2%)	22 (52.4%)
Chinese	17 (39.5%)	11 (26.2%)
Indian	6 (14.0%)	6 (14.3%)
Others	4 (9.3%)	3 (7.1%)
ASA		
I	19 (44.2%)	20 (47.6%)
II	24 (55.8%)	22 (52.4%)
Duration of surgery (minutes)	85.6 ± 13.1	86.9 ± 12.8

Table 2: Types of surgery. Values are expressed in numbers.

	Group A (n=43)	Group B (n=42)
Surgical		
Inguinal hernia repair	14	12
Fistula in ano repair	4	2
Others	4	4
Orthopaedic		
Arthroplasty	10	10
Femur instrumentations	7	9
Others	4	5

duration of surgery. All parameters were documented at 15-minute intervals till completion of surgery. The BIS score was recorded before OAAS assessment to ensure that the former was not affected by the verbal and tactile stimulation used to assess OAAS. The infusion was stopped at the end of skin closure. Offset time was defined as the interval between the cessation of infusion and the return of BIS score ≥ 90.

Any adverse events which occurred during the study was documented and treated accordingly. These included bradycardia (change of heart rate (HR) <20% baseline); tachycardia (change of HR > 20% baseline); hypotension (change MAP <20% of baseline); hypertension (change MAP >20% of baseline) and respiratory depression (respiratory rate (RR) ≤ 8 breaths/min). In the event of bradycardia, the drug infusion was reduced. Intravenous atropine 0.4 mg was administered depending on the severity of the bradycardia. If the patient became hypotensive, the drug infusion was reduced and fluid resuscitation with crystalloids (250-500 ml of Ringer's lactate solution) and/or bolus doses of ephedrine 6 mg or phenylephrine 50µg was given accordingly. If the patient's respiration was depressed, the drug infusion rate was reduced accordingly. However, if the SpO₂ subsequently dropped to ≤ 95%, the infusion was stopped. These patients were supported with appropriate airway devices, and assisted ventilation initiated. Those who required conversion to general anaesthesia were excluded from analysis.

Statistical analysis

This study was powered to detect a 15% difference in intraoperative MAP or HR from baseline, with an alpha value of 0.05 and beta value of 0.2. Using the power and sample size software PS by Dupont, a sample size of 40 patients per arm was obtained with a power of study of 0.8. Allowing for a dropout rate of 10%, a total of 88 patients were required for this study.

For statistical evaluation, all data analysis was done using the SPSS version 17.0 software. Student's t-test was used for analyzing age, weight, MAP, HR, RR, duration of surgery and offset times, while Chi-Square test was used to analyze gender, race, ASA class and types of surgery between the two groups. A p-value of less than 0.05 was considered statistically significant.

Results

Of the 88 patients enrolled in the study, 85 were included in the final analysis, with 43 in Group A and 42 in Group B. One patient was excluded due to severe

bleeding affecting haemodynamic parameters and two others due to inadequate block intraoperatively, requiring conversion to general anaesthesia. There were no statistically significant differences ($p > 0.05$) in terms of demographic data (age, weight, gender and race), ASA class and the duration of surgery between the two groups as shown in Table 1. The types of surgery between both groups were not significantly different; surgical procedures (Group A; 51.2% versus Group B; 42.9%), and orthopaedic procedures (Group A; 48.8% versus Group B; 57.1%); (Chi-Square analysis; $p=0.443$). This is shown in Table 2.

Figure 1 shows that there was no significant difference ($p > 0.05$), in mean MAP between the two groups at every 15 minute interval. There was no significant difference ($p > 0.05$), in mean HR between the two groups at every 15 minute interval, as shown in Figure 2. Figure 3 shows that there was no significant difference ($p > 0.05$), in mean RR between the two groups at every 15 minute interval. None of the patients developed respiratory depression or $SpO_2 \leq 95$. The mean offset times was not statistically different ($p = 0.594$), between Group A and Group B, 7.0 ± 1.3 minutes and 6.8 ± 1.4 minutes, respectively.

Discussion

A loading dose of $1 \mu\text{g}/\text{kg}$ of dexmedetomidine has been associated with a biphasic response, i.e transient hypertension followed by severe hypotension (2,7,9), though the latter is more common (13-17). A loading dose of propofol prior to starting an infusion has also been associated with significant hypotension and bradycardia (1,2). In this study, the loading dose was omitted in both groups, and in the first 15 minutes, we observed no significant decrease in MAP and heart rate from baseline. In studies where a rapid loading dose was given at the beginning of drug infusion, a significant decrease in the MAP and heart rate was documented in the first 10 minutes with the use of either dexmedetomidine or propofol for sedation (7,9). In contrast, studies which omitted the loading dose showed insignificant changes in the heart rate from baseline (11,12).

