ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A randomized controlled interventional study for analgesic effects of intrathecal versus intravenous dexmedetomidine on subarachnoid anesthesia with hyperbaric bupivacaine

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Submission: 12-10-2024 Revision: 05-01-2024 Publication: 01-02-2025

ABSTRACT

Background: Various pharmacologic agents such as opioids, benzodiazepines, ketamine, and alpha2 adrenergic agonists are commonly used to increase the duration of subarachnoid block. Alpha2 agonists have analgesia and sedative properties when used as adjuvant in regional anesthesia. Stable hemodynamics and decreased oxygen requirement due to enhanced sympathoadrenal stability make them very useful adjuvants. **Aims and Objectives:** To evaluate the effects of intrathecal versus intravenous (IV) dexmedetomidine on the block, characteristics, and sedation in patients receiving subarachnoid block with hyperbaric bupivacaine. **Materials and Methods:** In this prospective, randomized controlled, double-blind study total of 90 patients with the American Society of Anesthesiologists grade I and II were randomly allocated into three groups: Group A (n = 30) received IV 20 mL 0.9% NaCl over 10 min followed by intrathecal 2.4 mL 0.5% hyperbaric bupivacaine + 0.2 mL normal saline, group B (n = 30) received IV 20 mL 0.9% NaCl over 10 min followed by intrathecal 2.4 mL 0.5% hyperbaric bupivacaine + 0.2 mL (5 mcg) dexmedetomidine, and group C (n = 30) received IV dexmedetomidine 1 mcg/kg in 20 mL 0.9% NaCl over 10 min followed by intrathecal 2.4 mL 0.5% hyperbaric bupivacaine + 0.2 mL normal saline. **Results:** The mean time for two-segment regression in group A was 100.57 ± 4.24 min, in group B it was 193.3 ± 7.07 min, and in group C was 170.23 ± 3.53 min. The duration of sensory and motor block was prolonged in groups B and C. The Visual analog scale scores were comparatively higher in group A than in groups B and C. The Sedation score in group C was significantly higher as compared to groups A and B. **Conclusion:** Both intrathecal and IV dexmedetomidine prolong the effect of intrathecal hyperbaric bupivacaine, improves post-operative analgesia, and provides arousable sedation without causing hemodynamic instability.

Key words: Dexmedetomidine; Analgesia; Prolonged spinal; Sedation

Access this article online

Website: https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i2.4273

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Subarachnoid anesthesia is the most popular technique for lower abdominal and lower limb procedures.[1] A high degree of post-operative pain after surgery precludes early mobilization, leading to a prolonged hospital stay.[2] Post-operative pain management remains a challenge despite recent advances in our understanding of the physiology of acute pain, the development of new opioid and non-opioid analgesics, novel methods of drug delivery

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(systemic, regional, and local), and more widespread use of pain-reducing minimally invasive surgical techniques.[3] Nowadays focus is being shifted to multimodal analgesia.

Spinal anesthesia has the advantages of rapid onset of action, is economical and easy to administer, and has a relatively low side effect rate.[4,5] Commonly used spinal anesthetics are 2-chloroprocaine, lidocaine, bupivacaine, and ropivacaine; however, using only local anesthetic results in a shorter duration of action and it is inadequate for visceral pain.[6,7] Although bupivacaine is a long-acting local anesthetic but the duration of post-operative analgesia is often inadequate. To combat this limitation various pharmacologic agents such as opioids, benzodiazepines, ketamine, and alpha2 adrenergic agonists are commonly used as adjuvants to provide better post-operative analgesia.[8]

Dexmedetomidine is a highly selective α_2 agonist and is being used widely as an adjuvant to intrathecal local anesthetics to provide a longer duration of analgesia. It causes anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression but prolongs the post-operative analgesic effect with minimal side effects.[9,10]

We conducted this study to compare the effects of intravenous (IV) versus intrathecal dexmedetomidine on the duration of the subarachnoid block, hemodynamic of the patient, and side effects, if any as an adjuvant to hyperbaric bupivacaine in patients undergoing lower limb surgery under spinal anesthesia.

