ORIGINAL ARTICLE

Evaluating effect of intravenous dexmedetomidine on hyperbaric bupivacaine spinal anesthesia

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ABSTRACT

Background & Aims: Intravenous dexmedetomidine is being increasingly used in perioperative setting including as an adjunct to local anesthetic in various regional techniques with an intent to either improve the block quality, increase the duration of block or to provide sedation and patient comfort during the periblock period. Intravenous dexmedetomidine when used just before or after spinal anesthesia has many desirable effects such as adequate sedation and patient comfort, longer sensory-motor blockade, prolonged postoperative analgesia and reduced post-anesthesia shivering. We aimed to study the effect of intravenous dexmedetomidine on spinal anesthesia with hyperbaric 0.5% bupivacaine.

Methodology: One hundred American Society of Anesthesiologists (ASA) physical status I and II patients undergoing orthopaedic surgeries under spinal anesthesia were randomized into two groups of 50 each. After giving spinal anesthesia with 3.5 ml of 0.5% hyperbaric bupivacaine, patients in Group D received a loading dose of 1 μg/kg of dexmedetomidine intravenously by infusion pump over 10 min followed by a maintenance dose of 0.5 μg/kg/h till the end of surgery, whereas patients in Group C received an equivalent quantity of normal saline. The two-dermatome pinprick sensory regression time, duration of the motor block, Ramsay sedation score (RSS), duration of analgesia and side effects of dexmedetomidine were assessed.

Results: The time taken for regression of sensory block to S1 dermatome and Bromage 0 motor block was increased significantly by addition of dexmedetomidine. Time to first requirement of analgesic in postoperative period was more in Group D compared to Group C. Sedation was more in patients of Group D compared to Group C ($P < 0.001$).

Conclusion: Intravenous dexmedetomidine significantly prolongs the duration of sensory and motor block of bupivacaine spinal anesthesia. The incidence of bradycardia is significantly higher when intravenous dexmedetomidine is used as an adjuvant to bupivacaine spinal anesthesia. Dexmedetomidine provides excellent intraoperative sedation and postoperative analgesia.

Key words: Dexmedetomidine; Bupivacaine; Ramsay sedation scale; Intrathecal; Spinal anesthesia

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INTRODUCTION

Pain is inherent to all surgeries causing significant morbidity. Perioperative pain management lies on the shoulders of anesthesiologists and there has been a constant struggle to bring out the best possible analgesic technique with least side effects.

Regional anesthesia and analgesia has the potential to provide excellent operating conditions and prolonged postoperative pain relief.[1] It is also known to reduce post-operative morbidity and

mortality by its positive influence like improved blood flow and optimum tissue functionality and improved recovery, thereby leading to its widespread use.[2]

Among all the regional techniques, subarachnoid block is still the first choice especially for below umbilical procedures because of its simplicity, rapid onset of action, less failure rate, cost-effectiveness, and superior level of blockade. However, post-operative pain control is a major problem because spinal anesthesia using only local anesthetics is associated with relatively short duration of action and thus early analgesic intervention is needed in post-operative period.[3]

To overcome this limitation, various adjuvants, e.g. opioids, benzodiazepines, ketamine, neostigmine and other drugs, have been used to prolong the duration of spinal anesthesia and hence provide better postoperative analgesia.[2] But these adjuvants (especially opioids) are associated with side effects like pruritus, respiratory depression, urinary retention, postoperative nausea and vomiting.[4]

Hence alpha 2 agonists have recently been used as adjuvants to potentiate the effects of local anesthesia without respiratory depression.[5] Dexmedetomidine is alpha-2 agonist that was approved by FDA in 1999 for use in humans as a short term medication for sedation/analgesia in the intensive care unit.

Dexmedetomidine is an S-enantiomer of medetomidine with a higher specificity for α-adrenoceptor (α2:α1, 1620:1) compared to clonidine (α2:α1, 220:1). It is highly selective α-2 adrenergic agonist possessing hypnotic, sedative, anxiolytic, sympatholytic, opioid-sparing and analgesic properties without producing significant respiratory depression.[5]It acts by inhibiting the release of nor-epinephrine at locus ceruleus. Small doses of dexmedetomidine used in combination with spinal bupivacaine produces a shorter onset of motor block and a prolongation in the duration of motor and sensory block with preserved hemodynamic stability and minimal side effects,[6,7] The enhanced anti-nociceptive effect is said to be related to its lipophilicity.[8]

With this in mind, this study was conducted to investigate the effect of intravenous administration of dexmedetomidine on the duration of sensory and motor block, as well as the hemodynamic parameters and the level of sedation.

METHODOLOGY

A prospective, randomized, double blind, placebo controlled study was conducted after obtaining approval of the institutional ethics committee and written informed consent from all the participants, between March 2015 to July 2015.

