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The comparison between propofol and dexmedetomidine infusion on perioperative anxiety during regional anesthesia

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Background/aim: Regional anesthesia for surgery is associated with increased anxiety for patients. This study aimed to compare the effect of propofol and dexmedetomidine infusion on perioperative anxiety during regional anesthesia.

Materials and methods: Eighty-four patients were randomly divided into two groups receiving either study drug infusion. Anxiety score, level of sedation using the Bispectral Index and Observer's Assessment of Alertness and Sedation, hemodynamic stability, and overall patient's feedback on anxiolysis were assessed.

Results: Both groups showed a significant drop in mean anxiety score at 10 and 30 min after starting surgery. Difference in median anxiety scores showed a significant reduction in anxiety score at the end of the surgery in the dexmedetomidine group compared to the propofol group. Dexmedetomidine and propofol showed a significant drop in mean arterial pressure in the first 30 min and first 10 min respectively. Both drugs demonstrated a significant drop in heart rate in the first 20 min from baseline after starting the drug infusion. Patients in the dexmedetomidine group (76.20%) expressed statistically excellent feedback on anxiolysis compared to patients in the propofol group (45.20%).

Conclusion: Dexmedetomidine infusion was found to significantly reduce anxiety levels at the end of surgery compared to propofol during regional anesthesia.

Key words: Regional anesthesia, anxiety, dexmedetomidine, propofol

1. Introduction

Regional anesthesia for surgery provides many benefits to patients such as postoperative analgesia, early mobilization in the postoperative period, and minimizing pulmonary complications (1). However, it is also associated with increased stress and anxiety with as many as 23% of patients reported to be anxious on arrival at the operating theater (2). At the start of surgery, some of these patients experienced anxiety at the sight of technical equipment and surgical instruments used.

Perioperative anxiety can lead to increased levels of catecholamines, which will result in undesirable metabolic changes such as increase in blood pressure, heart rate, and oxygen consumption (3). Anxiety can worsen patients' perception of pain and increase requirements for postoperative analgesia. Therefore, various agents such as propofol and dexmedetomidine are used to relieve anxiety and provide sedation during regional anesthesia (4,5).

Conventionally in our institution, midazolam is used for sedation during regional anesthesia. However, this mode of administration is associated with peaks and troughs in plasma concentration causing inadequate and unsatisfactory sedation, with most patients often being startled by excessive manipulation and loud noises during surgery (4,6). Midazolam also has a slower onset and offset of action when compared to propofol and dexmedetomidine.

Propofol is a phenol derivative widely used as an induction agent and as a sedative agent. Propofol has a favorable pharmacokinetic profile with a rapid onset and offset of action (4,7). Propofol infusion was found to have faster onset in achieving the desired sedation score and significantly lower mean anxiety score for conscious sedation during spinal anesthesia (4).

Dexmedetomidine is an α_2-adrenoceptor agonist. It is used as a sedative agent in the intensive care unit and

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in the operating theater (8). It acts by causing stimulation of α_2-adrenoceptors in the locus coeruleus, resulting in a decrease in noradrenaline release and centrally mediated sympathetic tone. Anxiolysis provided by dexmedetomidine infusion causes fewer respiratory depression effects when compared to other anxiolytic agent such as midazolam (5).

The aim of this study was to compare the effectiveness of propofol versus dexmedetomidine infusion in reducing perioperative anxiety, as well as comparing hemodynamic parameters, respiratory parameters, and patients' feedback between the drugs.

2. Materials and methods

This prospective, double blind, randomized controlled study was conducted over a period of 8 months in the operating theaters of a university hospital. The institutional medical research and ethics committee provided the ethics approval for this study (Registration No. FF-2016-057). The inclusion criteria included American Society of Anesthesiologists (ASA) I or II patients between 18 and 65 years of age who were scheduled for elective and emergency surgery requiring central neuraxial blockade. The exclusion criteria consisted of patients with known allergies and contraindications to the study drugs and neuraxial blockade, obese patients with body mass index (BMI) of more than 30, patients with underlying obstructive sleep apnea, patients with a past history of chronic pain or who were on regular analgesics, and a duration of surgery exceeding more than 3 h.