Aims and objectives

To evaluate the effects of intrathecal versus intravenous dexmedetomidine on the sensory and motor block and sedation in patients receiving subarachnoid anesthesia with hyperbaric bupivacaine. To determine the difference in mean time of two segment regression in three different groups.

MATERIALS AND METHODS

This prospective, randomized controlled, double-blind study was conducted in a tertiary care center after obtaining due permission from the institutional ethics committee. The study was registered in the clinical trial registry prospectively CTRI/2022/07/044353. All the patients gave written informed consent for participation in the study.

We included patients scheduled for elective lower limb surgeries under subarachnoid block of age between 18 and 60 years and belonging to the American Society of Anesthesiologists (ASA) grade I and II in this study. Patients not willing to participate in the study, with sepsis, bacteremia or skin infection of local sites, with a history of severe hypovolemia, anemia and compromised renal, cardiac or respiratory status, blood coagulopathies, and allergic to study drugs were excluded from the study.

After checking informed and written consent and confirming overnight fasting, the patient was taken to the operation table, and continuous electrocardiography, non-invasive blood pressure, heart rate, and oxygen saturation monitoring were established. Baseline vital parameters were noted upon arrival and subsequently every 5 min.

Ringer lactate infusion was started at 15–20 mL/min after securing IV access with an 18G cannula. Patients were randomly allocated into three groups by a simple random technique using a computer-generated random number table. Groups allocated were kept in a brown opaque envelope.

Group A (n=30): Patients received IV 20 mL 0.9% NaCl over 10 min followed by intrathecal 2.4 mL 0.5% hyperbaric bupivacaine+0.2 mL normal saline.

Group B (n=30): Patients received IV 20 mL 0.9% NaCl over 10 min followed by intrathecal 2.4 mL 0.5% hyperbaric bupivacaine+0.2 mL (5 mcg) dexmedetomidine.

Group C (n=30): Patients received IV dexmedetomidine 1 mcg/kg in 20 mL 0.9% NaCl over 10 min followed by intrathecal 2.4 mL 0.5% hyperbaric bupivacaine+0.2 mL normal saline.

Al-Mustafa et al.,[11] and Alam et al.,[12] used normal saline in their studies instead of sterile water and showed similar results.

A sample of 30 cases in each group was found to be adequate at 95% confidence and 80% power to predict the expected difference of 19.63±7.104 min in a change in mean two-segment regression time in three groups based on a previous study[13] receiving sterile water, intrathecal dexmedetomidine, and IV dexmedetomidine with subarachnoid anesthesia with hyperbaric bupivacaine. Dexmedetomidine in this dilution was prepared by withdrawing 0.25 mL (25 mcg) of dexmedetomidine from an ampoule of dexmedetomidine containing 100 mcg/mL into an insulin syringe containing 10 divisions. This 25 mcg of dexmedetomidine was then further diluted with sterile water to make up a total volume of 1 mL, i.e., 25 mcg/mL or 2.5 mcg/division.

Subarachnoid block was performed at L3-L4 interspace in the left lateral position using a 25 gauge Quincke needle under strict aseptic conditions. All patients were

immediately placed in a supine position following the injection. Pinprick tests were performed every 1 min until the maximum sensory blockade was achieved in the relevant body segment and subsequently every 5 min for the next 30 min. Thereafter, assessments were performed every 15 min until recovery of sensation in the L2 segment. The motor block was evaluated using a modified Bromage scale as reported in previous studies[13] (grade 0: No paralysis; grade 1: Unable to raise an extended leg but able to move the knees and ankles; grade 2: Unable to flex knees, can flex ankle, and grade 3: No movement). The pain was assessed using the Visual Analog Scale (VAS) between 0 and 10 (0=no pain, 10=most severe pain). It was assessed at 6 h and 24 h of surgery in all the groups.

The mean time duration of two segment regression, mean time to reach the highest sensory block, mean time to reach complete motor block (Bromage score 3), and mean time duration of sensory and motor block were noted. The mean time duration of the first dose of rescue analgesia and total dose of rescue analgesia given within 24 h post-operative period was also noted. Injection diclofenac 75 mg IV was given as a rescue analgesic and was given at VAS 4. A mean sedation score was also noted.

