Effect of intravenous dexmedetomidine administered as bolus or as bolus-plus-infusion on subarachnoid anesthesia with hyperbaric bupivacaine

Upadhya R Kavya, Shenoy Laxmi, Venkateswaran Ramkumar
Department of Anaesthesiology, Kasturba Medical College, Manipal, Karnataka, India

Abstract

Background: Subarachnoid anesthesia is a widely practiced regional anesthetic for infraumbilical surgeries. Intravenous dexmedetomidine is known to prolong both sensory and motor blockade when administered along with subarachnoid anesthesia.

Material and Methods: Seventy-five patients scheduled to undergo elective infraumbilical surgeries under subarachnoid anesthesia were randomly allocated to one of the three groups. Group B received intravenous saline over 10 min followed by 12.5 mg intrathecal bupivacaine and then intravenous saline over 60 min. Group bupivacaine + dexmedetomidine bolus (BDexB) received intravenous dexmedetomidine (1 μg/kg) over 10 min followed by 12.5 mg intrathecal bupivacaine and then intravenous saline over 60 min. Group bupivacaine + dexmedetomidine bolus-plus-infusion (BDexBI) received intravenous dexmedetomidine (0.5 μg/kg) over 10 min followed by 12.5 mg intrathecal bupivacaine and then intravenous dexmedetomidine (0.5 μg/kg) over 60 min. Onset of analgesia (at T10), complete motor block (Bromage score 3), and highest level of analgesia were noted. Sensory and motor levels were checked periodically till sensory recovery (at S2–S4) and complete motor recovery (Bromage score 0). Ramsay sedation score and incidence of bradycardia/hypotension were noted.

Results: Sensory recovery was significantly longer in Group BDexB (303 min) and Group BDexBI (288 min) as compared to Group B (219.6 min). Motor recovery was also significantly prolonged in Group BDexB (321.6 min) and Group BDexBI (302.4 min) as compared to Group B (233.4 min). Patients receiving dexmedetomidine were sedated but were easily arousable.

Conclusion: Intravenous dexmedetomidine given as bolus or bolus-plus-infusion with intrathecal hyperbaric bupivacaine prolongs both sensory and motor blockade.

Keywords: Intravenous dexmedetomidine bolus, intravenous dexmedetomidine bolus-plus-infusion, subarachnoid anesthesia

Introduction

Subarachnoid anesthesia is a widely practiced modality of regional anesthesia for lower abdominal and lower limb surgeries. Several adjuvants such as opioids and alpha-2 agonists added to intrathecal hyperbaric bupivacaine (0.5%) have been shown to prolong sensory and motor blockade.[1] An alpha-2 adrenoreceptor agonist such as clonidine administered intrathecally, intravenously, or orally is known to prolong the effect of spinal anesthesia.[2,3] In addition, lack of respiratory depression makes dexmedetomidine, a suitable adjunct in various clinical situations. Intravenous dexmedetomidine has also been shown to decrease anesthetic requirements during general anesthesia.[4] Low-dose intravenous dexmedetomidine prolongs motor and sensory blockade during spinal anesthesia without undesirable side effects.[5]
Dexmedetomidine is a highly selective alpha-2 agonist with relatively high α2/α1 activity (1620:1) as compared to clonidine (220:1). The elimination half-life is 2–3 h. It acts on presynaptic alpha-2 receptors situated in locus coeruleus in the brain stem bringing about sedative and analgesic effects. Postsynaptic activation in the central nervous system inhibits sympathetic activity, resulting in decrease in heart rate and blood pressure. In addition, dexmedetomidine infusion may result in increased activation of alpha-2 receptors at the spinal cord, resulting in inhibition of nociceptive impulse transmission.

Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions were studied by Hall et al. Both small and moderate doses of dexmedetomidine produce significant sedation. This sedation is easily reversible by verbal or physical stimuli. Once aroused, the individuals are able to perform various tasks that include verbal, motor, and cognitive domains.

Whizar-Lugo et al. administered intravenous dexmedetomidine or intravenous clonidine to prolong spinal anesthesia produced by 15 mg of 0.5% hyperbaric bupivacaine in patients undergoing open abdominal hysterectomy. Patients in the dexmedetomidine group received 1 µg/kg of dexmedetomidine started 20 min after spinal anesthesia and administered over 20 min followed by 0.5 µg/kg/h until the end of the surgical procedure while those in the clonidine group received 4 µg/kg of clonidine as an infusion over 20 min starting 20 min after the spinal block. Sensory and motor blockades were significantly prolonged in both the dexmedetomidine and clonidine groups.

