Original Article

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Dexmedetomidine as an Intrathecal Adjuvant with Hyperbaric Bupivacaine: A Randomized Double Blinded Case Control Study

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Abstract

Introduction: Spinal anesthesia is commonly used for abdominal and lower limb surgeries. Dexmedetomidine, the new highly selective α2 agonist, is now being evaluated as a potential neuraxial adjuvant. This study has been designed to evaluate the addition of 15 mcg of dexmedetomidine to 0.5% hyperbaric bupivacaine 3 ml intrathecally for elective abdominal and lower limb surgeries.

Aims and Objectives: To evaluate the onset and duration of sensory and motor block, the effect on hemodynamics, post-operative analgesia, and adverse effects of intrathecal dexmedetomidine with 0.5% hyperbaric bupivacaine.

Materials and Methods: A total of 40 patients (ASA PS I and II) undergoing elective lower abdominal and lower limb surgeries at the Basaweshwar Teaching and General Hospital, Gulbarga, between January 2012 and May 2013 were randomized into one of the two groups. Each patient received 3.5 ml drug consisting of 3 ml 0.5% hyperbaric bupivacaine and 0.5 ml normal saline (Group I) or 15 μg dexmedetomidine in 0.5 ml normal saline (Group II). Onset and duration of the sensory block, motor block, hemodynamics, pain, and sedation were assessed intraoperatively and postoperatively for 24 h. The incidence of adverse effects was recorded.

Results: The mean duration of motor block in Group I and II were 265.5 and 510.5 min, respectively. The mean duration of sensory regression to L1 in Group I and II were 257.25 and 469.5 min, respectively. Time to 2-segment regression in Group I and II were 88.5 and 138.75 min, respectively. The mean duration of analgesia in Group I and II were 238.5 min and 438 min, respectively. The patients in Group II had significant prolongation of the motor and sensory block ($P < 0.001$).

Conclusion: Intrathecal dexmedetomidine in the dose of 15 μg significantly prolongs the anesthetic effects of bupivacaine and can be beneficial in surgeries of long duration, precluding the need for an epidural or general anesthesia.

Key words: Alpha 2 agonist, Dexmedetomidine, Spinal anesthesia

INTRODUCTION

Spinal anesthesia is used extensively for lower abdominuteal and lower extremity surgeries as it is easy to learn, has a definite end point of visualization of cerebrospinal fluid, minuteimizes the stress response, provides optimal operative conditions with minute intraoperative blood loss, and less post-operative morbidity and post-operative analgesia.[1,2] Fear of post-surgical pain is a major concern for patients undergoing surgery. Adjuvants are drugs that increase the efficacy or potency of other drugs when given concurrently. Neuraxial adjuvants are used to improve or prolong analgesia and decrease the adverse effects associated with high doses of a single local anesthetic agent. In addition to their dose-sparing effects, neuraxial adjuvants are also utilized to increase the speed of onset of neural blockade (reduce latency) and prolong the duration of the neural blockade. Neuraxial adjuvants include opioids, sodium bicarbonate ($NaHCO_3$), vasoconstrictors, alpha-2 adrenoceptor agonists, cholinergic agonists, N-methyl-d-aspartate antagonists,

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and γ-aminoisobutyric acid receptor agonists.[3] Intrathecal administration of clonidine has been shown to significantly increase the duration of anesthesia produced by isobaric or hyperbaric bupivacaine with bradycardia, hypotension, arrhythmias, dry mouth as its side effects.

Dexmedetomidine is a more selective α2-adrenoreceptor agonist that has been recently evaluated as an adjuvant to intrathecal local anesthesia.[4-6] Based on previous animal[7,8] and human studies[5] that suggested a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine, we have conducted the study with 15 μg dexmedetomidine as an adjuvant to intrathecal bupivacaine.

Aim

To evaluate the onset and duration of sensory and motor block, hemodynamic effects, duration of post-operative analgesia, and incidence of adverse effects of intrathecal dexmedetomidine with 0.5% hyperbaric bupivacaine in spinal anesthesia.

MATERIALS AND METHODS

It was a prospective double blinded randomized case-controlled study conducted after Institution Ethical Committee approval and obtaining written, informed consent from all patients included in the study.

