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Comparison of effectiveness between two different doses of intravenous dexmedetomidine as adjuvant to subarachnoid block for sub umbilical surgeries

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ABSTRACT

Background. Spinal anesthesia was a commonly used technique in anesthetic practice for lower abdominal and lower limb surgeries. To prolong the duration of bupivacaine spinal anesthesia adjuvants like α2 agonists and opioids have been used intrathecally. Clonidine and dexmedetomidine have also been found to prolong the duration of spinal anesthesia when given intravenous. Dexmedetomidine was more suitable adjuvant to spinal anesthesia compared to clonidine as it has more sedative and analgesic effects due to more selective α2A receptor agonist activity. Dexmedetomidine has been shown to prolong the duration of analgesia of spinal anaesthesia in various studies. Here we compare the two doses of Dexmedetomidine in prolonging the duration of analgesia.

Material and methods. 60 American Society of Anaesthesiologists(ASA) physical status I/II patients scheduled for elective lower abdominal and lower limb surgeries under spinal anesthesia were randomized into two groups of 30 each. Immediately after subarachnoid block with 3.5ml of 0.5% hyperbaric bupivacaine, Group A patients received a loading dose of 0.5μg/kg of dexmedetomidine intravenously in 100ml NS over 10 mins whereas Group B received 1.0μg/kg of dexmedetomidine intravenously in 100ml NS over 10 mins.

Results. Time for rescue analgesic were higher in Group B compared to Group A which was statistically significant but clinically the extra duration was insignificant. Time for two segment regression and duration of motor blockade was significantly prolonged in Group B. Requirement of Mephentermine was comparable in both the groups. There was no excessive sedation in both the groups.

Conclusions. Dexmedetomidine administered as isolated loading dose of 0.5 μg/kg IV immediately after spinal anaesthesia was clinically equi-efficacious in prolonging the duration of analgesia of spinal anaesthesia compared to a larger dose of 1.0 μg/kg. The side effect profile, hemodynamic stability, sedation levels, need for vasopressors and atropine were comparable in both groups.

Introduction

Spinal anesthesia was a commonly used technique in anesthetic practice for lower abdominal and lower limb surgeries. To prolong the duration of bupivacaine spinal anesthesia adjuvants like α2 agonists and opioids have been used intrathecally [1]. Clonidine and dexmedetomidine have also been found to prolong the duration of spinal anesthesia when given intravenously [2]. Dexmedetomidine was initially launched for sedation in humans and most commonly used in ICUs globally for short term sedation [3]. It was a highly selective alpha 2 receptor agonist(alpha2: alpha 1 of 1600:1) when compared to Clonidine(200:1). The analgesic action of dexmedetomidine was by its action on presynaptic membrane, inhibiting the release of norepinephrine, which in turn induces hyperpolarization and inhibits the pain signals to the brain [4]. The usage of intravenous alpha agonists in prolonging the duration and quality of spinal anaesthesia was not very popular. Intrathecal usage of alpha agonists are more commonly employed though it was an off-label use of the drug. There are only limited studies describing the most effective doses of Dexmedetomidine as an intravenous adjunct to subarachnoid block.

In this study we try to compare the two commonly employed doses(1.0 µg/kg and 0.5 µg/kg over 10 minutes) of intravenous dexmedetomidine as an adjunct to spinal anaesthesia. We evaluate difference between the two doses with respect to total duration of analgesia(time to rescue analgesia), two segment regression of sensory blockade and motor blockade. Secondarily we also observe the differences if any, with regards to the hemodynamic stability(Heart rate, Blood pressure), side effect profile, sedation levels both intra-operative and in post-operative period.