Hypotension was defined as a mean arterial blood pressure <60 mm of Hg or a decrease in systolic blood pressure by >20% from baseline values and was treated by incremental doses of mephentermine 6 mg IV and IV fluid as required. Bradycardia was defined as a fall in heart rate below 50 beats/min and was treated with incremental doses of atropine 0.6 mg IV.

Statistical analysis

The collected data were entered into an Excel spreadsheet. Discrete data were summarized in the form of proportion and the difference in proportion was analyzed using the Chi-square test. The normality of the continuous data was checked by the Shapiro–Wilk test. Normal data were summarized in the form of mean and standard deviation, and the difference in mean among study groups was analyzed using the one-way analysis of variance (ANOVA) test and the *post hoc* Tuckey test was used to analyze significance level between two groups. Non-normal data were summarized in the form of median and interquartile range, and the Kruskal–Wallis H test was used to analyze differences in the median of study groups. The significance level was kept at 95% confidence. IBM Statistical Packages for the Social Sciences (SPSS) 25.0 version was used to analyze data.

Statistics

The collected data were entered into an Excel spreadsheet. Discrete data were summarized in the form of proportion and the difference in proportion was analyzed using the Chi-square test. The normality of the continuous data was checked by the Shapiro–Wilk test. Normal data were summarized in the form of mean and standard deviation, and the difference in mean among study groups was analyzed using the one-way ANOVA test, and the *post hoc* Tuckey test was used to analyze the significance level between the two groups. Non-normal data were summarized in the form of median and interquartile range, and Kruskal–Wallis H test was used to analyze differences in the median of study groups. The significance level was kept at 95% confidence. IBM SPSS 25.0 version was used to analyze data.

RESULTS

All three groups were comparable regarding age, sex, and ASA physical status (Table 1).

The mean time of onset of the sensory blockade at the T10 level in group A was 119.5±7.53 s, in group B was 119.2±7.38 s, and in group C was 120.67±9.48 s. The difference in the mean time of onset of sensory blockade at the T10 level in all study groups was statistically insignificant with P=0.765 using the one-way ANOVA test (Table 2).

The mean time of onset of motor blockade in group A was 232.68±11.79 s, in group B was 232.87±5.06 s, and in group C was 232.97±3.39 s. The difference in the mean time of onset of motor blockade in all study groups was statistically insignificant with P=0.985 using the one-way ANOVA test (Table 2).

The mean time of two segment regression in group B (193.3±7.07) and group C (170.2±3.53) was higher than group A (100.5±4.25) min. There was a statistically significant difference in the two-segment regression in cases of all study groups (P<0.001) using a one-way ANOVA test. There was a significant difference in two segment regression between group A versus B (P<0.001), A versus C (P<0.001), and B versus C (P<0.001) using the *post hoc* Tuckey test (Table 2).

The difference in the post-operative median motor block at different time intervals between cases of each study group was found to be statistically significant (P<0.001). Group B had a longer duration of motor block as compared to groups A and C (Figure 1).

Table 1: Demographic data

Parameter	Group A	Group B	Group C
Age (years) mean±SD	34.87±11.68	36.17±10.89	38.43±13.15
Sex (M/F)	23/7	24/6	23/7
ASA (1/2)	23/7	25/5	25/5

ASA: American Society of Anesthesiologists, SD: Standard deviation

Table 2: Sensorimotor parameters following subarachnoid anesthesia

Parameter	Group A	Group B	Group c	P-value
Onset of sensory blockade at T10 dermatomal level mean±SD (s)	119.5±7.53	119.2±7.38	120.67±9.48	0.765
Onset of motor blockade Mean±SD (s)	232.63±11.79	232.87±5.06	232.97±3.39	0.985
Two segment regression Mean±SD (min)	100.57±4.24	193±7.07	170.23±3.53	<0.001

The difference in the post-operative median sensory block at different time intervals between each study group was found to be statistically highly significant (P<0.001) except at 24 h (P=0.002). Group B had a longer duration of sensory block as compared to groups A and C (Figure 2).