Inclusion Criteria

1) Age group 18-60 years
2) ASA Grade I and Grade II
3) Body mass index 18.5-25.

Exclusion Criteria

1) Patients belonging to ASA Grades III, IV, and V
2) Patient refusal
3) Liver and renal dysfunction
4) Patients with cardiac dysrhythmias
5) Patients using adrenergic receptor blockers, calcium channel blockers or with sinus bradycardia
6) Weight >120 kg or height <150 cm
7) Patients with contraindications to spinal anesthesia
8) Allergy to the drugs under study.

A total of 40 patients undergoing elective lower abdominuteal and lower limb surgeries at the Basaweshwar Teaching and General Hospital, Gulbarga, between January 2012 and May 2013 were randomized into one of the two groups.

Patients in Group I: 3.0 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml saline.

Patients in Group II: 3.0 ml of hyperbaric bupivacaine with 15 μg dexmedetomidine in 0.5 ml saline.

In the operation theater, appropriate equipment for airway management and emergency drugs were kept ready. 18 G intravenous cannula was inserted, and the patient was preloaded with 15 ml/kg of lactated ringer's solution. Noninvasive blood pressure, pulse oximeter, and electrocardiogram leads were connected and baseline readings were recorded. Under aseptic precautions, a midline lumbar puncture was performed using a 25G Quincke needle in sitting position and the drug was injected. The drug was loaded by a doctor who took no further part in the study. Neither the patient nor the attending anesthesiologist was aware of the group the patient belonged to. The patient was then immediately placed in supine position. The time for intrathecal injection was considered as 0 and the following parameters were observed - sensory blockade, motor blockade, duration of analgesia and sedation. The pulse rate, systolic and diastolic blood pressure, SpO2, and respiratory rate were recorded for every 2 min for 10 min and then every 5 min throughout the intraoperative period and at the completion of surgery. Hypotension was defined as fall in systolic blood pressure > 20% from baseline or mean arterial pressure <60 mmHg and was managed with injection mephentermine 6 mg intravenous in increments. Bradycardia was defined as heart rate <50/min and this was managed with atropine 0.01 mg/kg intravenously. Respiratory depression defined as respiratory rate <8/min and or SpO2 <85%. This was planned to be managed with bag and mask ventilation or intubation if necessary. Following a subarachnoid block, the sensory block was assessed by loss of sensation to pinprick using 23G sterile needle starting immediately after injection and was continued for every 15 s till loss of pinprick sensation at T_{10} level. Onset of sensory block was taken as the time from intrathecal injection to loss of pinprick sensation at T_{10}. At 20 min interval after SAB, the dermatomal level of sensory block noted, and this was considered as the maximum level of sensory block. Motor block was assessed using Bromage score (1 - Free movements of legs and feet, 2 - Just able to flex knees with free movement of feet, 3 - Unable to flex knees but with free movement of feet, 4 - Unable to move hips, legs or feet). Assessment of motor block was started immediately after the intrathecal injection. It was tested for every 15 s till Bromage Score of 4 was reached. Onset of motor block was taken as the time taken to achieve Bromage score of 4 from the subarachnoid block. The degree of the motor block after 20 min of injection was noted, and this was considered the maximum degree of motor block. Thereafter, motor block regression was noted and duration of motor block was taken as the time from initiation of SAB to return to Bromage score of 1. Sedation was assessed using the Ramsay sedation score from 1 to 6. Pain was assessed using the Visual analog scale. Blood loss was replaced as necessary. The patient was shifted to a recovery room after

completion of surgery. The vital signs were recorded, for every 15 min in the 1st h after surgery and 30 min interval for next 2 h and thereafter at hourly intervals for next 3 hours. Sensory and motor block assessment was done for every 15 min till recovery of pinprick sensation to L1 and Bromage score of 1, respectively. Patients were shifted to the post-operative ward after complete resolution of motor blockade. At the end of the surgery, the degree of pain was assessed using Visual analog scale. In the recovery room, pain assessment was done for every 15 min till score >4 was reached. Whenever the patient complained of pain, the rescue analgesic intramuscular diclofenac 75 mg was given. Duration of effective analgesia was defined as time interval between onset of the subarachnoid block and the time to reach visual analog score ≥4. Patients were monitored for 24 h to detect the occurrence of side effects. Patients were also enquired about the occurrence of transient neurological symptoms, which was described as pain/paraesthesia in the neck, buttocks, legs or pain radiating to lower extremities after initial recovery from anesthesia within 72 h.