A total of 100 patients of ASA I and II of age 20-60 years undergoing elective orthopedic lower limb surgeries under spinal anesthesia in our hospital were randomly allocated into two groups: the dexmedetomidine group, (Group D) and the control group (Group C). Exclusion criteria were patients with infection at the puncture site, aged < 20 y and > 60 y, had coagulopathy, had hypersensitivity to drugs used, pregnant females and those who had psychiatric and neurological diseases

All patients were kept fasting overnight. In the operating room, all patients were connected to electrocardiography, peripheral oxygen saturation (SpO_2) and non-invasive blood pressure monitor and the basal parameters were recorded. An IV line was obtained with 18 or 20G cannula. After prior premedication with 4 mg of ondansetron all the patients were preloaded with 10 ml/kg of lactated ringer's solution.

Spinal anesthesia was given with 23G Quincke needle with 3.5 ml of 0.5% hyperbaric bupivacaine at L3-4 or L2-3 interspace in sitting or lateral position using standard midline approach. O_2 was given by face mask. Vital signs were recorded (heart rate, blood pressure, SpO_2, respiratory rate) immediately after the subarachnoid block, then every 5 min for the first 15 min, every 10 min for the first hour, after every 30 min till end of the surgery and then every 15 min in postanesthesia care unit (PACU).

The patients of Group D received loading dose of 1 μg/kg of dexmedetomidine by infusion pump over 10 min immediately after spinal anesthesia with 3.5 ml of 0.5% hyperbaric bupivacaine and then continuous infusion of 0.5 μg/kg of dexmedetomidine till the end of surgery.

The patients in Group C received similar volume of normal saline as loading 1 μg/kg followed by 0.5 μg/kg continuous infusion following spinal anesthesia with 3.5 ml of 0.5% hyperbaric bupivacaine. Sensory blockade was checked with pin prick by 24G hypodermic needle and the time taken for level T10 was noted. Sensory blockade was assessed till T10 achieved, during surgery and postoperatively. Motor blockade was assessed by modified Bromage Scale. (0 = no paralysis; 1 = unable to raise extended leg; 2 = unable to flex knee; 3 = unable to flex ankle). Time taken for motor blockade to

reach modified Bromage Scale 3 was noted. All the durations were calculated considering the time of spinal injection as time 0.

The level of sedation was evaluated both intra operatively and postoperatively every 60 mins using Ramsay sedation scale till the patient was discharged from PACU. Excessive sedation was defined as score greater than 4/6.

Hypotension, defined as systolic blood pressure < 90 mmHg or > 20% fall from baseline value, bradycardia (heart rate < 50/min) and postoperative complications, e.g. nausea and vomiting, shivering, urinary retention and headache etc., were noted and treated appropriately.

Postoperatively, time to sensory regression to S1 and time to motor block regression to modified Bromage grade 0 was noted. Vital signs were assessed every 15min. Pain was assessed using visual analogue scale (VAS) at 1st, 2nd, 3rd, 4th and 6th hour. Total duration of analgesia was defined as time from administration of SAB until the first complaint of pain (VAS ≥ 3). Injection diclofenac 75 mg intramuscular was used as rescue analgesic and study was ended.

RESULTS

The demographic data, ASA grade, type of surgery, and duration of surgery were comparable between the two groups (Table 1).

Time taken to reach T10 dermatome is shown in Table 2. The mean time for sensory block to reach T10 was 5.71 ± 1.13 min in Group C and 5.06 ± 1.03 min in Group D. There was no significant difference in attaining sensory level T10 in both the groups.

Time for motor block to reach Bromage 3 is shown in Table 2. The time observed was 6.8 ± 1.61 min in Group D and 7.25 ± 1.39 min in Group C. There was no significant difference in motor onset in both the groups.

Table 2 shows time taken for sensory regression to S1. The addition of dexmedetomidine resulted in prolongation of sensory regression to S1 segment. The prolongation in time to regress in Group C vs Group D was highly significant by Tukey's test ($p < 0.01$)

Motor block regression to Bromage 0 is shown in Table 2. Group D had significantly prolonged motor block than Group C ($p < 0.01$)

Statistical analysis by Tukey's test showed that the time for first analgesic rescue was significantly prolonged in Group D (7.55 ± 1.07 h) compared to Group C (4.61 ± 1.08 h) ($p < 0.01$)

Sedation was assessed by Ramsay sedation score. Intraoperative Ramsay sedation scores were significantly higher in Group D (mean 3.8 ± 0.7, range 2-5) as compared to Group C (mean 2.09 ± 0.1, range 1-3) ($P < 0.001$). Maximum scores in group D ranged from 2-5, with a mean of 3.8. In group D, the maximum sedation score of more