Materials and methods

After approval of Institutional Ethical committee clearance (IEC/NRIIMS/A/05/2019), sixty patients scheduled for surgeries under Subarachnoid block in NRI INSTITUTE OF MEDICAL SCIENCES, Visakhapatnam, India were enrolled into the study. The study was conducted during the period of October 2019 to November 2020. Sample size was calculated as 30 for each group, estimated based on study by Madhavi Unmesh Santpur et al [5]. Patients of age between 18 to 60 years, ASA(American Society of Anaesthesiologists) grade: I – II, Patients undergoing infra umbilical surgeries were included in the study. Patients in whom there was a contraindication for spinal anaesthesia, ASA grade III – V, Systolic blood pressure <90 mm Hg, Heart rate less than 50/min, patients on Calcium channel blockers, ACE inhibitors, clonidine, patients on opioids, patients on antidepressants a week prior to surgery and patients undergoing lower segment Caesarean sections were excluded from the study. Sixty patients were divided by computer generated random number table into Group A and Group B with 30 subjects in each group. **Group A** patients received a loading dose of 0.5 µg/kg of dexmedetomidine intravenously in 100 ml NS over 10 mins whereas **Group B** received 1.0 µg/kg of dexmedetomidine intravenously in 100 ml NS over 10 mins immediately after administration of Spinal anaesthesia.

During pre-anaesthetic evaluation an informed and written consent was taken from patients who were included in the study and patients were explained on the methods of sensory and motor assessments. Patients were also educated on the usage of Visual analogue scale in the post operative period. All patients in study groups were kept nil by mouth from midnight before day of surgery. On the day of surgery before commencement of anaesthesia, intravenous line was secured with 18-gauge cannula. Preloading was done with 15 ml/kg Ringer Lactate 30 min prior to procedure. Pulse oximeter, noninvasive blood pressure (NIBP), and electrocardiography monitors were connected to all patients on arrival to operating room and baseline parameters were noted. The patient and anesthesiologist were blinded to the study groups, and all the recordings were noted by an anesthesiologist, who was blinded to randomization schedule. Under strict aseptic precautions, lumbar puncture was done at the level of L3-L4 intervertebral space through midline approach by using a 25-gauge Quincke spinal needle. After confirmation of free flow of cerebrospinal fluid 17.5 mg of 0.5% hyperbaric bupivacaine was given intrathecally. Group A: Intravenous dexmedetomidine 0.5 µg/kg in 100 ml NS loading dose was administered in the first 10 min immediately after

spinal anesthesia. Group B: Intravenous dexmedetomidine 1 µg/kg in 100 ml NS loading dose was administered in the first 10 min immediately after spinal anesthesia. Heart rate, non-invasive blood pressure, and saturation of oxygen was recorded before the subarachnoid block, every five-minute interval in the initial 30 mins of surgery, later for every 15 mins throughout surgery, and after 30 minutes in postoperative period.

Sensory blockade was checked with pin prick in mid axillary line from caudal to cephalad direction. Onset of analgesia was checked by loss of sensation to pinprick at T10 dermatome. The highest level of analgesia after 10 min was assessed. Time for two segment regression from highest level of sensory block (duration) was noted. Time from onset of subarachnoid block to the time of administration of rescue analgesia was considered as duration of analgesia. Motor blockade was assessed by Modified Bromage Scale. Time taken for motor blockade to reach Modified Bromage Scale 3 was taken as onset of motor blockade and regression to Modified Bromage Scale 0 was taken as duration of motor blockade. The sedation level was evaluated using Ramsay Level of Sedation Scale The level of sedation was assessed intraoperatively for every 5 for initial 30 min and for every 15 mins till the end of the surgery and for every 30 min till 12 h. in postoperative period in PACU. Excessive sedation was considered as score greater than 4/6. Hypotension, defined as decrease in systolic blood pressure of more than 20% from baseline and was treated with an intravenous bolus dose of 6 mg mephenteramine. The total number of bolus doses required throughout the intraoperative period was noted. Heart rate <50, defined as bradycardia, was treated by a bolus dose of 0.6 mg atropine. The total number of doses of atropine required was noted. Pain score was measured using visual analogue scale in postoperative period for every 30 min for 2h, thereafter for every 1hr. Rescue analgesic was given when VAS score was greater than 3. Time for rescue analgesic was noted. Patients were given 100 mg of Tramadol as slow IV as rescue analgesic.

Descriptive statistical analysis was done in present study. Results of continuous measurements are represented as Mean ± SD and results of categorial measurements are represented in Number (%). Chi-square test was used for calculation of significance of study parameters on categorial scale between two or more groups. Fishers exact test was used for calculation of significance of the study parameters on categorial scale (frequency tables). Paired t test was used for calculation of significance of the study parameters on continuous scale within group. Student independent t test was used for calculation of significance of the study parameters on continuous scale between groups. P value <0.05 was considered as statistically significant. Jamovi software [6] was used for analysis of the data and Microsoft word and excel were used to generate graphs, tables.