Patients recruited into the study were assessed and informed regarding the procedure, and written consent was obtained prior to surgery by the primary investigator. A visual analog scale (VAS) for anxiety was used to determine the patient's baseline anxiety score during the preoperative assessment. It consisted of a line with 100 mm scale from 0 (no anxiety) on the left to 100 (maximum anxiety) on the right. It is simple, short, and easy assessment tool to assess a patient's anxiety level (9). Premedication was omitted for all patients recruited into the study to prevent possible respiratory depression due to compound effects following administration of the study drug infusion. It also allowed better cooperation by patients when positioning them in the sitting position during regional anesthesia. Patients fasted for at least 6 h prior to surgery.

In the operating room, intravenous access was obtained using an 18 G cannula in all patients and Hartmann's infusion was started at a rate of 5 mL/kg/h within 15 min as coloading before regional anesthesia. Standard anesthesia monitoring with continuous electrocardiography (ECG), noninvasive blood pressure monitoring (NIBP), and pulse oximetry was used where heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO_2), and respiratory rate (RR) were monitored and recorded at 10 min intervals.

The bispectral index (BIS) was monitored continuously with the Aspect BIS Covidien Monitor. The BIS is a technique that processes the electroencephalography (EEG) to calculate a single dimensionless number as a monitor for the depth of sedation. The BIS index ranges from 0 to 100, where a BIS value near 100 represents an awake clinical state, 60–80 represents light to moderate sedation in which patients may respond to loud commands or mild shaking, and 40–60 represents a general anesthesia state. Sedation was monitored with the Observer's Assessment of Alertness and Sedation (OAAS) score, at every 15 min after starting the infusion. OAAS scores were rated as follows: 5: response readily to name spoken in normal tone, 4: lethargic response to name spoken in normal tone, 3: response only after name was spoken loudly and repeatedly, 2: response to gentle shaking or pushing, 1: no response to gentle shaking or pushing. Baseline BIS and OAAS values were taken prior to the initiation of the study drug infusion. The BIS readings were charted as well at 15 min intervals together with the OAAS scores to compare the correlation between BIS values and OAAS scores. Neuraxial blockade was then performed under an aseptic technique and adequate anesthetic distribution was determined using the 'pinprick' technique according to the required dermatomal level before allowing surgery to commence. All patients were given oxygen supplementation via nasal cannula of 2 L/min.

The primary investigator prepared the study drug for infusion. Patients were randomly assigned into one of the two groups by using computerized generated randomized numbers. Patients in the dexmedetomidine group (Group D) received an intravenous (IV) loading dose of dexmedetomidine at 0.5 μg/kg over 10 min followed by an initial maintenance infusion of 0.5 μg/kg/h titrated to the targeted OAAS score. Patients in the propofol group (Group P) received an IV loading dose of propofol 1% at 0.5 mg/kg over 10 min followed by an initial maintenance infusion of 3 mg/kg/h titrated to the targeted OAAS score. Both drugs were administered through a syringe pump with the syringe and its tubing covered, while the infusion rate was titrated by the primary investigator. The infusion rate was adjusted accordingly, reducing the rate with lower scores and increasing with higher OAAS scores to achieve a target score of 4.