OBSERVATION AND RESULTS

The results were computed using the Unpaired *t*-test. $P < 0.05$ was considered significant and $P < 0.001$ was considered highly significant.

The two groups (Groups I and II) were comparable with respect to ASA class, type, and duration of surgery. The groups were similar with respect to the demographic data, i.e., age, height, weight, and sex with $P > 0.05$ (Table 1).

Sensory and motor block parameters were represented as mean ± standard deviation except maximum sensory level attained and number of diclofenac injections in first 24 h postoperatively which were represented as median (Table 2).

There was significant shortening of the time of onset of sensory block, prolongation of time to two segment regression, and sensory recovery time to L1 in the dexmedetomidine group (Group II) compared to the control group. The number of doses of diclofenac injections required in the first 24 h postoperatively were also reduced in the dexmedetomidine group (Group II) compared to Group I. The patients in the dexmedetomidine group also had a significantly quicker onset of motor blockade and prolonged duration of the motor block compared to those in the control group.

The dexmedetomidine group (Group II) had a significant increase in the incidence of bradycardia i.e., 50% of the patients had an episode of significant bradycardia, which was amenable to therapy with single dose of intravenous atropine 0.6 mg. Patients in the Group II had good anxiolysis, desirable sedation (median Ramsay sedation score of 2 vs. RSS of 1 in Group I) (Table 3).

From statistical analysis, it was computed that there was no statistically significant difference in the overall hemodynamic status of both the groups ($P > 0.05$) although a higher percentage of patients in the Group II developed bradycardia at some point in the course (Graphs 1 and 2).

DISCUSSION

Intrathecal dexmedetomidine is thought to produce its analgesic effect by inhibiting the release of C fibers transmitters and by the hyper polarization of postsynaptic dorsal horn neurons.

In our study, the mean time to onset of the sensory block is 294.75 s in Group I and 93 s in Group II. Onset of sensory block up to T10 is statistically significantly faster in Group II compared to Group I. Al-Mustafa *et al.*[6] found that the mean time of sensory block to reach T10 was 4.7 ± 2 min in D10 group (10 μg dexmedetomidine), 6.3 ± 2.7 min in D5 (5 μg dexmedetomidine), and 9.5 ± 3 min in Group N (control). Kim *et al.*[9] observed that the patients in dexmedetomidine group (D) demonstrated a shorter time to reach the peak sympathetic and sensory block level compared to the patients in control Group S ($P < 0.01$).

In the present study, the mean time for two segment regression was 138.75 min in Group II and 88.5 min in Group I. The time for two segment regression is significantly prolonged in Group II ($P < 0.001$). In our study, there is significant difference between the groups in terms of the time to sensory regression to L_1 - with Group II requiring a much longer time (469.5 min) compared to Group I (257.25 min) which is highly significant with $P < 0.001$. Hala *et al.*[10] concluded that dexmedetomidine significantly prolonged time to two segment regression, sensory regression to S_1, in a dose-dependent manner. Al-Mustafa *et al.*[6] found that the regression time to S1 dermatome was 338.9 ± 44.8 min in group D10, 277.1 ± 23.2 min in D5, and 165.5 ± 32.9 min in Group N (control) ($P < 0.001$).

There was an insignificant difference among the groups in maximum level of sensory block. The median of the maximum sensory level reached in both the groups was T_4. Hala *et al.*[10] found that the median and range of the peak sensory level reached were T6 (T3 - T10) in Group B, T5 (T3 - T9) in Group D1, and T7 (T4 - T9) in Group D2, not

Table 1: Demographic data

Variable	Group I (*n*=20)	Group II (*n*=20)	*P* value
Age in years (mean±SD)	40.6±13.57	37.66±10.83	0.683
Height in centimeter (mean±SD)	141.2±3.7	141±3.4	0.846
Weight in kilogram (mean±SD)	46.9±4.7	47.5±3.9	0.679
Sex (out of 20)			
Male	11	12	
Female	9	8	
ASA (out of 20)			
I	15	16	
II	5	4	