Results

This study was carried out on 60 patients operated under spinal anesthesia. Demographic data, intraoperative and postoperative hemodynamics, oxygen saturation, Ramsay sedation scores, postoperative analgesia and side effects were compared between Group A and Group B.

Demographic data: The mean age of Group A was 42.03 ± 10.85 yrs. compared to 41.27 ± 8.20 yrs. in the Group B and difference was statistically not significant (P value 0.759). BMI: The mean BMI in Group A was 24.91 ± 4.94 kg/m^2, compared to 23.23 ± 3.02 kg/m^2 in Group B and difference was statistically insignificant (P value-0.118). Weight distribution in both the groups as summarized [**Table 1**]. ASA grading of patients from both the groups was not statistically significant (P value-0.417). The mean duration of surgery of Group A was 104.83 ± 17.83 minutes, compared to 106.83 ± 22.07 minutes in Group B and the difference was not statistically significant (P value – 0.701) [**Table 1**]. Gender distribution in both groups was also not statistically significant (P value – 0.592) [**Table 2**].

There was no significant difference in time for onset of sensory and motor blockade as shown in [**Table 3**]. Preoperative, intraoperative and postoperative heart rate in both the groups are shown in (**Figure 1**). The average systolic blood pressure was lower in Group B (Dexmedetomidine 1 µg/kg) (116.24 ± 9.77), compared to Group A (Dexmedetomidine 0.5 µg/kg) (120.25 ± 13.44). The average postoperative SBP was lower in Group B (112.00 ± 12.96 mmHg) as compared to Group

Table 1. Baseline Characteristics of the groups.

	Group A	Group B	(p-value)
Age	42.03 ± 10.85	41.27 ± 8.2	0.759
BMI	24.91 ± 4.94	23.23 ± 3.02	0.118
Surgery duration	104.83 ± 17.83	106.83 ± 22.07	0.701

Table 2. Gender distribution.

Study groups	Gender	Frequency	%	P value
Group A	Male	18	60	0.592
	Female	12	40	
	Total	30	100	
Group B	Male	20	66.7	
	Female	10	33.3	
	Total	30	100	

A (117.27 ± 17.02 mmHg) (**Figure 2**). Intraoperative and postoperative DBP in both groups was summarized in **Figure 3**. There was no statistically significant difference in SPO2 levels between both groups during surgery and in postoperative period. VAS scores are summarized in **Figure 4**. Intraoperative Ramsay sedation scores were high in Group B (3.93 ± 0.25) compared to Group A (3.20 ± 0.66) (P value <0.05). Ramsay sedation scores are summarized in **Figure 5**. Requirement of Mephentermine and Atropine doses in both groups was also comparable.

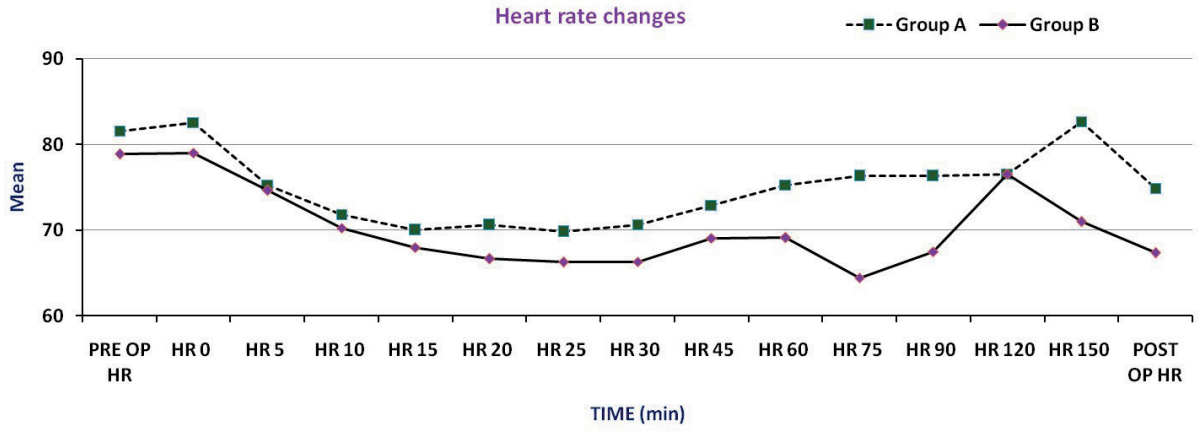

Figure 1. Heart rate changes.