Patients were further assessed regarding anxiety scores after the target level of sedation was achieved, using the VAS at 10 and 30 min after starting surgery, at the end of the surgery, 30 min postsurgery in the recovery room,

and prior to discharge to the general ward. Assessment of anxiety scores and charting of hemodynamic parameters was done by a second investigator who was blinded to the type of drug infusion given. Perioperative side effects, which included hypotension (blood pressure decrease of more than 20% from the baseline value), bradycardia (heart rate of less than 40 beats/min), hypopnea (RR ≤ 8 breaths/min), oxygen desaturation (SpO_2 ≤ 93%), nausea, vomiting, and dizziness were recorded and treated accordingly. Hypotension was treated with infusions of crystalloid fluids and/or IV 6 mg ephedrine boluses when needed. Bradycardia was treated with 0.5 mg IV atropine sulfate bolus. Intravenous granisetron at 20 μg/kg was given to patients with nausea and vomiting during operation. Patients who required conversion from regional to general anesthesia needing airway support were removed from the study. The study drug infusion was stopped on completion of skin closure. Patients were then monitored in the recovery area for at least 30 min where the patient's feedback on anxiolysis was obtained using a four point graded scale (excellent, good, fair, and poor) before being discharged to the general ward.

2.1. Statistical analysis

The sample size was calculated based on a previous study by Pakti et al. (4), which was a total of 84 patients. This sample size calculation included a 10% dropout rate. Data analysis for this study was done using SPSS 23 (IBM Corp., Armonk, NY, USA). Demographic data were analyzed using t-tests. The duration of surgery and the duration of study drug infusion in demographic data were analyzed using the Mann–Whitney U test. The VAS was analyzed using the Mann–Whitney U test. Parameters such as HR, MAP, SpO_2, and RR were compared using t-tests. Incidences of side effects such as hypotension, bradycardia, hypopnea, nausea, vomiting, dizziness, and pain on injection were analyzed using the chi-square test. $P < 0.05$ was considered statistically significant.

3. Results

A total of 84 patients were recruited for the study (42 patients in the propofol group and 42 patients in the dexmedetomidine group). None of the patients were removed from the study. The demographic data, type of surgery, and type of regional anesthesia were comparable in both groups as shown in Table 1. However there was a significant number of elective cases in the dexmedetomidine group. The duration of surgery and the duration of study drug infusion were also significantly longer in the dexmedetomidine group.

Median anxiety scores within each group for both study infusions were seen to be significantly reduced at 10 and 30 min after starting surgery as shown in Table 2 ($P < 0.001$). Difference in median anxiety scores showed that there was a significant reduction in anxiety score at the end of surgery in the dexmedetomidine group compared to the propofol group (Table 3).

The target OAAS score of 4 correlated to BIS readings ranging between 78 and 83 for propofol and 77 and 86.5 for dexmedetomidine respectively is shown in Table 4. There was a significant moderate correlation between OAAS and BIS ($r = 0.589$, $P < 0.001$) as shown in Figure 1. The OAAS score of 3 is correlated to BIS readings of 67–77 and 74 respectively for propofol and dexmedetomidine infusion, whereby there was also a significant moderate correlation between OAAS and BIS ($r = 0.566$, $P < 0.001$).

Dexmedetomidine showed a significant drop in MAP in the first 30 min after starting the drug infusion compared to propofol, which showed a significant drop in MAP in the first 10 min after starting the drug infusion (Figure 2). Both dexmedetomidine and propofol showed a significant drop in HR in the first 20 min from baseline after starting the drug infusion (Figure 3). Mean SpO_2 and RR remained stable throughout the study of drug infusion with no statistical difference between the groups (Figures 4 and 5).

Only patients in the propofol group (16.7%) complained of pain on intravenous drug infusion ($P = 0.012$). Other side effects like nausea, vomiting, and dizziness were insignificant in both groups.

Overall, 32 patients (76.20%) in the dexmedetomidine group expressed statistically excellent feedback on anxiolysis during surgery compared to 19 patients (45.20%) in the propofol group ($P = 0.012$).

4. Discussion

Propofol and dexmedetomidine have favorable pharmacokinetic properties that can lead to rapid titration of sedation levels while preserving protective airway reflexes and avoiding sympathetic stimulation during surgical procedures under regional anesthesia (4,5). In this study, both drugs showed a significant fall in median anxiety score at 10 and 30 min after starting surgery. However, the difference in median anxiety scores from baseline showed that there was a significant reduction in median anxiety score at the end of surgery in the dexmedetomidine group.

