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A comparative evaluation of Equi-sedative doses of dexmedetomidine and propofol for peri-operative sedation in surgeries under regional anaesthesia

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Abstract
Objective: This study was conducted to compare the effects of equi-sedative doses of dexmedetomidine and propofol in patients undergoing elective surgical procedures after taking place regional anesthesia.
Method: A prospective double-blind study was carried out in 80 patients of either sex, aged between 20 to 60 years and American Society of Anaesthesiologist (ASA) grade I, II and III. Patients were randomly allocated into two groups of 40 patients in each group. Group I (D) received i.v. dexmedetomidine (1 µg/kg initial loading dose for 10min, maintenance 0.5-0.7µg/kg/min). GroupII (P) received i.v. propofol (75µg/kg/min for 10min; maintenance 30-60µg/kg/min), two groups were compared in terms of cardio-respiratory effects, time to achieve and terminate sedation (using BIS index and OAA/S score), post-operative analgesia, side effects and complications of these drugs.
Results: Both groups were comparable with regard to demographic variables. Time to achieve sedation was early in group II (10-15 min) as compared to group I (25 min). In post-operative period, the value of OAA/S after 5 min was lower (4.22±0.42) in group I as compared to group II (4.45±0.50) and termination of sedation in group I was late as compared to group II. Intraoperatively, fall in mean blood pressure and heart rate were statistically significant in both groups but fall in MBP was more in group II and fall in HR was more in group I ($p<0.05$). In post-operative period, blood pressure and heart rate remained lower in group I but in group II these parameters reached near the base line value. VAS score remained lower in group I than group II which was statistically significant ($p<0.05$) and more analgesic doses were recquired in group II (propofol) in recovery period. No significant changes were seen with regards to SpO_2, respiratory rate and postoperative nausea vomiting.
Conclusion: Dexmedetomidine provided similar levels of sedation to propofol, with a slower onset and offset of sedation with an additional advantage of postoperative analgesia. Thus, Dexmedetomidine with its stable cardio-respiratory profile, better sedation, overall patient's satisfaction, and analgesia could be a valuable adjunct for intraoperative sedation during regional anesthesia especially when postoperative pain might be predicted to be worse than usual.

Keywords: Consious sedation, propofol, dexmedetomidine, regional anaesthesia, BIS-OAA/S.

Introduction
Regional anaesthesia is advantageous as compare to general anaesthesia (cardiovascular and respiratory stability, rapid postoperative recovery, and preservation of protective airway reflexes are the most important advantages), however, the apprehension of surgery, operation room (OR) unfamiliar environment, the sounds and sights of OR instruments, and the masked faces makes the patient panic. Continuous supine position, the inability to move the body or body parts and intense sensory and motor block, also brings a feeling of discomfort and phobia in many patients [1, 2].
Sedation during regional anaesthesia is a well-recognized technique to improve patients' acceptance and comfort. The use of this technique is growing and is nowadays applied not only in the operating room (OR) but also in other different facilities within and outside the hospital.
The goal of conscious sedation under regional anaesthesia is to enhance patient comfort, avoid painful stimuli, protective airway reflexes preservation and haemodynamic stability during the whole surgical procedure.
The centrally active adjuvant drugs available to optimize surgical conditions for both patient and surgeon include benzodiazepines (midazolam), sedative doses of hypnotic agents (propofol), short acting opioid analgesics (Remifentanil) and α_2-receptor agonist dexmedetomidine and clonidine.

In many cases, only light sedation is needed and patient remains in verbal contact with their anaesthesiologists throughout the surgical procedure. Therefore, this kind of sedation is known as "conscious sedation" or "monitored anaesthesia care" (MAC) [3].

Dexmedetomidine has a slower onset and offset of sedation compared with propofol and is associated with improved analgesia [4]. At therapeutic doses, dexmedetomidine is notable to provide profound levels of sedation without respiratory depression. Dexmedetomidine is useful adjunct in the intensice care setting and procedural sedation because of these properties (sedation, analgesia, and respiratory-sparing). Dexmedetomidine is highly selctive alpha 2 adrenergic receptor agonist, however, it is unknown if the perioperative sympatholysis might result in untoward hemodynamic effects when used for intraoperative sedation [4]. Thus, the primary purpose of this study was to evaluate cardio-respiratory equi-sedative dose effect of dexmedetomidine and propofol for elective surgical procedures under regional anesthesia. Time to achieve sedation onset and offset, postoperative analgesic requirements were Secondary end points for comparison.