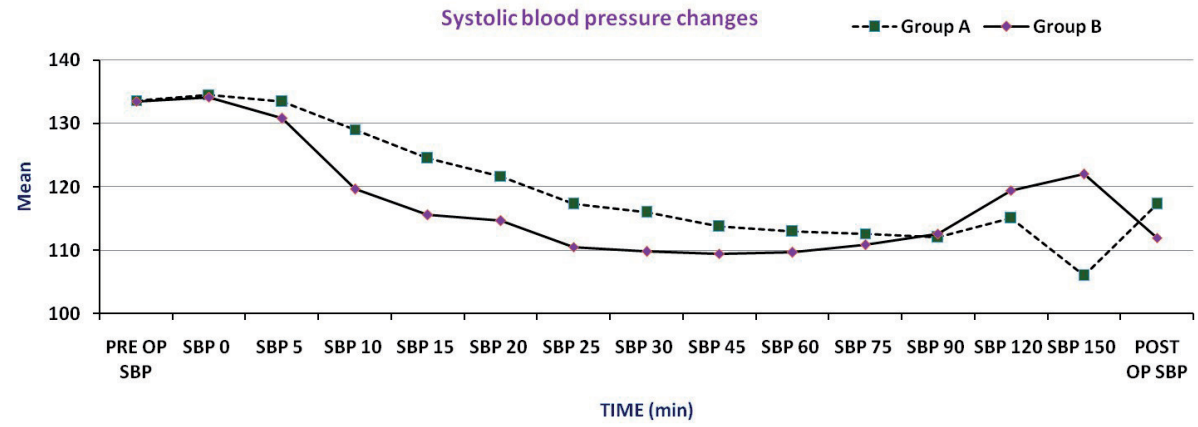

Figure 2. Systolic Blood Pressure changes.

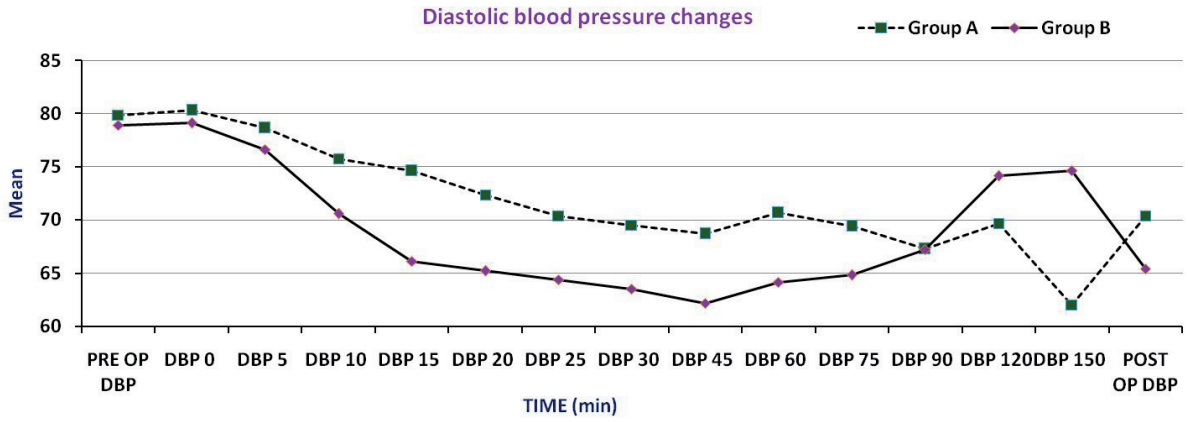

Figure 3. Diastolic BP.