Patients from the dexmedetomidine group were found to have a higher baseline anxiety score as compared to the propofol group in this study. This could be explained by the fact that there were significantly more elective cases in the dexmedetomidine group as compared to the propofol group. Long waiting lists for an elective surgery have been implicated to cause higher emotional distress and anxiety levels among patients (10). However, the results from our

Table 1. Demographic data, type of surgery, type of regional anesthesia, duration of surgery, and duration of study drug infusion.

Variables	Group P (n = 42)	Group D (n = 42)	P-value
Age (years)	40.60 ± 15.18	40.43 ± 14.81	0.960
Weight (kg)	69.93 ± 11.72	69.75 ± 7.67	0.933
Height (m)	1.70 ± 0.06	1.70 ± 0.05	0.951
BMI (kg/m^2)	24.04 ± 3.47	23.99 ± 2.39	0.954
Sex (Male: Female)	31: 11 (73.8%: 26.2%)	29: 13 (69.0%: 31.0%)	0.629
Race: Malay Chinese Indian Others	32 (76.2%) 6 (14.2%) 2 (4.8%) 2 (4.8%)	32 (76.2%) 6 (14.2%) 3 (7.2%) 1 (2.4%)	0.912
ASA: I II	25 (59.5%) 17 (40.5%)	26 (61.9%) 16 (38.1%)	0.823
Type of surgery: Elective Emergency	 20 (47.6%) 22 (52.4%)	 31 (73.8%) 11 (26.2%)	 0.014* 0.014*
Type of regional anesthesia: Spinal Combined spinal epidural	 29 (69.0%) 13 (31.0%)	 22 (52.4%) 20 (47.6%)	 0.118
Duration of surgery (min)	46.50 (33–125)	80.00 (50–112.5)	0.022*
Duration of study drug infusion (min)	57.50 (42–140)	100.00 (72.7–132.5)	0.016*

*: P < 0.05. Values are presented as mean ± SD, number with percentages in parentheses, or as median (interquartile range).

Table 2. Median anxiety scores (preoperatively, 10 and 30 min after starting surgery, at the end of surgery, and 30 min postsurgery).

Anxiety scores	Group P (n = 42)	Group D (n = 42)	P-value
Preoperative	45 (30–51.2)	50 (30–70)	0.038*
10 min after starting surgery	20 (10–40)	27.5 (10–46.2)$^{\alpha}$	0.069
30 min after starting surgery	10 (0–10)$^{\beta}$	10 (0–20)$^{\beta}$	0.284
End of surgery	0 (0–10)$^{\mu}$	0 (0–10)$^{\mu}$	0.731
30 min postsurgery	0 (0–10)	0 (0–10)	0.908

*: P < 0.05 compared between groups. Values presented as median (interquartile range).
$^{\alpha}$: P < 0.001 when compared to preoperative anxiety score.
$^{\beta}$: P < 0.001 when compared to anxiety score 10 min after starting surgery.
$^{\mu}$: P < 0.01 when compared to anxiety score 30 min after starting surgery.

Table 3. Difference in median anxiety scores 10 and 30 min after starting surgery, at the end of surgery, and 30 min postsurgery when compared to baseline anxiety score.

Anxiety scores	Group P (n = 42)	Group D (n = 42)	P-value
10 min after starting surgery	–20 (–22.5 to –10)	–20 (–30 to –13.7)	0.097
30 min after starting surgery	–30 (–46.2 to –20)	–40 (–50 to –30)	0.161
End of surgery	–35 (–50 to –20)	–50 (–60 to –30)	0.037*
30 min postsurgery	–35 (–50 to –27.5)	–50 (–60 to –30)	0.061

*: P < 0.05 compared between groups. Values presented as median (interquartile range).

Table 4. BIS and OASS scores at 15 min intervals of the study.