Table 1: Demographic data of study variables

Parameter	Group C	Group D	p-value
Age (years)	34.37 ± 9.01	35.17 ± 11.15	
Male	27	28	
Female	23	22	
ASA 1	26	23	> 0.05
ASA 2	24	27	
Weight (kg)	58.93 ± 8.22	56.73 ± 7.52	
Height (cm)	165.30 ± 3.41	164.33 ± 3.58	

Table 2: Comparative study parameters

Parameter	Group C	Group D	p-value
Time to reach sensory level T10 (min)	5.71 ± 1.13	5.06 ± 1.03	NS
Time to reach Bromage 3 (min)	7.25 ± 1.39	6.8 ± 1.61	NS
Time to reach S1 dermatome (min)	189.5 ± 39.83	403.16 ± 46.52	p < 0.01
Time to reach Bromage 0 (min)	290.16 ± 40	603.16 ± 46.52	p < 0.01
Duration of analgesia (hours)	4.61 ± 1.08	7.55 ± 1.07	p < 0.01
Ramsay sedation score	2.09 ± 0.1	3.8 ± 0.7	*P* < 0.001

than 4 was achieved in 23 (46%) of patients. Maximum scores in Group C ranged from 2 to 3, with a mean of 2.09. There was no significant difference in sedation scores between the groups in the postoperative period.

The hemodynamic data, complications, and intraoperative requirement of atropine / mephentermine / IV fluids were assessed at various time intervals. Higher number of patients in Group D had bradycardia and fall in systolic blood pressure. Systolic, diastolic, and mean arterial blood pressures were relatively lower in Group D compared to Group C. More patients in Group D (26% vs. 4%; *p* value = 0.004) required atropine for management of bradycardia. Mephentermine required to treat hypotension was comparable in both the groups.

DISCUSSION

The mechanism by which intrathecal α-adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well known. Activation of post-synaptic α2-A receptors in CNS results in hypotension and bradycardia by decreasing the sympathetic activity. Activation of post-synaptic α2-C receptors in CNS results in anxiolysis, whereas activation of post-synaptic α2-B receptors in peripheral vasculature results in transient hypertension.

Dexmedetomidine intravenously in this study is used as a loading dose 1 μg/kg over 10 min followed by an infusion has been found to prolong the duration of analgesia and motor blockade in the present study. Lugo *et al*.[9] in their study noted prolongation of sensory block and duration of analgesia without significant effect on motor block while using 1 μg/kg bolus followed by 0.5 μg/kg/h infusion of dexmedetomidine. Al-Mustafa *et al*.[10] also observed similar findings in their study and in addition, there was prolongation of motor blockade with a similar dose of dexmedetomidine. The local anesthetic acts by blocking sodium channels whereas α-adrenergic agonists are said to act by binding to pre-synaptic C-fibres and post-synaptic dorsal horn neurons. Their analgesic action is a result of depression of the release of C-fiber transmitters and hyperpolarisation of post-synaptic dorsal horn neurons and prolonged motor block might be caused by direct impairment of excitatory amino acids release from spinal interneurons.[11]

Several studies reported prolonged duration of motor block following use of 1 μg /kg initial bolus dose followed by infusion. However, in a study by Kaya *et al*[12] use of a single dose of 0.5 μg/kg of dexmedetomidine did not affect the duration of motor block. The prolongation of motor block in spite of use of 1 μg/kg initial loading dose, observed by us may be attributed to continuous infusion following loading dose. In this study the time to reach t10 sensory level and modified Bromage scale 3 motor block was similar in both groups.

With respect to sensory blockade, the highest sensory level achieved was similar in both groups but two dermatomal regression was significantly prolonged in Dexem group. In our study, the mean time for two-dermatomal regression of sensory blockade was significantly prolonged in the dexmedetomidine group (403 ± 46.52 min) compared to the control group (189.5 ± 39.83 min).

Prolongation of spinal anesthesia after IV dexmedetomidine is hypothesised to be by its supra-spinal action at locus ceruleus and dorsal raphe nucleus. There are three subtypes of α2 receptors: A, B, and C. Dexmedetomidine is a more selective α2-A receptor agonist than clonidine. Activation of presynaptic α2-A receptors at locus ceruleus decreases norepinephrine release and causes sedative and hypnotic effects, whereas its effect on descending medullo spinal noradrenergic path way results in analgesia by terminating pain signal propagation. At substantia gelatinosa of the spinal cord, it decreases firing in nociceptive neurons and release of substance P, thus producing analgesia. So, dexmedetomidine has a role in modulating pain and inhibiting the transmission and perception of pain. Hong *et al*[13] reported that the mean time to two-segment regression was prolonged in the dexmedetomidine group (78 min vs. 39 min for cold and 61 min vs. 41 min for pinprick for dexmedetomidine group and control group, respectively). Similar observations were noted by others[11-14] in the dexmedetomidine and control groups, respectively.