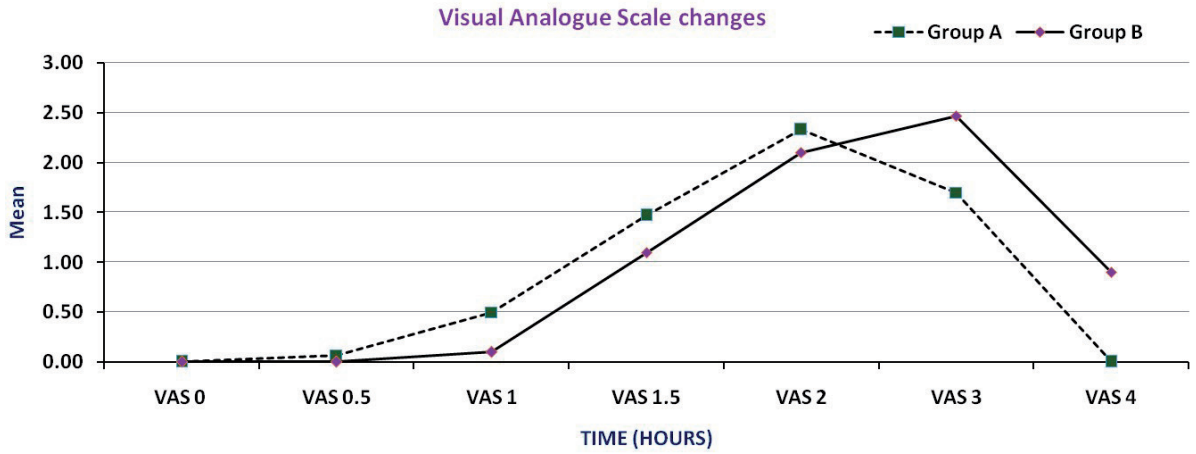

Figure 4. VAS scores.

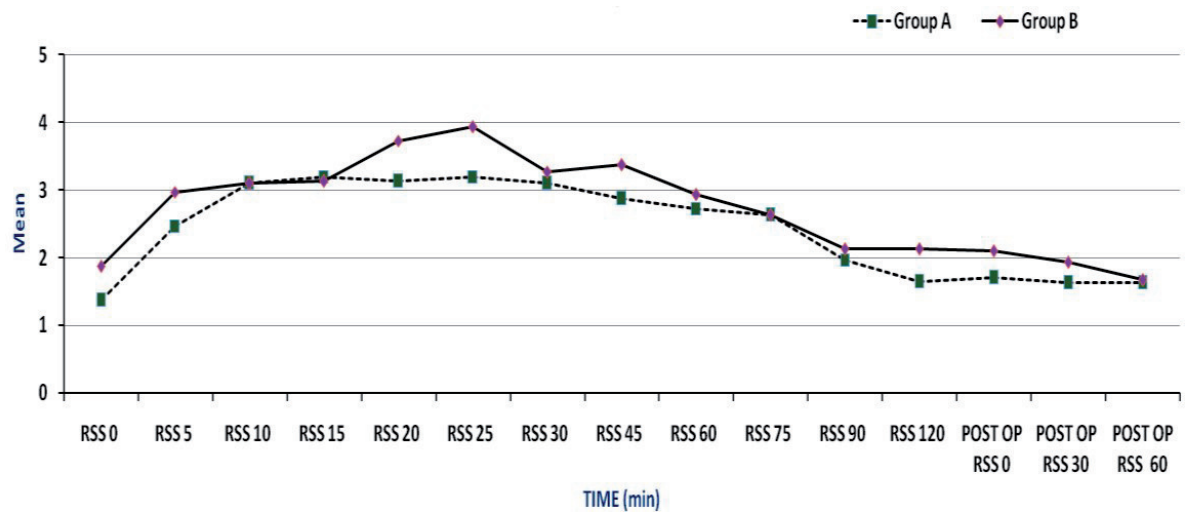

Figure 5. Ramsay sedation scores.

Table 3. Sensory and motor blockade in both groups.

	Group A	Group B	(p-value)
Onset sensory (min)	2.96 ± 0.52	2.78 ± 0.54	0.184
Onset motor (min)	5.19 ± 1.01	4.99 ± 0.99	0.448
Duration of motor	265 ± 19.61	276.83 ± 20.53	0.026
Time to two segment regression	Group A	116.83 ± 11.33	0.025
	Group B	123 ± 9.34	

The duration for two segment regression of sensory blockade and duration of motor block i.e, regression to Modified Bromage Scale 0 was significantly prolonged in Group B(123 ± 9.34) as compared to Group A(116.83 ± 11.33) (P value < 0.05) (**Table 3**). Time for first request of analgesic was longer in Group B (276.00 ± 13.80) compared to Group A) p value 0.07 as statistically significant [**Table 3**].