Variables	Group P (n = 42)		Group D (n = 42)	
	BIS	OAAS	BIS	OAAS
Baseline	97 (91–98) 83	5 (5–5)	97 (93–98)	5 (5–5)
15 min after test drug infusion	(78–89.2)	4 (4–4)	86.5 (79–91.2)	4 (4–5)
30 min after test drug infusion	78 (73–80)	4 (3–4)	81 (73.7–86)	4 (3–4)
45 min after test drug infusion	77 (66–80)	3 (3–4)	77 (70.7–82)	4 (3–4)
60 min after test drug infusion	73 (66–80)	3 (2–4)	74 (63–80)	3 (3–4)
75 min after test drug infusion	67 (62–80)	3 (2–4)	74 (65–78)	3 (3–4)
90 min after test drug infusion	72.5 (62.7–80.5)	3 (2–4)	74 (66.2–78)	3 (3–4)

Values presented as median (interquartile range).

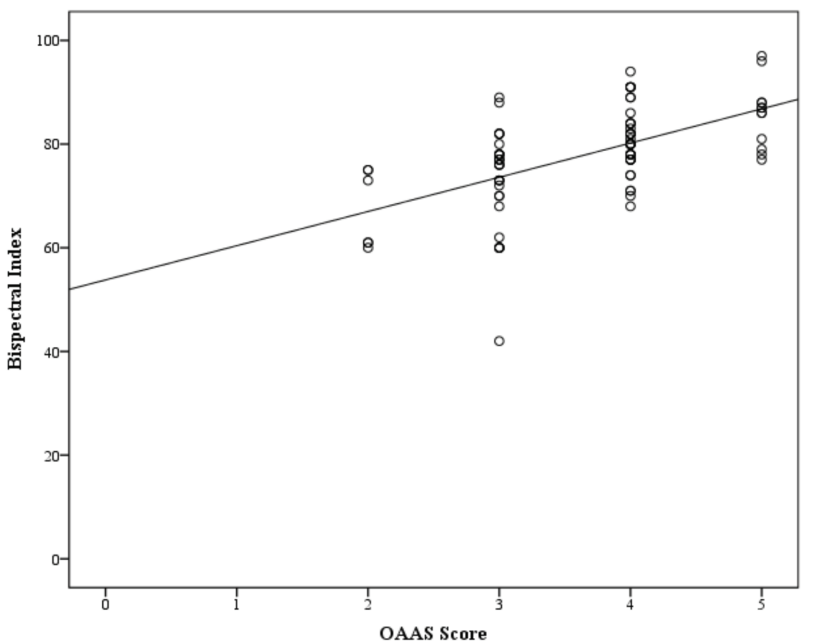

Figure 1. Scatter plot for correlation between BIS and OAAS.

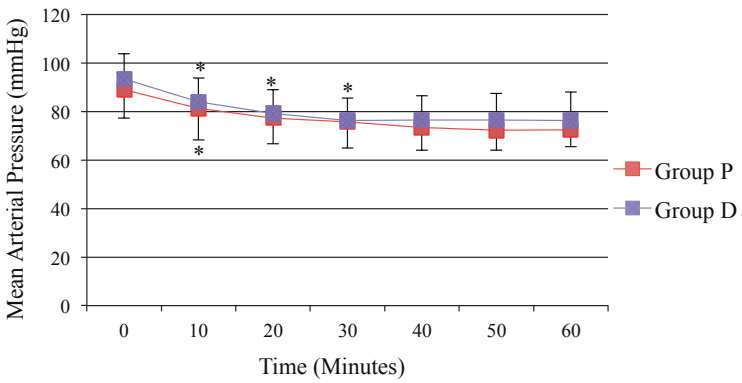

Figure 2. Mean arterial pressure (MAP) in both groups during the study drug infusion. *: P <0.05 compared to the baseline value.