The effect of intravenous dexmedetomidine on duration of spinal anesthesia using 4 mL of 2% prilocaine was studied by Tekin et al. Patients who received a loading dose of dexmedetomidine 1 µg/kg within 10 min of spinal anesthesia followed by a maintenance dose of 0.4 µg/kg/h for 50 min showed significant prolongation of sensory as well as motor blockade. A similar study by Al-Mustafa et al. showed that intravenous dexmedetomidine given following spinal anesthesia prolongs sensory and motor blockade.

Patients receiving intravenous dexmedetomidine had a Ramsay sedation score that ranged between 2 and 5 (on a scale of 1–6).

Intravenous dexmedetomidine was found in several studies to prolong sensory and motor blockade produced by spinal anesthesia using either bupivacaine or ropivacaine. Similar findings were reported in a systematic review and meta-analysis conducted by Abdallah et al. that included 364 patients from 7 intermediate to high-quality randomized controlled trials. Another meta-analysis that included 412 patients from 8 trials looked at the effects of intravenous and intrathecal dexmedetomidine on spinal anesthesia. The reviewers concluded that both intravenous and intrathecal dexmedetomidine produced significant prolongation of the duration of sensory and motor blockade following spinal anesthesia.

Current evidence in literature supports the use of intravenous (as well as intrathecal) dexmedetomidine for producing a significant prolongation of the sensory and motor blockade following spinal anesthesia. We wanted to investigate the influence of administering a calculated dose of 1 µg/kg of dexmedetomidine intravenously either as a bolus (1 µg/kg) or as a bolus-plus-infusion (0.5 µg/kg each) on the sensorimotor effects following subarachnoid anesthesia with 12.5 mg of hyperbaric bupivacaine. We also wanted to determine whether administering the same dose of dexmedetomidine in two regimes (bolus vs. bolus-plus-infusion) would alter the adverse effect profile.

Material and Methods

Following approval from the Institutional Ethics Committee, 75 consenting adults aged between 18 and 65 years belonging to American Society of Anesthesiologists Physical Status (ASA-PS) 1 or 2 scheduled to undergo elective infraumbilical or lower limb surgery in the supine position under subarachnoid anesthesia were enrolled into this prospective, randomized, double-blind study. A detailed preoperative evaluation was performed on the day before surgery, and standard fasting orders advised.

While one of the two anesthesiologists not involved in collecting the data picked the lot and prepared the solutions to be administered intravenously, another anesthesiologist who was blinded to the study drug administered performed subarachnoid block and recorded the sensorimotor effects of spinal anesthesia. Patients were randomly allocated into one of the three groups using a computer-generated random number table. Patients in bupivacaine group (Group B) received 20 mL of 0.9% NaCl intravenously over 10 min followed by another 20 mL of 0.9% NaCl over next 60 min. Patients in bupivacaine-dexmedetomidine bolus (BDexB) group received 20 mL of 0.9% NaCl containing 1 µg/kg of dexmedetomidine (rounded to nearest 10 micrograms) intravenously over 10 min followed by 20 mL of 0.9% NaCl over next 60 min. Patients in bupivacaine-dexmedetomidine bolus-plus-infusion (BDexBI) group received intravenous dexmedetomidine in a total dose of 1 µg/kg (rounded to nearest 10 micrograms). Half of this dose (0.5 µg/kg) diluted in 20 mL of 0.9% NaCl was administered over the first 10 min, followed by the remaining half dose (0.5 µg/kg)
diluted in 20 mL of 0.9% NaCl over the next 60 min. Intrathecal bupivacaine (2.5 mL of 0.5% bupivacaine heavy) was administered in all three groups at L₃–L₄ or L₄–L₅ interspace using a 25 standard wire gauge Quincke-Babcock spinal needle at the end of the first 10 min when delivery of “test drug infusion” was complete.