Discussion

Adjuvants to local anaesthetics such as epinephrine, magnesium sulphate, sodium bicarbonate, opioids and α2 agonists such as clonidine and dexmedetomidine have been used to extend the duration of spinal anaesthesia [7]. Clonidine, an α2 agonist, was commonly used as adjuvant to prolong spinal anaesthesia via oral, intrathecal, and intravenous methods [8]. Both intrathecal and intravenous dexmedetomidine have been demonstrated to prolong spinal anaesthesia in recent studies. Due to its more selective α2 receptor agonist activity, dexmedetomidine was a better adjuvant to spinal anaesthesia than clonidine because it provides more sedative and analgesic effects.[9] Dexmedetomidine acts at the spinal level, lamina VII and VIII of the ventral horns, to cause analgesia when injected intravenously or intrathecally. Sedation and analgesia are also produced by the drug, which acts on the locus coeruleus and dorsal raphe nucleus [4]. Prolongation of spinal anaesthesia following intravenous dexmedetomidine was due to this supra spinal effect [9]. Present study was designed to compare the effect of two different doses of intravenous dexmedetomidine on bupivacaine spinal anaesthesia. Comparing both the groups with respect to Age, Sex, BMI, ASA physical status of the patients that were enrolled into the groups we found that both groups are evenly matched without any statistically significant mismatch. In our study, we observed that the onset of sensory block had a mean duration of 2.96 ± 0.52 minutes in Group A (Dexmedetomidine 0.5 µg/kg) whereas it was 2.78 ± 0.54 minutes in Group B (Dexmedetomidine 1 µg/kg). Student unpaired T test was used to compare the above data and the resultant P value was 0.184. There was no significant difference in the mean duration of onset of sensory block between both groups. This correlates with the study conducted by Mi Hyeon Lee et al [11], which showed both 0.5 and 1 µg/kg of dexmedetomidine as isolated boluses without maintenance infusions showed no significant difference in duration of onset of sensory block. Similarly, Upadhya R Kavya et al [12] in their study also showed time of onset of sensory blockade was not significantly altered by use of dexmedetomidine. In our study, we observed that two segment regression had mean duration of 116.83 ± 11.33 minutes in Group A (Dexmedetomidine 0.5 µg/kg) whereas it was 123 ± 9.34 minutes in Group B (Dexmedetomidine 1 µg/kg). Student unpaired T test was used to compare the above data and the resultant P value was 0.025. Mean duration of two segment regression was slightly higher in Group B compared to Group A, which was statistically significant. In contrast to our study Mi Hyeon Lee et al [11], showed that there were no statistically significant differences in time for two segment regression of sensory blockade between 0.5 and 1 µg/kg dexmedetomidine. The highest level of sensory block was comparable in both groups, 3 patients (47.9%) in Group A achieved T4 sensory level compared to 4 patients (57.1%) in Group B. P value was 0.3 by using fishers exact test. There was no difference in highest level of sensory block achieved in both the groups, which was thus not statistically significant. In our study, we observed that onset of motor blockade was 5.19 ± 1.01 minutes in Group A, whereas it was 4.99 ± 0.99 minutes in Group

B. Student unpaired T test was used to compare the above data and the calculated P value was 0.448. There was no difference in mean duration of onset of motor blockade between both the groups, which was statistically not significant. Similar to our study, Upadhya R kavya et al [12], showed that there was no difference in onset of motor block between Control group, Dexmedetomidine 1mcg/kg bolus Group and Dexmedetomidine 0.5 µg/kg bolus plus 0.5 µg/kg/min infusion Group. Dinesh CN et al [10] also showed that using dexmedetomidine doesn't change onset of motor block.