In our study, the regression time to reach the modified Bromage scale 0 was significantly prolonged in the dexmedetomidine group (603 ± 46.52 min) compared to the control group (290.16 ± 40 min). Similar prolongation of motor blockade was reported in previous studies; Al Mustafa et al.[8] 199 ± 42.8 min vs. 138.4 ± 31.3 min ($p < 0.05$), Whizar-Lugo et al.[9] 191 ± 49.8 min vs. 172 ± 36.4 min (*P* value not significant), Tekin et al.[11] 215 min vs. 190.8 min ($p < 0.001$) in dexmedetomidine group and control group, respectively. Elcicek *et al*.[15] and Hong *et al*.[13] also found that complete

resolution of motor blockade was significantly prolonged in the dexmedetomidine group. Contrary to the above studies, Kaya *et al*.[12] reported no significant prolongation in the duration of motor block in the dexmedetomidine group compared to the control group.

Hemodynamic response following dexmedetomidine infusion depends upon the dose and speed of infusion. A sequence of transient hypertension with reflex bradycardia, followed by hypotension is seen with higher dose and rapid infusion.[16,17] The subsequent decrease in heart rate and blood pressure may be due to decrease in central sympathetic outflow. This effect is due to sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation. There was a minimal decrease in heart rate and blood pressure in patients receiving dexmedetomidine in our study, similar to observations of other authors.[8] Most of studies have noted bradycardia as a prominent side effect, with incidence varying from 30% to 40% sometimes requiring treatment with atropine, following use of a bolus dose of 1 μg/kg and infusion greater than 0.4 μg/kg/h. However, the incidence of bradycardia in our study was low and also transient, probably owing to a lower bolus dose used and augers well with observations of Kaya *et al*.[12] Incidence of hypotension in our study was comparable with other studies. The infusions were continued during episodes of hypotension and/or bradycardia and the severity of these effects did not warrant stoppage of infusions at any point of time.

Intra-operative sedation provided by dexmedetomidine eliminates the need for additional sedatives. Dexmedetomidine produces sedation by its central effect and seems to be dose dependant.[15,16] Activation of presynaptic α2-A receptors at locus ceruleus decreases norepinephrine release and causes sedative and hypnotic effects. Most of patients receiving dexmedetomidine were sedated, but easily arousable in the present study. Contrary to observations of Al-Mustafa *et al*.[10] and Hong *et al*.[9] who used higher doses of dexmedetomidine and noted excessive sedation in 3 out of 25 and 2 out of 26 patients respectively in their study, Kaya *et al*[12] also had similar observations regarding sedation in their study

Dexmedetomidine does not cause significant respiratory depression despite providing good sedation resulting in wide safety margins.[4] Total duration of analgesia was defined as time from administration of SAB until the first complaint of pain (VAS $\geq$ 3).The duration of analgesia was significantly prolonged in the dexmedetomidine group (7.55 $\pm$ 1.07 h) compared to the control group (4.61 $\pm$ 1.08 h) in our study, similar to the results of other studies[8,9] in the dexmedetomidine and control groups, respectively.

In our study, the time to first request for postoperative analgesic was significantly prolonged and the 24-h mean requirement of analgesics was significantly less in the dexmedetomidine group compared to the control group. Similarly, Hong *et al*.[13] noticed that postoperative pain intensity was lower and the mean time to first request for postoperative analgesia was longer in the dexmedetomidine group compared to the control group (6.6 h vs. 2.1 h). Kaya *et al*.[12] in their study observed that dexmedetomidine increased the time to first request for postoperative analgesia and decreased the analgesic requirements. Whizar-Lugo *et al*.[9] in their study noticed that the time to first request for postoperative analgesic in the dexmedetomidine group was (220 $\pm$ 30 min) significantly prolonged as compared to the control group (150 $\pm$ 20 min).

Loading dose of dexmedetomidine was given prior to surgical incision in our study. As dexmedetomidine has a role in modulating pain, inhibiting the pain transmission and perception of pain, its role as a pre-emptive analgesic needs to be assessed.

CONCLUSION

On the basis of the results of our study, we conclude that IV supplementation of loading dose of dexmedetomidine 1 μg/kg followed by infusion at 0.5 μg/kg/h prolongs the duration of sensory block, motor block and duration of analgesia with hemodynamic stability. Dexmedetomidine also provides excellent sedation during surgery and significantly reduces analgesic demand in first 24 hours. Dexmedetomidine seems to be an attractive adjuvant to spinal bupivacaine especially in surgical procedures of long duration as an alternative to epidural or prolonged general anesthetics and can preclude intravenous anesthetics. Future studies with larger sample size are required to confirm this hypothesis.

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Authors' contribution:
HC: Concept of the study, Manuscript Drafting
VG: Data Collection, Manuscript Drafting
VS: Statistical Analysis

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