SD: Standard deviation

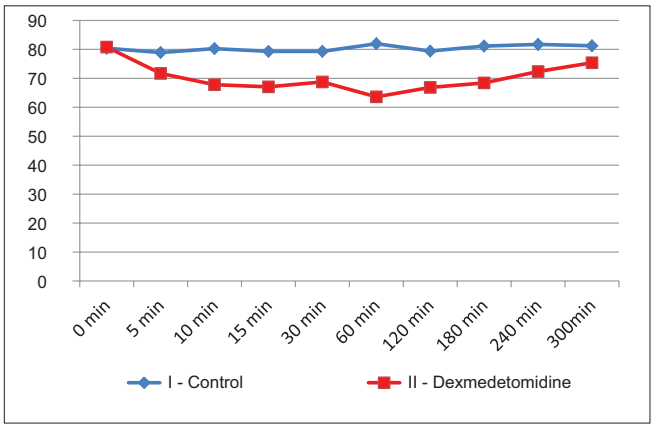
Table 2: Sensory and motor block parameters (values expressed as mean±SD and median were mentioned)

Variable	Group I	Group II	*P* value
Onset of sensory blockade (s)	294.75±115.5	93±35.96	0.0001
Time to two segment regression (min)	88.50±14.51	138.75±75	0.0001
Sensory recovery time to L1 (min)	257.25±56.39	469.50±41.03	0.0001
Maximum sensory level attained (median)	T4	T4	
No. of diclofenac injections in first 24 h post-op (median)	2	1	
Onset of motor blockade (s)	155.25±60.44	57.75±17.73	0.0001
Motor recovery time (min)	265.50±55.72	510.50±45.18	0.0001

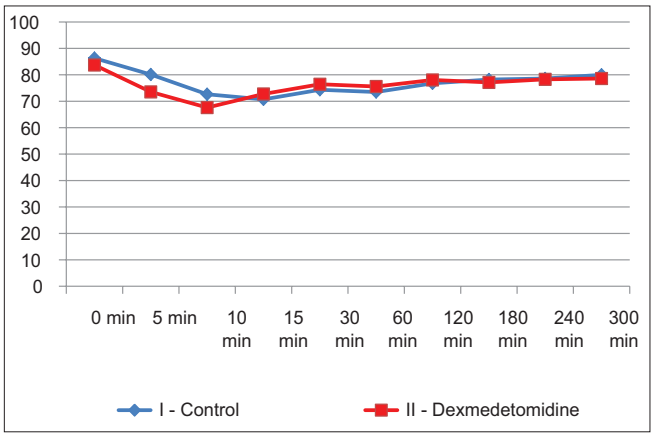
SD: Standard deviation

Table 3: Side effects (values expressed as numbers out of 20)

Side effect	Group I	Group II
Bradycardia	2	10
Hypotension	6	7
Excess sedation	0	0
Hypoxia	0	0
Anxiety	5	0
Shivering	3	3
Nausea, vomiting	1	1
Headache	2	3
Urine retention	3	3



Graph 1: Mean pulse rate in both the groups at various time intervals



Graph 2: Means of mean arterial blood pressure in both the groups at various time intervals

statistically different among the groups ($P = 0.08$). Gupta *et al.*[11] found no difference between Group D and R in the highest level of block (T5 and T6, respectively) when dexmedetomidine was added to ropivacaine as intrathecal adjuvant (D) versus control (R).

There is a significant difference between groups in total duration of analgesia with Group II having a much longer duration compared to Group I ($P < 0.001$). Group I has a mean duration of analgesia of 238.5 min, Group II has 438 min. Thus, the analgesic requirement in the first 24 h postoperatively in Group II was significantly lesser than that in Group I. Hala *et al.*[10] concluded that intrathecal dexmedetomidine in doses of 10 μg and 15 μg significantly prolong the anesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose-dependent manner. Addition of 10 ug or 15 ug increased the duration of analgesia provided by spinal bupivacaine by about 240 or

520 min, respectively. The increased duration of analgesia in their study may be due to the lower dermatomal levels needed in anterior cruciate ligament surgery for pain relief in comparison to our study which included abdominuteal surgeries as well which require higher dermatomal levels of sensory blockade.