This study found that patients sedated with propofol had a lower MAP throughout the study, compared to patients sedated with dexmedetomidine. However, this difference was statistically insignificant and in keeping with previous studies which showed similar findings (8,10,13). These studies also reported that in both groups, the mean heart rate was also reduced from baseline readings throughout the infusion time (10,13). However, the reduction was not statistically significant and was most probably due to the sympatholytic effect

of dexmedetomidine, and partly due to the direct myocardial depressant effect of propofol.

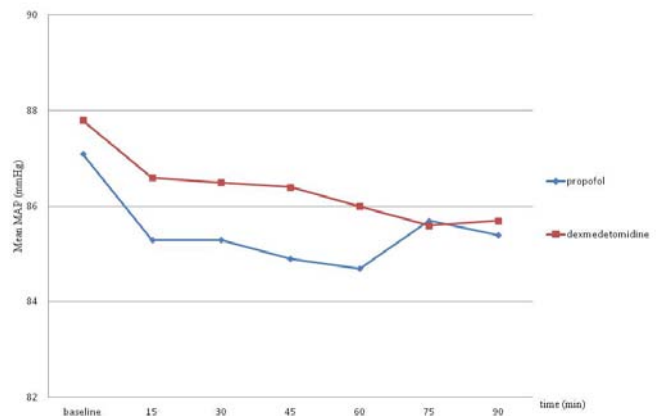


Figure 1: Mean values of mean arterial pressure (MAP) at 15 minute intervals.

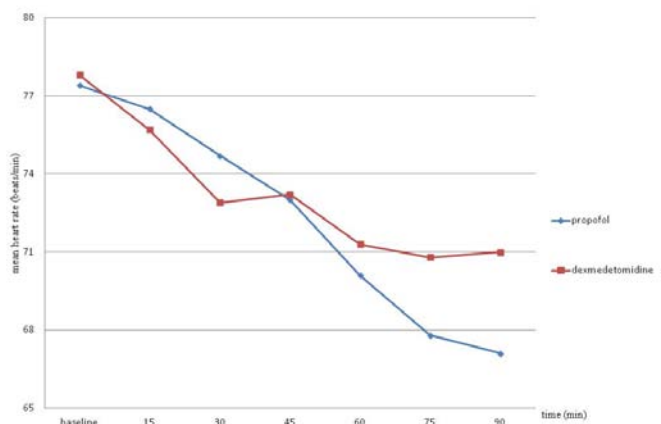


Figure 2: Mean heart rate (HR) at 15 minute intervals.

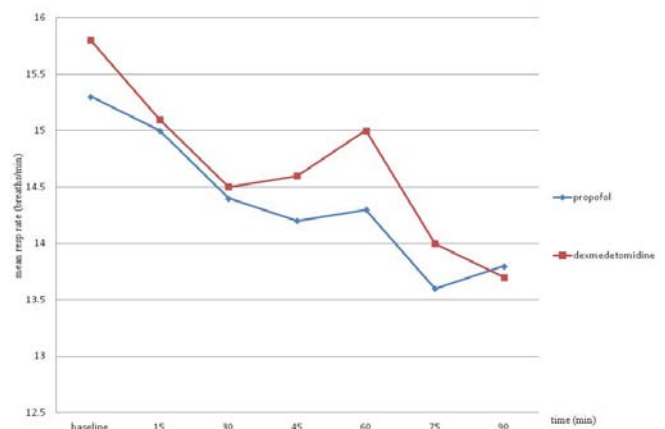


Figure 3: Mean respiratory rate (RR) at 15 minute intervals.

Anecdotal reports described incidences of respiratory depression during infusion of propofol for sedation (1,2). However, in this study, patients who received propofol did not show any significant respiratory depression requiring adjustment of rate of infusion, or $SpO_2 \leq 95\%$ requiring assisted ventilation. This preservation of respiratory function may be related to the study design which did not include a loading dose of propofol at the onset of infusion. The difference in the mean respiratory rate between the dexmedetomidine and propofol groups in this study was not statistically significant, and this was in agreement with findings in previous studies (9,10,15). Both drugs showed no respiratory depression, possibly due to the fact that the drugs were carefully titrated to the targeted sedation score, and immediate dose adjustments were done when needed.

In this study, the offset time was slightly prolonged, though not statistically significant, with dexmedetomidine compared to propofol. This finding was similar to previous studies (8,9). This may be explained by the 2 hour elimination half life ($t_{1/2 \beta}$) of dexmedetomidine compared to the elimination half life of propofol which ranges between 21 to 69 minutes. However, in another study, a statistically significant prolonged offset time of sedation with dexmedetomidine was found when compared to propofol (10). The cause of this discrepancy was not explained and further studies may be needed to evaluate this issue.

BIS was used to maintain equivalent sedative levels in the two groups. It has been shown to be a simple tool in assessing the level of consciousness during the period of sedation (2,12). However, some studies showed variable BIS scores when it was used alone to correlate the depth of anaesthesia (1,6). To optimize accuracy in maintaining the depth of sedation, the OAAS was used together with the BIS score for monitoring the depth of sedation during regional anaesthesia. Previous studies have shown good correlation between the two scores (2,15).