In our study, we observed that duration of motor block (regression to Bromage 0) was 265 ± 19.61 minutes in Group A compared to 276.83 ± 20.53 minutes in Group B. Student unpaired T test was used to compare the above data and calculated P value was 0.026, which was statistically significant. Mean duration of motor block was slightly higher in Group B compared to Group A, which was statistically significant. Upadhya R Kavya et al [12] also showed duration of motor block was 321.6 ± 35.7 minutes in Dexmedetomidine 1 µg/kg bolus Group, 302.4 ± 18.2 minutes in Dexmedetomidine 0.5 µg/kg bolus plus 0.5mcg/kg/min maintenance Group, and 233.4 ± 34.1 minutes in control group, P value <0.001. In contrast to our study Mi Hyeon Lee et al [11], showed that there was no statistically significant difference in time of regression of motor blockade to Bromage 0 between Dexmedetomidine 0.5 µg/kg bolus Group and Dexmedetomidine 1 µg/kg bolus Group.

In our study the time for first request of analgesic in Group A was 265.5 ± 15.11 minutes, where as it was 276 ± 13.8 minutes in Group B, student unpaired T test was used to compare the above data and calculated P value was 0.007. The mean time for rescue analgesic was slightly higher in Group B compared to Group A, which was statistically significant but clinically the increased duration was not of much significance. Similar to our study Jyotsna Kubre et al [13] in their study showed that first request for postoperative analgesic was significantly prolonged 234.67 ± 7.649 minutes in dexmedetomidine 0.5 µg/kg loading dose group compared to control group 164.17 ± 6.170 minutes. Hong J et al [14], in their study also showed that mean time to first request for postoperative analgesia was longer with dexmedetomidine 1 µg/kg loading dose group 6.6h compared to control group 2.1h. In our study Intraoperative Ramsay Sedation Scores in series were slightly high in Group B compared to Group A. Maximum mean score in Group B was 3.93 ± 0.25, whereas it was 3.20 ± 0.66, P value < 0.05 by using Student unpaired T test. There was no excessive sedation (RSS > 4) in either of the groups. Upadhya R kavya et al [12], showed that patients receiving dexmedetomidine in their study had higher sedation scores (score 3 or 4) with minimal respiratory depression, they were easily arousable. In our study in postoperative period the maximum mean score of sedation in Group B was 2.10 ± 0.61, whereas it was 1.70 ± 0.61 in Group A, P value was 0.006, which was statistically significant. Though it was statistically significant, it was clinically insignificant, which can be attributed to the shorter duration of action of dexmedetomidine. Upadhya R kavya et al [12], Dinesh CN et al [10], failed to detect any difference in postoperative sedation. The average systolic blood pressure was lower in Group B 116.24 ± 9.77, compared to Group A 120.25 ± 13.44. The average postoperative SBP was lower in Group B 112.00 ± 12.96, compared to Group A 117.27 ± 17.02. In our study 2 patients in Group A and 2 patients in Group B had hypotension. The difference was not statistically significant in the incidence of hypotension between 2 groups. Hypotension was easily treatable with IV fluids and Mephenteramine. In similar to our study, Mohammad K AI Nobani et al [15] reported that there was no statistically significant difference in incidence of hypotension between IV dexmedetomidine and control groups. Intraoperative lowest mean heart rate was lower in Group B 64.47 ± 7.60 compared to Group A 69.80 ± 9.09. In our study 2 patients in Group B and none of them in Group A had bradycardia. Incidence of bradycardia was noted in dexmedetomidine 1 µg/kg group and was treated with Atropine 0.6 mg IV. Similar to our study Mohammad K AI Nobani et al [15] reported that higher doses of dexmedetomidine are associated with higher incidence of bradycardia. There was no oxygen desaturation in both groups, though there was increased sedation.

Conclusions

We conclude that Dexmedetomidine prolongs the duration of analgesia/sensory blockade when administered intravenously before administration of spinal anaesthesia. Dexmedomidine in a dose of 1.0 µg/kg has a slightly longer duration of analgesia as well as longer duration of motor blockade compared to a dose of 0.5 µg/kg (10-20 minutes longer approximately) but this duration is not significant in a clinical setting.

We didn't find any major variations between the two doses with regards to the Motor blockade duration, side effects profile, hemodynamic profile, or intra and post-op sedation levels. Hence we recommend that 0.5 µg/kg intravenously should be the preferred dosing as a co-analgesic with spinal anaesthesia.

Limitations

The findings of this study were based on the data having relatively small sample size from single centre.

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Conflict of interest statement
The authors declare no conflict of interest.

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