The mean time to onset of Bromage 2 motor block is 155.25 s in Group I and 57.75 s in Group II. There is a statistically significant difference among the groups ($P < 0.001$). It correlates with the study by Al-Mustafa *et al.*[6] who found that the mean time to reach Bromage 3 scale was 10.4 ± 3.4 min with 10 μg dexmedetomidine, 13 ± 3.4 min with 5 μg dexmedetomidine, and 18 ± 3.3 min in control group. Kanazi *et al.*[5] also found that the patients who received 12 mg of bupivacaine supplemented with 3 μg of dexmedetomidine intrathecally had a faster onset of the maximum motor block compared to plain bupivacaine.

The median of the maximum motor block attained is Bromage Grade 4 in both the groups. Therefore, there is no statistical difference between the groups in this regard. Hala *et al.*[10] found that all the patients achieved modified Bromage 3 motor block. Kim *et al.*[9] also observed that the peak block level was similar for the two groups receiving either dexmedetomidine 3 μg ($n = 27$) or normal saline ($n = 27$) intrathecally with 6 mg of 0.5% hyperbaric bupivacaine.

The mean duration of motor block in Groups I and II are 265.5 min and 510.5 min, respectively ($P < 0.001$). Thus, there is a significant prolongation of the duration of motor block by dexmedetomidine. Hala *et al.*[10] also found that motor block regression to modified Bromage 0 were significantly prolonged in Group D2 (15 μg dexmedetomidine) than in Group D1 (10 μg dexmedetomidine) and Group B (control) and in Group D1 than in Group B. Al-Mustafa *et al.*[6] observed that the regression to Bromage 0 was 302.9 ± 36.7 min in D10 (10 μg dexmedetomidine), 246.4 ± 25.7 min in D5 (5 μg dexmedetomidine), and 140.1 ± 32.3 min in Group N (control). Onset and regression of motor block were highly significant (N vs. D5, N vs. D10, and D5 vs. D10, $P < 0.001$).

In our study, there is no significant difference between the two groups with respect to intraoperative and post-operative mean heart rates with $P > 0.05$. Groups I and II have comparable values of mean systolic blood pressure, diastolic blood pressure, and mean arterial pressure throughout the intraoperative and post-operative periods with $P > 0.05$. Thus, the hemodynamic stability is maintained even in the presence of dexmedetomidine. Hala *et al.*[10] found that the mean values of mean blood pressure and heart rate were comparable between the three groups throughout the study duration. Al-Mustafa *et al.*[6] also observed that the three groups in their study had comparable hemodynamics throughout the period of study.

The median Ramsay sedation score in both the groups is 2. Therefore, there is no significant difference although 100% of the cases in the dexmedetomidine have a desirable sedation score of 2. Al-Mustafa *et al.*[6] also observed that all the patients in the three groups in their study had a RSS of 2. Hala *et al.*[10] found that the patients in Group B and Group D1 had a median RSS of 2 (2-3) at all assessment times ($P > 0.05$). Patients in Group D2 had a higher median sedation score (3.5-4) between 60 min and 195 min ($P < 0.05$). There was no significant difference in the sedation scores between the groups at the other time points.

The incidence of hypotension and thus the use of vasopressor was significantly higher in Group II (30%) than in Group I (15%) which was insignificant statistically. The incidence of bradycardia and thus the use of atropine was significantly higher in Group II (50%) than in Group I (10%) but it was amenable to therapy with single dose of intravenous atropine 0.6 mg. 25% of the patients in Group I were anxious whereas all the patients of the dexmedetomidine Group (II) were tranquil. All the patients had peripheral oxygen saturation >95% at all times and did not require additional oxygen. No patient had a respiratory rate below 10/min. Three patients each in Groups I and II had shivering, which was managed with intravenous tramadol 25 mg. Complete recovery of sensory and motor function was observed in all the studied patients. 2 weeks after the surgery at the post-operative follow-up visit, patients did not show any neurological deficit.

CONCLUSION

The longer sensory and motor blockade produced by 15 μg dexmedetomidine with hyperbaric bupivacaine and the desirable level of sedation can be beneficial in surgeries of long duration, precluding the need for an epidural or general anesthesia.

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