Materials and methods

A prospective double-blinded study was conducted at tertiary care hospital after written informed consent for 80 patients of either sex, belonging to ASA grade I and II, aged between 20 to 60 years, posted for elective surgeries under regional anaesthesia (epidural, spinal or a peripheral nerve block). Patients were randomized into two groups comprising 40 patients in each group by using envelope method.

Group I (D) received i.v. dexmedetomidine (1 µg/kg loading dose for 10 min followed by maintenance dose of 0.5-0.7µg/kg/min) and Group II (P) received i.v. propofol (75µg/kg/min for10 min followed by maintenance dose of 30-60µg/kg/min).

Patients with haematological diseases, psychiatric diseases, cardiac problems, diabetes, history of drug abuse and allergy to local anaesthetics were excluded from the study. Pre-anaesthetic assessment was done and all patients were kept nil by mouth (NBM) for 6 hrs preoperatively. After arriving in operating room, routine monitoring (NIBP, ECG, Pulse oximetry) were applied and additional monitor bispectral index score (BIS) was attached to the patients for measuring sedation score. Observer's assessment of alertness/sedation scale (OAA/S) was also used for sedation assesment. Routine general anaesthesia equipments and workstation, Bain's circuit, laryngoscope, endotracheal tubes, oxygen masks, drugs required for general anaesthesia and emergency drugs were kept ready as protocol.

Intra-operative sedation level was targeted to achieve a BIS and OAA/S value of 70-80 [5] 3 respectively. All baseline parameters were recorded prior to procedure. IV line secured with 18G cannula and crystalloid solution was started. Under aseptic precautions, regional anaesthesia was given; supplemental oxygen was given throughout the procedure at 4-5 L/min of fresh gas flow in all the patients by oxygen mask. Above mentioned drug infusion started according to the group allocated and on achieving the targeted BIS and OAA/S, surgery was started and infusion doses were adjusted to maintain the BIS between 70 and 80, or an OAA/S score 3.

Observer's assessment of alertness/sedation scale (OAA/S) [6]

Score	Responsiveness
5	Responds readily to name spoken in a normal tone
4	Lethargic response to name spoken in a normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Monitoring was done throughout the surgery with cardio-respiratory end points documented at 5 min interval. At the end of surgery HR, mean BP, SpO_2, RR and OAA/S score were recorded and drug infusion were stopped. In the recovery room (postoperatively), sedation assessments by observer's assessment of alertness/ sedation scores and cardio- respiratory variables such as pulse, mean BP, SpO_2, respiratory rate were recorded at 5 min, 20 min, 35 min, 50 min & 65 min. When VAS score was ≥3, inj. nalbuphine 10 mg i.v. was given.

The incidence of untoward effects such as nausea, vomiting, dizziness, and pruritus were evaluated by a yes/no survey. Respiratory depression was defined as a decrease in respiratory rate more than 25% or a decrease in oxygen saturation <90%. We considered hypotension as decrease in MAP >20% from baseline value. Hypertension was considered as increase in MAP >20% from baseline value. Bradycardia was considered as HR under 60 beats per minute.

Hypotension and bradycardia were treated by i.v. fluid bolus, ephedrine, or atropine, as necessary.

Statistical Analysis

All data compiled and statistical analysis was done using the Statistical Package for Social Sciences (SPSS version 17). Normally distributed continuous variables were analysed using student t' test and categorical variables were analysed with 'CHI-SQUARE' test. All data were expressed either as mean ± SD (standard deviation) or number and percentage. Value of $p<0.05$ was considered significant.

Results

There was no statistically significant difference in the demographic variables between the two groups (Table-1).

Table 1: Demographic Variables

Variables		Group I (D)(n=40)	Group II (P)(n=40)
Age(years) (mean ±SD)		36.85±11.51	36.75±12.33
Weight(kg) (mean ±SD)		65.85±7.63	63.48±7.16
Sex(M/F)		25/15	27/13
ASA grade I/II		18/22	15/25
Type of surgery	General	10	9
	Gynaecological	7	3

	Orthopaedic	23	28
Type of anaesthesia	Spinal	18	15
	Epidural	11	13
	Blocks-Interscalene, Brachial plexus	11	12
Duration of surgeries(min)		80.5±17.57	77.87±20.19

Above table shows that mean age was 36.85 ± 11.51 in group I and 36.75 ± 12.33 in group II and mean weight in group I was 65.85 ± 7.63 and in group II was 63.48 ± 7.16 (p>0.05). Majority of the patients in both groups belonged to orthopaedic surgery.

