Effect of intrathecal dexmedetomidine versus intravenous dexmedetomidine on subarachnoid anesthesia with hyperbaric bupivacaine

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Introduction
Subarachnoid anesthesia is the most popular technique for lower abdominal and lower limb procedures.[1] Dexmedetomidine, a selective α-2 adrenergic agonist, through its synergistic action with local anaesthetics, prolongs the effect of subarachnoid anesthesia.[2-4] Studies have demonstrated that intrathecal as well as low-dose intravenous dexmedetomidine can prolong sensory and motor blockade during subarachnoid anesthesia without undesirable side effects.[4-11]

Several studies have compared the effect of intravenous with intrathecal dexmedetomidine on subarachnoid anesthesia.[12-14] Hence, we conducted a study to evaluate the effects of intrathecal versus intravenous dexmedetomidine on the sensory

Abstract

Background and Aim: Alpha-2 agonists such as dexmedetomidine when given intravenously or intrathecally as an adjuvant potentiate subarachnoid anesthesia. We studied the difference in subarachnoid anesthesia when supplemented with either intrathecal or intravenous dexmedetomidine.

Material and Methods: Seventy-five patients posted for lower limb and infraumbilical procedures were enrolled for a prospective, randomized, double-blind, placebo-controlled study and divided into three groups: Group B (n = 25) received intravenous 20 mL 0.9%NaCl over 10 min followed by intrathecal 2.4 mL 0.5%bupivacaine + 0.2 mL sterile water; Group B_DexIT (n = 25) received intravenous 20 mL 0.9%NaCl over 10 min followed by intrathecal 2.4 mL 0.5%bupivacaine + 0.2 mL (5 µg) dexmedetomidine; Group B_DexIV (n = 25) received intravenous dexmedetomidine 1 µg/kg in 20 mL 0.9%NaCl over 10 min followed by intrathecal 2.4 mL 0.5%bupivacaine + 0.2 mL sterile water. Onset and recovery from motor and sensory blockade, and sedation score were recorded. Onset of sensory and motor block was assessed using Kruskal–Wallis test, whereas 2-segment regression and recovery was analyzed using ANOVA and post hoc Tukey’s test to determine difference between the three groups. P value <0.05 was considered statistically significant.

Results: Although onset of sensory and motor block was similar in the three groups, motor recovery (modified Bromage scale 1) and two-segment sensory regression was prolonged in Group B_DexIT > Group B_DexIV > Group B (P < 0.001). Patients in Group B_DexIT and Group B_DexIV were sedated but easily arousable.

Conclusion: Intrathecal dexmedetomidine prolongs the effect of subarachnoid anesthesia with arousable sedation when compared with intravenous dexmedetomidine.

Keywords: Anesthesia, dexmedetomidine, subarachnoid

How to cite this article: Sharma A, Varghese N, Venkateswaran R. Effect of intrathecal dexmedetomidine versus intravenous dexmedetomidine on subarachnoid anesthesia with hyperbaric bupivacaine. J Anaesthesiol Clin Pharmacol 2020;36:381-5.

Received: 11-Nov-2017 Revised: 25-Dec-2018
Accepted: 22-Jun-2019 Published: 14-Sep-2020
and motor block as well as hemodynamic stability and sedation in patients receiving subarachnoid anesthesia.

**Material and Methods**

The study was commenced after getting approval from the Departmental Dissertation Committee and the Institutional Ethics Committee. It was prospective, randomized, and double-blind in nature. Patients aged between 18 and 65 years of either gender undergoing elective infraumbilical or lower limb surgery under subarachnoid anesthesia belonging to American Society of Anesthesiologists Physical Status 1 or 2 were included in the study. Exclusion criteria included coagulopathy, hypovolemia, body mass index >35 kg/m², subarachnoid abnormalities, chronic use of sedatives or antidepressants, history of regular alcohol consumption, and local infection over lumbar spine.

A detailed preoperative evaluation of the patient was done on the day prior to surgery by one of the investigators. Written informed consent was obtained and all patients were kept nil per oral (6 h for solids and 3 h for clear fluids).

An anesthesiology faculty who was not otherwise involved in the study picked the lot and prepared the solutions to be administered intravenously and intrathecally. One investigator (blinded to the drug given intrathecally as well as intravenously) recorded the onset of sensory and motor blockade, maximum level of sensory and motor block, time for two-segment regression, time to recovery from sensory and motor blockade, hemodynamic parameters, and any complications arising during the study period.