VAS score was comparatively higher in group A than in B and C group and this difference in median VAS score at different time intervals was found to be statistically significant (P<0.001) using the Kruskal–Wallis H test. VAS score was lowest in group B as compared to groups A and C (Figure 3).

The mean time of rescue analgesia in group B (21.5±1.41) and C (21.4±1.57) h was higher than in group A (6.63±1.33) h. There was a statistically significant difference in the meantime of rescue analgesia in cases of all study groups (P<0.001) using the one-way ANOVA test. There was a significant difference between group A versus B (P<0.001) and A versus C (P<0.001), whereas no significant difference between B versus C group (P<0.993) using the *post hoc* Tuckey test.

The mean dose of rescue analgesia required in 24 h in group B (0.7±0.47) and group C (0.47±0.63) was much lower than in group A (3.03±0.72). There was a statistically significant difference in the mean dose of rescue analgesia in 24 h among all study groups (P<0.001) using a one-way ANOVA test. There was a significant difference in the mean dose of rescue analgesia in 24 h between group A versus B (P<0.001) and A versus C (P<0.001), whereas no significant difference was seen between group B versus C (p=0.309) using the *post hoc* Tuckey test.

The difference in the post-operative sedation score in cases of each study at 1 h, 2 h, 4 h, and 8 h was found to be statistically significant (P<0.001) and this difference at 12 h (P=0.603) and 24 h (P=1.000) was statistically insignificant. The sedation score of group C was significantly higher as compared to groups A and B (Table 3).

Hypotension was seen among three (10%) cases in each study group. The difference in the proportion of cases who had hypotension in each study group was found to be statistically insignificant (P=1.000) (Table 4).

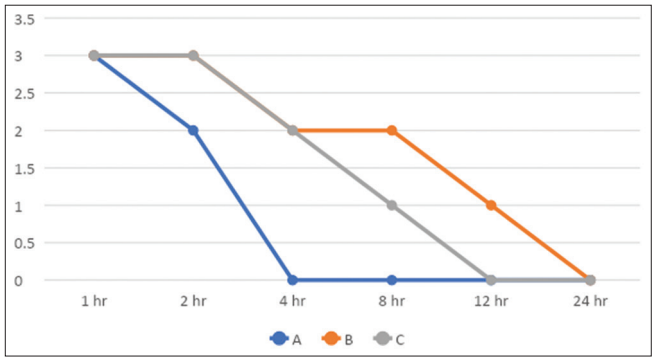

Figure 1: Comparison of motor block postoperatively at different time intervals

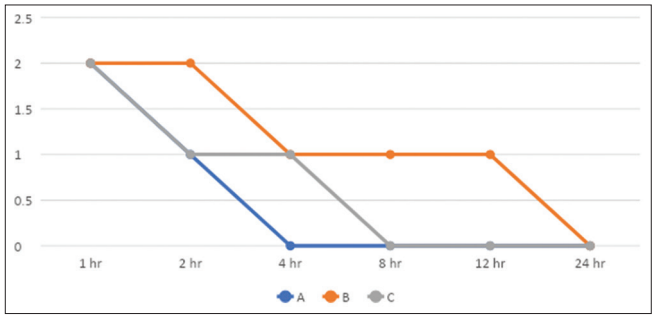

Figure 2: Comparison of sensory block postoperatively at different time intervals

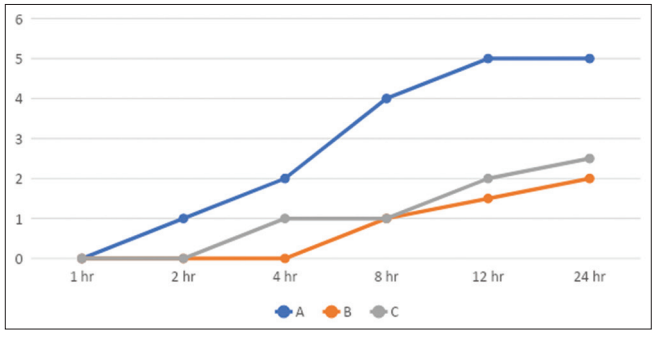

Figure 3: Comparison of Visual Analog Scale score postoperatively at different time intervals