Time to achieve and terminate sedation of study drugs

Desired level of conscious sedation was achieved at BIS Index between 70-80 and OAA/S score 3. In group I, BIS Index between 70-80 was achieved at 25 min and in group II, it was achieved at 15 min. same as OAA/S score value close to 3 was achieved in group I at 25 min and in group II at 10 min. So in both methods, time to achieve sedation in group I was 25 min and in group II it was 10-15 min. In post-operative period the value of OAA/S after 5 min was lower in group I (4.22±0.42) as compared to group II (4.45±0.50) and termination of sedation in group I was late as compared to group II. When fall in the values of BIS and OAA/S score in both groups at different time interval were analysed statistically, it was found to be significant.

Table 2: Comparison of BIS at various time intervals

Time Interval (min)	Group I (D)	Group II (P)	p Value
	Mean±SD		
Intra op			
0 min	97.25±1.55	98.27±1.15	>0.05
5 min	95.85±1.12	85.97±2.62	<0.05
10 min	92.10±1.48	81.67±2.42	<0.05
15 min	89.35±1.67	79.85±2.13	<0.05
20 min	83.15±2.00	77.77±2.91	<0.05
25 min	78.72±2.57	77.52±2.23	<0.05
30 min	77.80±2.11	78.97±2.73	<0.05
35 min	77.40±2.25	76.22±2.94	<0.05
40 min	74.50±2.37	74.72±2.60	<0.05
45 min	72.32±2.57	75.17±2.50	<0.05
50 min	74.30±2.90	75.72±2.80	<0.05
55 min	75.55±2.67	78.62±2.90	<0.05
60 min	78.55±2.94	79.85±2.72	<0.05

Above table shows BIS changes in both groups at different time intervals. The BIS decreased significantly in both groups in intraoperative period. Desired level of BIS (between 70-80) was achieved in group I at 25 min and in group II at 15 min. When fall in the values of BIS in both groups at different time interval were analysed statistically it was found to be significant. (P<0.05).

Table 3: Comparision of (OAA/S) at various time intervals

Time Interval (min)	Group I (D)	Group II (P)	p Value
	Mean±SD		
Pre op	4.85±0.36	4.90±0.30	>0.05
Intra op			
0 min	4.77±0.40	4.55±0.50	<0.05
5 min	4.40±0.50	3.70±0.72	<0.05
10 min	4.17±0.39	2.82±0.64	<0.05
15 min	3.85±0.40	2.57±0.60	<0.05
20 min	3.55±0.50	2.77±0.62	<0.05
25 min	3.10±0.63	2.80±0.52	<0.05
30 min	2.70±0.46	2.92±0.52	<0.05
35 min	3.05±0.50	2.92±0.46	<0.05
40 min	2.72±0.55	2.95±0.45	<0.05
45 min	3.05±0.55	2.72±0.55	<0.05
50 min	3.00±0.55	2.72±0.50	<0.05
55 min	3.22±0.58	2.92±0.61	<0.05
60 min	3.05±0.55	2.75±0.59	<0.05
At the end of surgery	3.32±0.61	3.05±0.55	<0.05
Post op			
5 min	4.22±0.42	4.45±0.50	<0.05
20 min	4.22±0.42	4.57±0.50	<0.05
35 min	4.17±0.45	4.45±0.50	<0.05
50 min	4.30±0.46	4.55±0.50	<0.05
65 min	4.25±0.44	4.65±0.48	<0.05

Above table shows OAA/S changes in both groups at different time intervals. The OAA/S decreased significantly in both groups in intraoperative period. There occur maximum fall in OAA/S in group I at 30 min and in group II at 15 min. In post-operative period OAA/S reached near to the base line value in both groups. When fall in the values of OAA/S in both groups at different time interval were analysed statistically it was found to be significant (P<0.05).

Heart Rate

Baseline mean heart rate was almost similar in both groups. It was 78.62±11.40 in group I and 78.05±10.86 in group II. The mean heart rate decreased significantly in both groups in intraoperative period. At the end of surgery, it was 69.57±3.48 in group I and 72±5.53 in group II. In post-operative period heart rate remained lower in group I but in group II heart rate reached near to the base line value. HR changes at different time interval in both groups were statistically significant.

Mean Arterial Pressure

Baseline value of MAP was similar in both groups. After administration of study drug, mean blood pressure decreased significantly in both groups and there occured maximum fall (16.38%) in MAP (81.75±5.92) in group II at

10 min. At the end of surgery, it was 88.15±4.93 in group I and 86.05±3.57 in group II. In post-operative period, MAP remained lower in group I but in group II MAP reached near to the base line value. When fall in the values of MAP in both groups at different time interval were analysed statistically, it was found to be significant.