Patients were randomly allocated into one of the three groups using computer-generated random number table to receive 20 ml of intravenous test drug over 10 min as soon as the intravenous access was established and baseline vital signs recorded, and 2.4 mL of 0.5% hyperbaric bupivacaine with 0.2 mL of intrathecal test drug for subarachnoid block at the end of intravenous test drug infusion. Patients in Group B received 0.9% NaCl intravenously and 0.2 mL of sterile water intrathecally as test solutions. Those in Group B IT received 0.9% NaCl intravenously and 0.2 mL of dexmedetomidine (5 μg) intrathecally. Dexmedetomidine in this dilution was prepared by withdrawing 0.25 mL (25 μg) of dexmedetomidine from an ampoule of dexmedetomidine containing 100 μg/mL into an insulin syringe containing 10 divisions. This 25 μg of dexmedetomidine was then further diluted with sterile water to make up a total volume of 1 mL, i.e., 25 μg/mL or 2.5 μg/division. Two divisions of dexmedetomidine diluted thus (0.2 mL containing 5 μg) was then added to 2.4 mL of 0.5% hyperbaric bupivacaine.

Patients in Group B_Dex IV received dexmedetomidine 1 μg/kg (rounded to the nearest 10 μg) in 20 mL of 0.9% NaCl intravenously and 0.2 mL of sterile water intrathecally.

After shifting the patient to the operating room, electrocardiographic (ECG) monitoring of leads II and V₅, noninvasive blood pressure (NIBP), and pulse oximetry were established and the baseline vitals recorded. Intravenous access was secured with an 18 SWG intravenous cannula in the nondominant hand and an infusion of Ringer lactate started.

Patients were then administered subarachnoid anesthesia in left lateral decubitus position using a 25 SWG Quincke-Babcock needle in L₅-L₆ interspace. The study drug was injected intrathecally over a period of 10 s once free flow of clear cerebrospinal fluid was obtained. The study drug was prepared by the anesthesiology faculty not involved in the study and handed over to the anesthesiologist performing the subarachnoid anesthesia. The time of intrathecal drug injection was noted as time “0” and the patient was turned supine.

Ability to appreciate a cold swab was evaluated every 2 min along the midclavicular line on both sides. The higher of the two sides was taken as end point. Onset of analgesia at T₁₀ was noted. The sensory level was checked every 2 min as described above until the level remained unchanged for four consecutive readings. This dermatomal level was noted as the highest level of analgesia. Sensory level was checked every 5 min till the end of 1 h, and every 15 min thereafter till two-segment regression (defined as recovery of sensory block by two segments from the highest level achieved in that patient) and sensory recovery (around S₂-S₄ segments) occur.

Motor blockade was assessed by modified Bromage scale at 2-min intervals till a modified Bromage scale score of 3 was obtained or till maximum motor blockade was achieved.[15] This time was noted as onset of motor blockade. The time at which modified Bromage scale 1 was obtained denoted recovery from motor blockade.

Sedation score was recorded every 15 min throughout the first 3 h using the six-point Ramsay Sedation Score.[16] as detailed below:

**Ramsay Sedation Score**[16]

- 1 - Anxious, agitated/restless or both
- 2 - Patient cooperative, oriented, and tranquil
- 3 - Patient responds to commands only
- 4 - Brisk response to light glabellar tap or loud auditory stimulus
- 5 - Sluggish response to light glabellar tap or loud auditory stimulus
- 6 - Patient shows no response.
Blood pressure and heart rate was recorded every 5 min for the first hour and every 15 min thereafter till complete sensory and motor recovery as defined above had been achieved. More than a 25% decrease in mean arterial pressure was treated with intravenous fluids and vasopressor (boluses of 3 mg of mephentermine). A heart rate <50/min was considered as bradycardia and treated at the discretion of the primary anesthesiologist. A respiratory rate <8/min or pulse oximetric values <95% on room air were taken as significant and nasal oxygen at 3–5 L/min was used as rescue. Incidence of adverse effects, such as nausea, vomiting, arterial desaturation, or pruritus, was noted.

Statistical analysis
An interim statistical analysis was done (ANOVA) after collecting data for nine patients (3 in each group) in Phase I of the study. Aiming for a study power of 80% with an α-error of <0.05 for a 70 min difference in duration of analgesia (sensory recovery), the sample size was determined to be 23 patients in each group. We included 25 patients in each group for better validation of results.

Statistical analysis was done using SPSS Version 20. Onset of sensory and motor blockade was assessed using nonparametric test (Kruskal–Wallis test), whereas two-segment regression and recovery from sensory and motor blockade were analyzed using ANOVA and post hoc Tuke7’s test to determine difference between the three groups. P value <0.05 was considered statistically significant.