DISCUSSION

We designed this study to compare the effects of intrathecal versus IV dexmedetomidine on subarachnoid block characteristics with hyperbaric bupivacaine as a primary outcome and sedation and side effects as a secondary

Table 3: Comparison of sedation score postoperatively at different time intervals

Sedation score	A	B	C	P-value
1 h	1 (1–1)	2 (2–2)	3 (3–3)	<0.001
2 h	1 (1–1)	2 (2–2)	3 (3–2.75)	<0.001
4 h	1 (1–1)	2 (2–1)	2 (2–2)	<0.001
8 h	1 (1–1)	1 (1–1)	1 (2–1)	<0.001
12 h	1 (1–1)	1 (1–1)	1 (1–1)	0.603

Table 4: Proportion of side effects

Side Effects	Group A	Group B	Group C	P-value
Hypotension	3 (10)	3 (10)	3 (10)	1.000

outcome.

Our study showed that the duration of motor and sensory block was prolonged by both IV and intrathecal dexmedetomidine but the duration was prolonged more by an intrathecal route which is shown in a study by Gautam et al.,[14] also. Mayank Gupta et al.[15] further show that increasing the dose of dexmedetomidine enhances its action on sensory as well as motor blocks.

The study by Harsoor et al. reported a faster onset of sensory block in the dexmedetomidine group compared with the control group (66 vs. 129.6 s)[16] but the results in our study were comparable in all three groups.

The mean time for two-segment regression was longest in group B, followed by group C as shown in other studies also.[13,17] Hence, our study shows that intrathecal dexmedetomidine prolongs the duration of the subarachnoid block more in comparison to the IV drug.

We observed that the VAS score was comparatively higher in group A than in groups B and C. Our results were comparable with other studies.[16,18]

The mean dose of rescue analgesia given was significantly higher in group A as compared to groups B and C as in the study conducted by Dinesh et al.,[19] and Nwachukwu et al.[20]

The sedation score of group C was significantly higher as compared to groups A and B as can be seen in the study by Ebert et al.[21] All patients were easily arousable.

In our study, hypotension was seen among three (10%) cases in each study group. Our results were contradictory to Farouk et al.[22] Which concluded that the use of dexmedetomidine resulted in slightly reduced hemodynamic stability as compared to other groups. As we know, the hemodynamic response following IV administration of dexmedetomidine depends upon the dose and speed of infusion. We administered dexmedetomidine as a slow IV infusion over 10 min, this could possibly explain low incidences of hypotension following IV dexmedetomidine.

Our study was limited only to elective surgeries of the lower limb including patients of ASA grade I and II and between age group 18 and 60 years. Hence, the results cannot be generalized to other groups.

Limitations of the study

- Our study included only those patients who needed lower limb surgery with ASA I and II.
- The results may vary from investigations performed on other ethnic groups as there can be differences in body height and variations in subjective anesthetic sensitivity.
- Our findings cannot be generalized to younger population(age<18 years) and older population(age>60 years) as these age groups are not included in our study.

CONCLUSION

Hence, we conclude that dexmedetomidine prolongs the duration of the sensory and motor block during subarachnoid anesthesia, and provides prolonged post-operative analgesia without causing much hemodynamic instability and sedation when given as an adjuvant with hyperbaric bupivacaine. Second, intrathecal administration provides better results as compared to the IV route.

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https://doi.org/10.1016/j.bjane.2021.02.004

Authors' Contribution:
AG- Concept, design, literature search, data analysis, manuscript editing, and manuscript review; **M-** Experimental studies, data acquisition, and manuscript preparation; **AK-** Literature search, data acquisition, statistical analysis, and manuscript preparation.

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Source of Support: Nil, **Conflicts of Interest:** None declared.