On arrival in the operating room, standard monitors including 5-electrode electrocardiogram monitoring Lead II and V₅, noninvasive blood pressure, and pulse oximetry were established and baseline vitals recorded. Intravenous access was secured in the nondominant hand, and an infusion of Ringer lactate was started at 100 mL/h. Hyperbaric 0.5% bupivacaine (12.5 mg) was injected at L₃–L₄ or L₄–L₅ interspace after confirming free flow of clear cerebrospinal fluid. The time of intrathecal drug injection was noted as time “0” and the patient turned supine.

Onset of sensory blockade at T₁₀ was noted. In addition, 2-segment regression time (defined as recovery of sensory block by two segments from the highest sensory level achieved in that patient) and sensory recovery (defined as recovery at S₂–S₄ dermatomes) were also noted. Motor blockade was periodically assessed till a modified Bromage score of 3 (inability to flex hip, knee, and ankle) was obtained. This time was denoted as onset of motor blockade. Attainment of a modified Bromage score of 0 (ability to flex hip, knee, and ankle) was noted to herald recovery from motor blockade.

Sedation score was noted on a 6-point Ramsay sedation score as also blood pressure, heart rate, respiratory rate, and oxygen saturation. Adverse effects such as nausea, vomiting, and pruritus were noted.

**Statistical methods**

After collecting the data for 30 patients (10 in each group) in Phase I of the study, we did an interim statistical analysis. Aiming for a power of study of 80% to detect at least 60 min difference in duration of analgesia (sensory recovery), the sample size required was 23 patients in each group. The sample size was determined using ANOVA. We included 25 patients in each group for better validation of results. Statistical analysis was done using SPSS for Windows Version 16.0, SPSS Inc., Chicago, Illinois, USA. Onset of sensory and motor blockade was analyzed by nonparametric test while recovery characteristics were analyzed using ANOVA. Sedation score was analyzed using Fisher’s exact test. P < 0.05 was considered to be statistically significant.

**Results**

Demographic data including age, weight, height, gender, and ASA-PS were comparable in the three groups [Table 1]. Sensorimotor parameters following subarachnoid anesthesia are summarized in Table 2. The onset of sensory blockade at T₁₀ was 2 min and was comparable in all three groups. The duration of sensory blockade as reflected in the 2-segment regression time was longer in both dexmedetomidine 1 µg/kg bolus and 1 µg/kg (total) bolus-plus-infusion groups than the control group. The time to complete sensory recovery (recovery of S₂–S₄ dermatomes) was also longer in the dexmedetomidine bolus-plus-infusion groups.

**Table 1: Demographic data**

| Parameter          | Group B (n=25) | Group BDexB (n=25) | Group BDexBI (n=25) |
|--------------------|---------------|-------------------|---------------------|
| Age, years (mean±SD) | 40.5±12.1     | 46.3±9.2          | 45.2±10.3           |
| Weight, kg (mean±SD) | 69.9±10.1     | 66±12.3           | 72.8±11.8           |
| Height, cm (mean±SD) | 165.4±6.1     | 166.9±7.4         | 167.0±7.3           |
| Male/female        | 23/2          | 21/4              | 22/3                |
| ASA-PS             | 15/10         | 13/12             | 15/10               |

Group B=Group bupivacaine, Group BDexB=Group bupivacaine +dexmedetomidine bolus, Group BDexBI=Group bupivacaine +dexmedetomidine bolus-plus-infusion, ASA-PS=American Society of Anesthesiologists Physical Status, SD=Standard deviation

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

| Parameter                              | Group B (n=25) | Group BDexB (n=25) | Group BDexBI (n=25) | Significance (P) |
|----------------------------------------|---------------|-------------------|---------------------|------------------|
| Onset of sensory blockade at T₁₀ (min) | 2             | 2                 | 2                   | NS               |
| Duration of sensory blockade (2-segment regression), min (mean±SD) | 133.2±28.2 | 178.2±21.8 | 166.2±26.7  | <0.001          |
| Complete sensory recovery (S₂–S₄), min (mean±SD) | 219.6±35.9 | 303±32.4          | 288±22.9            | <0.001           |
| Onset of motor blockade, min (Bromage 3) | 2             | 2                 | 2                   | NS               |
| Motor recovery, min (mean±SD)          | 233.4±34.1    | 321.6±35.7        | 302.4±18.2          | <0.001           |
| Ramsay sedation score (2 vs. 3 or 4)   | 22/3          | 2/23              | 1/24                | <0.001           |

Group B=Group bupivacaine, Group BDexB=Group bupivacaine +dexmedetomidine bolus, Group BDexBI=Group bupivacaine + dexmedetomidine bolus-plus-infusion, SD=Standard deviation, NS=Not significant
1 µg/kg bolus and 1 µg/kg (total) bolus-plus-infusion groups than the control groups.