Results
The age, weight, height, and gender of patients were comparable in the three groups [Table 1]. There was no statistical significant difference in the time taken for sensory onset in the three groups [Table 2].

Maximum modified Bromage score (motor onset) observed was three in all three groups. There was no statistical difference between the groups with respect to onset of motor blockade [Table 2].

The mean two-segment regression time as depicted in Table 2 was longest in group receiving intrathecal dexmedetomidine along with hyperbaric bupivacaine (Group B_{Dex IT}) than in the other two groups. There was significant difference between Group B and Group B_{Dex IT} (P < 0.001) as well as between Group B and Group B_{Dex IV} (P < 0.001).

The mean time taken for sensory recovery to S3-S4 dermatomes was longer in the group receiving intrathecal dexmedetomidine among the three groups. There was a statistically significant difference between Group B and Group B_{Dex IT}, as well as between Group B and Group B_{Dex IV} (P < 0.001) [Table 2].

The mean time for motor recovery was longest in group receiving intrathecal dexmedetomidine. There was a statistically significant difference between Group B and Group B_{Dex IT}, as well as between Group B and Group B_{Dex IV} (P < 0.001) [Table 2].

Patients receiving dexmedetomidine by the intrathecal as well as the intravenous routes were more sedated as compared with the control group (Chi-square test; P = 0.011) [Table 3].

Patients experienced side effects such as hypotension and bradycardia as shown in Table 4. Other adverse effects, such as nausea, vomiting, desaturation, and pruritus, were not noticed in any patient.

Discussion
Dexmedetomidine is a highly lipophilic drug that gets rapidly absorbed into the cerebrospinal fluid and bind to alpha-2-adrenergic receptor of spinal cord to produce analgesia. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration whether epidural, caudal, or spinal.[17] Intravenous dexmedetomidine is also known to prolong the duration of sensory block of local anesthetics during spinal anesthesia and peripheral nerve block but the underlying mechanism of this effect is unclear.[18,19] The supra-spinal, direct analgesic, and/or vasoconstricting actions of dexmedetomidine are suggested to be involved in this mechanism.[19] Our study analyzed the sensorimotor effects of intrathecal versus intravenous dexmedetomidine on subarachnoid anesthesia. The dose of dexmedetomidine to be used intrathecally as well as intravenously was decided based on previous studies.[3,6,9] As per the review by Naaz et al. safe dose of intrathecal dexmedetomidine can be 0.1–0.2 µg/kg.[17] Kavya et al. found that intravenous dexmedetomidine given as bolus or bolus-plus-infusion prolongs both sensory and motor blockade of intrathecal hyperbaric bupivacaine without any untoward side effects.[20] Hence, we chose to give intravenous dexmedetomidine 1 µg/kg as bolus over 10 minutes prior to subarachnoid anesthesia. Only patients scheduled for infraumbilical and lower limb surgeries were included for the study so that they could be maintained in the supine position following administration of subarachnoid anesthesia. Assumption of any other position for surgery could have altered the spread of the local anaesthetic solution and confounded our results.

In our study, the time taken for onset of sensory blockade was not significantly shortened by the use of dexmedetomidine.
However, Harsoor et al. reported a faster onset of sensory block in dexmedetomidine group compared with control group (66 vs. 129.6 s).\[21\]

The onset of motor blockade was also found to be comparable in all three groups as was the case in other studies.\[12-16\] The mean time for two-segment regression of sensory blockade was significantly prolonged in our study. This is similar to other studies.\[11,21,22\] Duration of analgesia was taken as sensory recovery at S_2–S_4 dermatomes. Sensory recovery was prolonged with the use of intrathecal as well as intravenous dexmedetomidine which is in agreement with the findings in earlier studies.\[12-14\] The intrathecal route was found to prolong the duration of analgesia even more as compared with the intravenous route. Motor blockade was significantly prolonged in both the groups receiving dexmedetomidine, with the prolongation being more with intrathecal dexmedetomidine. Similar prolongation was observed in other studies.\[13,14\] However, some studies reported no significant prolongation of duration of motor blockade.\[12\] This difference could be attributed to the different end points that were taken to indicate recovery from motor blockade.