There were a number of limitations to this study. Firstly, there was no control group as it would be unethical to deprive those patients in whom sedation was warranted. Secondly, the variability of central neuraxial blockade used (spinal, epidural or combined spinal epidural) may have influenced the haemodynamic profiles exhibited by the patients, thus it would have been better to standardize the use of one regional technique rather than employing multiple regional techniques. Variability in surgical procedures in this study may have also influenced changes in

haemodynamic parameters (due to differences in blood and third space losses) during drug infusion, thus affecting the type of intervention that was required (in terms of amount of fluid resuscitation and vasopressors used). Haemodynamic parameters were also measured at 15 minute intervals within which significant changes may have occurred and missed.

Dexmedetomidine or propofol when used at appropriate infusion rates alleviate the fear and anxiety faced by patients undergoing surgical procedures under regional anaesthesia. Additionally, with dexmedetomidine, presynaptic and postsynaptic activation of the α_2 -adrenoceptors in the central nervous system terminate the propagation of pain signals, and inhibit sympathetic activity respectively. These combined effects produce analgesia, sedation, and anxiolysis, thus avoiding the potential side effects when multiagent therapies are used (18). Dexmedetomidine is also associated with a lower rate of shivering (19) which is an added benefit as patients given central neuraxial blocks may have intraoperative shivering secondary to loss of heat from peripheral vasodilatation.

We concluded that there were no significant differences in terms of haemodynamic parameters, respiratory rates and offset times between dexmedetomidine and propofol when used for conscious sedation, in patients undergoing elective orthopaedic and surgical procedures under regional anaesthesia.

References

1. Morgan GE, Mikhail MS, Murray MJ. Clinical Anesthesiology. 4th edition. McGraw-Hill companies. 2006, pp-289-324.
2. Hohener D, Blumenthal S, Borgeat A. Sedation and regional anaesthesia in the adult patient. Br J Anaesth 2008; 100(1): 8-16
3. Nishiyama T. Propofol infusion for sedation during spinal anaesthesia. J Anesth 2007; 21(2): 265-269.
4. Oei-Lim VLB, White M, Kalkman CJ, et al. Pharmacokinetics of propofol during conscious sedation using TCI in anxious patients undergoing dental treatment. Br J Anaesth 1998;80(3):324-331.
5. Pollock JE, Neal JM, Liu SS, Burkhead D, Polissar N. Sedation during spinal anaesthesia. Anesthesiology 2000; 93 (3): 728-734.

6. Ibrahim AE, Taraday JK, Kharasch ED. Bispectral Index Monitoring during sedation with sevoflurane, midazolam and propofol. *Anesthesiology* 2001; 95 (5): 1151-1159.
7. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000; 90(3): 699-705.
8. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patients and clinicians perspectives. *Br J Anaesth* 2001; 87(5): 684-690.
9. Koroglu A, Teksan H, Sagir O, Yucel A, Toprak HI, Ersoy OM. A comparison of the sedative, haemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. *Anesth Analg* 2006; 103(1): 63-67.
10. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth Analg* 2002; 95(2): 461-466.
11. Akeda S, Takeda S, Yoshida Y, et al. The efficacy of dexmedetomidine in patients with noninvasive ventilation: a preliminary study. *Anesth Analg* 2008; 107(1): 167-170.
12. Nemoto S, Takemoto K, Ishii H, et al. Dexmedetomidine sedation without loading dose for pediatric patients after cardiovascular surgery. *J Clin Anesth* 2005; 29(10): 1616-1620.
13. McCutcheon CA, Orme RM, Scott DA, Davies MJ, McGlade DP. A comparison of dexmedetomidine versus conventional therapy for sedation and haemodynamic control during carotid endarterectomy performed under regional anaesthesia. *Anesth Analg* 2006; 102(3): 668-675.
14. Lafreniere G, Milne B, Brunet DG, Adams MA, Parlow JL. Autonomic circulatory and cerebrocortical response during increasing depth of propofol sedation/ hypnosis in humans. *Can J Anaesth* 2000; 47(5): 441-448.
15. Kaygusuz K, Gokce G, Gursoy S, Ayen S, Mimaroglu C, Gultekin Y. A comparison of sedation with dexmedetomidine or propofol during shockwave lithotripsy: a randomized control trial. *Anesth Analg* 2008; 106(1): 114-119.
16. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY. Monitored anesthesia care with dexmedetomidine: A prospective, randomized, double-blind, multicenter trial. *Anesth Analg* 2010; 110(1): 47-54.
17. Seyhan TO, Sungur MO, Senturk E et al. BIS guided sedation with propofol during spinal anaesthesia: influence of anaesthetic level on sedation requirement. *Br J Anaesth* 2006; 96(5): 645-649.
18. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)* 2001;14(1):13-21.
19. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. *Anesthesiology* 1997;87(4):835-841.