The onset of motor blockade (Bromage score 3) was 2 min and was comparable in all three groups. The time to complete motor recovery (Bromage score 0) was longer in the dexmedetomidine 1 µg/kg bolus and 1 µg/kg (total) bolus-plus-infusion groups than the control group.

Patients in the study groups who received intravenous dexmedetomidine were noted to be more sedated as compared to the control group (Ramsay sedation score 3 or 4 vs. Ramsay sedation score of 2) (Fisher’s exact test P < 0.001).

The incidence of adverse effects is summarized in Table 3. While bradycardia and arterial desaturation occurred more frequently in patients receiving intravenous dexmedetomidine, they were easily treatable. Hypotension occurred more often in the patients receiving only spinal anesthesia (and no intravenous dexmedetomidine). Review of the sensory level achieved in individual patients in the three groups showed that the number of patients in whom the level of sensory block was between T₄ and T₆ was comparable in all three groups (3 each in group bupivacaine or group BDexB and 4 in group BDexBI). The number of patients in whom the level of sensory block was between T₅ and T₁₂ was likewise comparable in all three groups (22 each in group bupivacaine or group BDexB and 21 in group BDexBI). As the level of sensory block was comparable in all the three groups in our study, we believe that the higher incidence of hypotension in our patients who received only spinal anesthesia with bupivacaine (without any intravenous dexmedetomidine) was a chance occurrence.

Nausea was noted only in one patient (control group).

Discussion

We studied the effect of intravenous dexmedetomidine given either as a bolus or a bolus-plus-infusion on subarachnoid anesthesia with intrathecal hyperbaric bupivacaine.

Table 3: Adverse effects following intravenous dexmedetomidine and subarachnoid anesthesia

| Parameter | Group B (n=25) | Group BDexB (n=25) | Group BDexBI (n=25) |
|-----------|---------------|-------------------|-------------------|
| Hypotension | 7            | 1                 | 1                 |
| Bradycardia | 3            | 7                 | 7                 |
| Nausea   | 1             | -                 | -                 |
| SpO₂ <95% | -             | 2                 | 2                 |

Group B=Group bupivacaine, Group BDexB=Group bupivacaine + dexmedetomidine bolus, Group BDexBI=Group bupivacaine+dexmedetomidine bolus-plus-infusion

Time for onset of sensory blockade was not significantly altered by the use of dexmedetomidine and was comparable to the previous studies. However, Harsoor et al. reported a faster onset of sensory block in dexmedetomidine group compared to control group (129.6 s vs. 66 s). The mean time for 2-segment regression of sensory blockade was significantly prolonged in our study which is in agreement with the previous studies.

Onset of motor blockade was also found to be comparable in all three groups. The onset of motor block was found to be no different in an earlier study. In another study, a difference in onset of motor block of 1 min was seen with the use of dexmedetomidine.

Duration of analgesia was taken as the time for sensory recovery to occur at S₂–S₄ dermatomes. Sensory recovery was prolonged in both groups of patients who received dexmedetomidine compared to the control group which was similar to the findings of earlier studies. Intravenous dexmedetomidine used either as a bolus or bolus-plus-infusion produced significant prolongation of motor blockade during subarachnoid anesthesia with hyperbaric bupivacaine. Similar prolongation of motor blockade was also reported in the previous studies.

We also did a post hoc analysis as we had three groups – one group receiving intravenous saline, one group receiving intravenous dexmedetomidine bolus, and the other receiving intravenous dexmedetomidine bolus-plus-infusion. There was no significant difference when the two groups receiving dexmedetomidine was compared. As there are no previous studies that have compared dexmedetomidine bolus with dexmedetomidine bolus-plus-infusion, we suggest further studies to validate our findings.