Table 4: Changes in mean arterial pressure

Time Interval (min)	Group I (D) Mean±SD		Group II (P) Mean±SD		p VALUE
	MAP (mm Hg)	HR (bpm)	MAP (mm Hg)	HR (bpm)	
Pre op	99.72±6.30	78.62±11.40	97.77±6.49	78.05±7.33	>0.05
Intra op					
0 min	99.87±6.66	78.22±10.91	95.97±8.44	73.87±6.35	<0.05
5 min	97.50±8.07	77.55±11.93	88.57±5.94	73.15±6.35	<0.05
10 min	95.9±8.73	70.52±6.50	81.75±5.92	74.50±8.91	<0.05
15 min	94.65±8.34	68.58±5.96	85.22±3.58	71.55±6.22	<0.05
20 min	92.88±7.90	67.97±5.91	85.05±3.92	71.87±4.70	<0.05
25 min	93.45±7.22	66.12±4.62	85.82±4.25	72.20±6.07	<0.05
30 min	93.05±8.28	65.02±3.65	85.17±4.35	72.02±5.68	<0.05
35 min	92.72±7.08	65.45±3.62	84.42±5.92	69.40±5.00	<0.05
40 min	91.22±4.15	67.10±4.07	86.47±5.26	70.22±4.33	<0.05
45 min	90.97±6.45	67.62±3.65	85.40±5.83	70.62±4.14	<0.05
50 min	89.77±6.02	67.82±3.81	85.40±3.65	71.27±4.33	<0.05
55 min	90.00±4.52	67.97±3.94	85.10±2.52	71.27±5.29	<0.05
60 min	88.95±4.16	68.62±3.56	84.75±3.33	71.90±5.28	<0.05
At the end of surgery	88.15±4.93	69.57±3.48	86.05±3.57	72.00±4.65	<0.05
Post op					
5 min	87.95±3.21	68.82± 3.05	89.85±4.82	72.75±4.93	<0.05
20 min	86.82±3.65	68.25±2.67	90.90±6.22	73.47±4.65	<0.05
35 min	86.50±4.13	67.7±3.34	92.10± 6.37	72.65±4.44	<0.05
50 min	86.60±2.78	66.38±2.98	93.60±6.39	74.17±4.79	<0.05
65 min	85.72±2.82	67.6±2.49	94.62± 6.56	72.50±4.56	<0.05

Visual Analog Scale for pain (VAS score)

In post operative period, VAS score remained lower in group I compared to group II. VAS score changes at different time interval in both groups were statistically significant (p<0.05). In conclusion, our study found that group I (dexmedetomidine) was useful agent for postoperative analgesia.

Table 5: Visual Analog Scale for pain (VAS score)

Time	Group I Mean VAS (mm) ± SD	Group II Mean VAS (mm) ± SD	P Value
Pre op	11.62 ± 11.46	13.00 ± 12.18	>0.05
At the end of surgery	0.75 ± 2.67	2.75 ± 5.06	<0.05
Post op			
5 min.	2.50 ± 4.93	5.5 ± 7.14	<0.05
20 min.	2.75 ± 5.54	8.5 ± 8.33	<0.05
35 min.	3.50 ± 7.00	9.25 ± 8.28	<0.05
50 min.	3.25 ± 6.94	9.75 ± 8.32	<0.05
65 min.	3.50 ± 7.00	13.00 ± 8.83	<0.05

Table 6: Rescue analgesic doses in postoperative period

No. of analgesic doses in recovery period	Group I (D)		Group II (P)	
	No. of Patients	%	No. of Patients	%
0	38	95	33	82.50
1	2	5	7	17.50
2	0	0	0	0
3	0	0	0	0

Above table shows that 38 patients in group-I (95%) did not require any additional analgesia while in group-II 33 patients (82.5%) did not require any additional analgesia.

SpO_2 and respiratory rate

We had not found any statistically significant difference at different time intervals compared to baseline value in all groups. Majority of the patients in both groups had more than 97% Spo_2 at all-time intervals and Respiratory rate more than 15 and less than 17 (P>0.05).

Side effects and complications

In both groups, incidence of nausea and vomiting was same. Hypotension was 12% in group I and 24% in group II, so incidence of hypotension was more in group II compared to group I. Bradycardia was noticed more in group I (25%) as compared to group II (7.5%).