A meta-analysis conducted by Niu et al. concluded that dexmedetomidine prolonged the duration of subarachnoid anesthesia and improved postoperative analgesia while at the same time not increasing the incidence of hypotension and other adverse events.\[23\] The meta-analysis also noted that there was a greater need for using atropine to reverse bradycardia when dexmedetomidine was used in the context of subarachnoid anesthesia. The database analyzed had a high degree of heterogeneity caused by different doses of dexmedetomidine and bupivacaine used for different types of surgical procedures. There was no unified method of delivering the drug and the criteria used to define sensory and motor recovery were different. Our study comparing intrathecal with intravenous dexmedetomidine concluded that motor blockade was significantly prolonged with both intrathecal dexmedetomidine as well as intravenous dexmedetomidine with the prolongation being more with intrathecal dexmedetomidine which correlates with a study done by Hamed et al.\[13\]

Patients receiving dexmedetomidine had a Ramsay sedation score of 3 or 4 with no respiratory depression and were easily arousable. Such finding was also documented by Abdallah et al. who failed to detect any serious complication with respect to sedation in the postoperative period attributable to the use of dexmedetomidine as an adjunct to subarachnoid anesthesia.\[22\]

Hemodynamic response following dexmedetomidine depends on the dose and speed of intravenous infusion. Higher doses of dexmedetomidine are associated with bradycardia and decreased cardiac output. Bearing this in mind, we administered dexmedetomidine as a slow intravenous infusion over 10 min. This could possibly explain why we had a low incidence of bradycardia and hypotension following intravenous dexmedetomidine. Even these few instances were easily treated with intravenous atropine and/or intravenous mephentermine. A study by Abdallah et al. also reported a 3.7-fold increase in transient reversible bradycardia in patients receiving intravenous dexmedetomidine, with the incidence being higher when the initial loading dose was administered over a short duration of time.\[15\]

There was no significant difference in terms of hypotension as seen in various trials, which was summarized in a meta-analysis by Abdallah et al.\[21\] The incidence reported was 14%, 17%, 23%, and 27% with infusion doses of 0.25, 0.5, 1, and 2 µg/kg, respectively.

In comparison to some recent studies evaluating the effect of two different route of dexmedetomidine on subarachnoid

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**Table 1: Demographic data**

| Parameters       | Group B | Group B_{DexIT} | Group B_{DexIV} |
|------------------|---------|-----------------|-----------------|
| Age (years)      | 49.71±14.196 | 44.19±12.17 | 47.27±13.44 |
| Weight (kg)      | 62.42±7.336 | 64.12±11.45 | 63.20±10.751 |
| Height (cm)      | 161±8.11 | 166.38±8.73 | 161.96±8.97 |
| Male/Female      | 23/2    | 21/4           | 21/4           |

*Group B: Group bupivacaine, Group B_{DexIT}: Group bupivacaine with intrathecal dexmedetomidine, Group B_{DexIV}: Group bupivacaine with intravenous dexmedetomidine*  

**Table 2: Sensorimotor parameters following subarachnoid anesthesia**

| Parameter                                  | Group B (n=25) | Group B_{DexIT} (n=25) | Group B_{DexIV} (n=25) | P     |
|--------------------------------------------|----------------|-------------------------|------------------------|-------|
| Onset of sensory blockade at T10 dermatomal level (min) Median (Interquartile range) | 2 (2.4) | 2 (2.4) | 2 (2.4) | 0.057 |
| Onset of motor blockade (min) Median (Interquartile range) | 4 (2.6) | 4 (2.6) | 4 (2.6) | 0.186 |
| Two-segment regression Mean±SD (min)       | 106.04±31.34 | 194.23±42.70 | 174.60±31.32 | <0.001 |
| Sensory recovery to S2 to S4 dermatomes Mean±SD (min) | 189.29±46.07 | 315.92±63.14 | 247.48±46.39 | <0.001 |
| Motor recovery Mean±SD (min)               | 208.67±50.2  | 344.38±57.77 | 272.52±53.57 | <0.001 |

*Group B: Group bupivacaine, Group B_{DexIT}: Group bupivacaine with intrathecal dexmedetomidine, Group B_{DexIV}: Group bupivacaine with intravenous dexmedetomidine*
Table 3: Ramsay sedation score

| Group         | Sedation score 2 | Sedation score 3 or 4 |
|---------------|------------------|-----------------------|
| Group B (n=25) | 16               | 9                     |
| Group BDexIT (n=25) | 11            | 14                    |
| Group BDexIV (n=25) | 6              | 19                    |

Chi-square test; \( P=0.011 \)

Table 4: Adverse effects

| Group         | Bradycardia | Hypotension |
|---------------|-------------|-------------|
| Group B       | 0           | 4           |
| Group BDexIT  | 0           | 3           |
| Group BDexIV  | 4           | 2           |
| Total         | 4           | 9           |

Conclusion

We conclude that while both intrathecal and intravenous dexmedetomidine prolong the sensorimotor effect of subarachnoid anesthesia with reasonable hemodynamic stability and arousable sedation, intrathecal dexmedetomidine produces greater prolongation of motor and sensory block than intravenous dexmedetomidine.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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