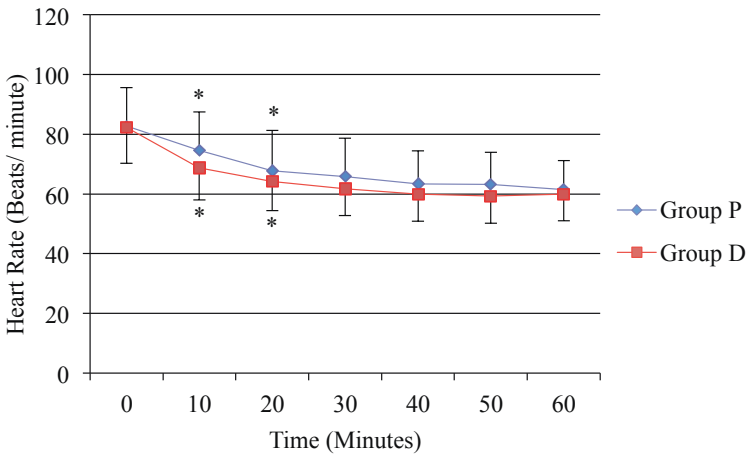

Figure 3. Heart rate (HR) in both groups during the study drug infusion. *: P < 0.05 compared to the baseline value.

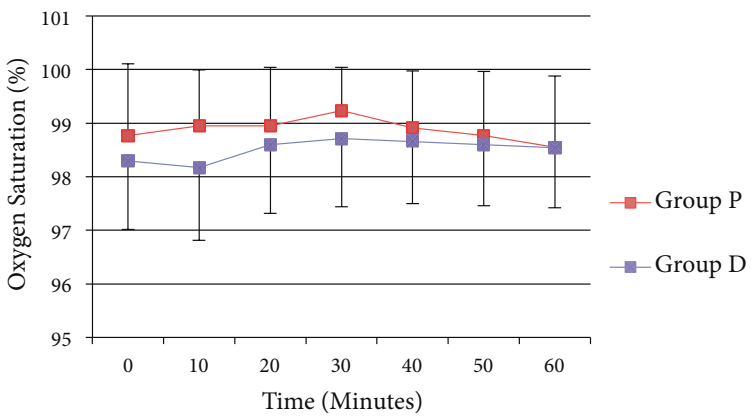

Figure 4. Oxygen saturation (SpO_2) in both groups during the study drug infusion.

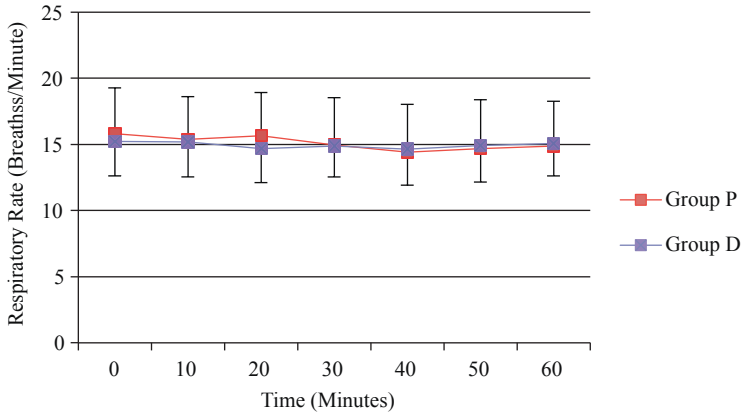

Figure 5. Respiratory rate (RR) in both groups during the study drug infusion.

study contradicted the findings from another study by Latif et al. (11), which showed that anxiety scores were higher in patients undergoing emergency surgery.