Table 7: Incidence of side effects and complications between two groups

Side Effects	Group I (D)		Group II (P)	
	No. of Patients	%	No. of Patients	%
Nausea & Vomiting	02	5	02	5
Hypotension	12	30	24	60
Hypertension	0	0	0	0
Bradycardia	10	25	03	7.5
Respiratory depression	0	0	0	0
Dry mouth	02	5	0	0
Pain	02	5	07	17.5

Above table shows side effects of drugs given for sedation in regional anaesthesia. Mild nausea and vomiting were seen in both groups. Most of the patients in both the groups have shown hypotension and bradycardia. Hypotension was seen in 30% patients in group I and 60% patients in group II while bradycardia was seen in 25% and 7.5% in group I and II respectively. Complain of pain was more in group II compared to group I and complain of dry mouth was seen in only group I in 5% percentage of patients.

Discussion

The present study was carried out to evaluate the efficacy, side effects, and recovery characteristics of dexmedetomidine and propofol for intra operative sedation. In regional anaesthesia, sedation is given to diminish anxiety and fear associated with the operation room activity and surgical preparation. The centrally active adjuvant drugs available for sedation are benzodiazepines (midazolam), sedative doses of hypnotic agents (propofol), short acting opioid analgesics (Remifentanil) etc.

Propofol (2, 6-diisopropylphenol) is a short-acting, IV administered hypnotic/amnestic agent. It can be used for the induction and maintenance of general anaesthesia, sedation for mechanically ventilated patients and procedural sedation. Propofol has no analgesic property, and hence opioids such as fentanyl are used as adjunct to alleviate pain [7]. Common adverse effect of propofol includes hypotension, hypoxemia, and respiratory depression.

Dexmedetomidine is a new drug, which is highly selective alpha-2-adrenoceptors agonist with sympatholytic, sedative, amnestic and the analgesic properties [8]. In recent years, it has been used as a safe adjunct in many clinical applications. It provides a unique “conscious sedation” (patients appear to be asleep but are readily arousable) and analgesia, without respiratory depression.

In both groups, time to achieve sedation in group I (D) was 25 min and in group II (P) it was 10-15 min. The early onset time of sedation in the propofol group

compared to dexmedetomidine group occurs because propofol is highly lipophilic and distributes rapidly into the central nervous system. Similar results were obtained by Barr J [9], Arain SR and Ebert TJ [4], Abdelkareim, *et al*. [10], Sethi P, *et al*. [11] and Shah PJ, *et al*. [12].

Mean duration of effective analgesia was significantly prolonged in the dexmedetomidine group as compared to propofol group. Our finding is comparable to the results of other author [13, 14]. Dexmedetomidine produces analgesia by binding to adrenoreceptors in the spinal cord. Jorm and

Stamford, observed that dexmedetomidine has an inhibitory effect on the locus coeruleus which is located at the brain stem [15]. This supraspinal action could explain the prolongation of spinal analgesia after i.v. administration of dexmedetomidine. Similar results were also found by Arain SR and Ebert TJ [4], Olutoye OA, Glover CD, *et al*. [16] and Shah PJ, *et al*. [12].

In our study, a significant decrease in mean HR with dexmedetomidine was observed at 5 min of starting the infusion. This difference persisted throughout the procedure and could be attributed to sympatholytic properties and vagal mimetic effects of dexmedetomidine. The results of our study correlate well with Al-Mustafa, *et al*. [14] and Mahmoud, *et al*. [17]. MBP was significantly decreased in Group P at 5 min after starting infusion and persisted throughout the procedure as compared to Group D. There was no significant difference in MBP from baseline value in Group D throughout the whole duration of procedure. The fall in MBP in patients receiving propofol could be attributed to direct powerful inhibitory effect of propofol on sympathetic outflow causing vasodilatation. Dexmedetomidine is also known to decrease sympathetic outflow and circulating catecholamine levels and would, therefore, be expected to cause a decrease in MBP similar to those of propofol. However, larger doses of dexmedetomidine have a direct effect at the postsynaptic vascular smooth muscle to cause vasoconstriction, and it is possible that the sympathoinhibitory effects of dexmedetomidine were slightly opposed by direct α-2 mediated vasoconstriction. Results similar to our study were observed by Arain, *et al*. [4] Al-Mustafa, *et al*. [14] and Mahmoud, *et al*. [17].

Both propofol and dexmedetomidine are known to have minimal respiratory depression when used as sedative agents which is evident for our results. Thus, better sedation, stable cardiorespiratory profile and analgesic effect resulted in significantly better overall patient satisfaction in the dexmedetomidine group. Results of our study correlate well with those of Arain, *et al*. [4], Sethi P, *et al*. [11] and Shah PJ, *et al*. [12].

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