In this study, BIS monitoring was used to determine the level of sedation together with the OAAS. Both drugs were comparable in achieving the targeted OAAS value of 4 at 15 min after starting the drug infusion. It was an acceptable time period for the drugs to work while preparing the patient for surgery, such as putting on the tourniquet, patient positioning, and waiting for the surgeon to scrub up. Therefore, the amount of loading and the maintenance dose used for propofol and dexmedetomidine in the study were deemed appropriate. A previous study by Dipanjan et al. (12) showed that an OAAS of 4 correlated with a BIS range of 70–80 while OAAS of 3 correlated with a BIS value range of 60–70. Kasuya et al. (13) and Uddalak et al. (14) in their studies reported that patients receiving dexmedetomidine infusion showed significantly lower BIS values when compared to propofol despite both infusions producing similar OAAS scores. Uddalak et al. (14) postulated that the reason for no correlation between the OAAS and BIS was the different mechanisms of sedation of the two drugs. Dexmedetomidine produced sleep by hyperpolarization of noradrenergic locus coeruleus neurons as opposed to the gamma-amino butyric acid (GABA) agonist effect of propofol. However, we found that there was a significant moderate correlation between the OAAS and BIS when using either propofol or dexmedetomidine ($P < 0.001$), which implies that the BIS is comparable to the OASS as a method of assessing sedation levels.

Dexmedetomidine showed a significant drop in MAP in the first 30 min after starting the drug infusion compared to propofol, which had a significant drop in MAP in the first 10 min after starting the drug infusion. Wang et al. (15) found that both dexmedetomidine and propofol showed a significant decrease in MAP from baseline in the first 30 min after starting the drug infusion. Patients in their dexmedetomidine group were infused with similar loading and maintenance doses as in our study, therefore producing a similar drop in MAP. However, patients in their propofol group were infused with a higher loading dose of 2 mg/kg over 10 min when compared to our study. It is possible that the prolonged drop in MAP in their propofol group could have been attributed to the higher loading dose used. Despite the significant drop in MAP, no treatment was required for either group as it did not reach the hypotension limits defined in our methodology to warrant rescue treatment.

Both dexmedetomidine and propofol showed a significant drop in HR in the first 20 min from baseline after starting the drug infusion. Similar results were reported by Ghali et al. (16) in which there were similar significant reductions in HR compared to baseline in the first 25 min after starting the drug infusion. However, patients in their dexmedetomidine group received a higher loading dose of 1 μg/kg over 10 min while patients in their propofol group received a higher loading dose of 0.7 mg/kg over 10 min. Our relatively lower loading dose of dexmedetomidine and propofol used in our study is thus preferable as it was able to provide adequate anxiolysis during regional anesthesia without causing any significant incidence or prolonged adverse hemodynamic events such as bradycardia and hypotension that required treatment when compared to other studies (17,18).

Patients' feedback scores regarding anxiolysis received were found to be significantly higher in the dexmedetomidine group as compared to the propofol group. Some patients from the propofol group expressed slight discomfort and pain during the drug infusion. However, once adequately sedated, patients were

comfortable throughout the rest of the study infusion period. This finding was also similarly reported by Shah et al. (19).

Another limitation in our study was that targeted levels of sedation were difficult to titrate with manually controlled infusion using conventional infusion pumps. Over time, the OAAS scores continued to drop to 3 despite attempts to achieve the targeted level of sedation by reducing the infusion dose. This could be explained by the fact that prolonged drug administration resulted in increased tissue saturation producing deeper sedation levels. Target-controlled infusion (TCI) would be a better approach for administration of sedative agents. It has a preselected pharmacokinetic model of a drug, targeting the effect site concentration; therefore, it is able to maintain a steady-state plasma concentration at equilibrium (7). Sedation levels could then be easily titrated by changing the target concentration of TCI and the depth of sedation can be evaluated to match the desired level within a few minutes. However, the development of an optimized pharmacokinetic model of dexmedetomidine using TCI is still in progress (20). Therefore, we had to use conventional syringe pumps for standardization during our study.

In conclusion, dexmedetomidine infusion was found to significantly reduce anxiety levels at the end of surgery and confers better patient feedback on anxiolysis received compared to propofol during regional anesthesia. However, both drugs were comparable in terms of hemodynamic and respiratory parameters.

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