Sedation was monitored in our study using a 6-point Ramsay sedation score. Although patients receiving dexmedetomidine in our study had a higher sedation score (score of 3 or 4) with minimal respiratory depression, they were easily arousable. Such a finding has also been validated by other studies. Four patients in the dexmedetomidine groups had a drop in arterial saturation (SpO₂ <95%) in our study, but this drop was not clinically significant and was easily managed with oxygen supplementation. None of the patients in the reviewed trials by Abdallah et al. had serious respiratory complications. Furthermore, they failed to detect any difference in postoperative sedation which can be attributed
to the shorter duration of action of dexmedetomidine, making it a suitable adjunct to neuraxial anesthesia.

**Conclusion**

Administration of intravenous dexmedetomidine in a dose of 1 µg/kg over 10 min as well as in a dose of 0.5 µg/kg over 10 min followed by 0.5 µg/kg over the next 60 min prolongs the duration of sensory and motor blockade produced by 12.5 mg of intrathecal hyperbaric bupivacaine. Intravenous dexmedetomidine administered in either manner produces adverse effects such as sedation bradycardia and arterial desaturation. However, these adverse effects are easily treatable.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Pitkanen M. Spinal (subarachnoid) blockade. In: Cousins MJ, Bridenbaugh PO, Carr DB, Horlocker TT, editors. Neural Blockade in Clinical Anesthesia and Pain Medicine. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 213-38.
2. Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. Acta Anaesthesiol Scand 2003;47:1001-5.
3. Bonnet F, Buisson VB, Francois Y, Catoire P, Saada M. Effects of oral and subarachnoid clonidine on spinal anaesthesia with bupivacaine. Reg Anesth 1990;15:211-4.
4. Reves JG, Glass P. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller’s Anesthesia. 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2010. p. 756.
5. Harsoor S, Rani DD, Yalamuru B, Sudheesh K, Nethra S. Effect of supplementation of low dose intravenous dexmedetomidine on characteristics of spinal anaesthesia with hyperbaric bupivacaine. Indian J Anaesth 2013;57:265-9.
6. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology 2000;93:1345-9.
7. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000;90:699-705.
8. Whizar-Lugo V, Gomez-Ramfrez IA, Cisneros-Corral R, Martinez-Gallegos N. Intravenous dexmedetomidine vs intravenous clonidine to prolong bupivacaine spinal anesthesia. A double blind study. Anest Mex 2007;19:143-6.
9. Tekin M, Kati I, Tomak Y, Kisli E. Effect of dexmedetomidine IV on the duration of spinal anesthesia with prilocaine: A double-blind, prospective study in adult surgical patients. Curr Ther Res Clin Exp 2007;68:313-24.
10. Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, Al-Ghanem SM. Intravenous dexmedetomidine prolongs bupivacaine spinal analgesia. Middle East J Anaesthesiol 2009;20:225-31.
11. Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, et al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth 2010;57:39-45.
12. Elcicek K, Tekin M, Kati I. The effects of intravenous dexmedetomidine on spinal hyperbaric ropivacaine anaesthesia. J Anesth 2010;24:544-8.
13. Hong JY, Kim WO, Yoon Y, Choi Y, Kim SH, Kil HK. Effects of intravenous dexmedetomidine on low-dose bupivacaine spinal anaesthesia in elderly patients. Acta Anaesthesiol Scand 2012;56:382-7.
14. Annamalai A, Singh S, Singh A, Mahrous DE. Can intravenous dexmedetomidine prolong bupivacaine intrathecal spinal anesthesia? J Anesth Clin Res 2013;4:372.
15. Reddy VS, Shaik NA, Donthu B, Reddy Sannala VK, Jangam V. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anaesthesia and analgesia: A randomized double-blind study. J Anaesthesiol Clin Pharmacol 2013;29:342-7.
16. Jung SH, Lee SK, Lim KJ, Park EY, Kang MH, Lee JM, et al. The effects of single-dose intravenous dexmedetomidine on hyperbaric bupivacaine spinal anesthesia. J Anesth 2013;27:380-4.
17. Lee MH, Ko JH, Kim EM, Cheung MH, Choi YR, Choi EM. The effects of intravenous dexmedetomidine on spinal anesthesia: Comparison of different dose of dexmedetomidine. Korean J Anesthesiol 2014;67:252-7.
18. Dinesh CN, Sai Tej NA, Yatish B, Pujari VS, Mohan Kumar RM, Mohan CV. Effects of intravenous dexmedetomidine on hyperbaric bupivacaine spinal anesthesia: A randomized study. Saudi J Anaesth 2014;8:202-8.
19. Gupta K, Tiwari V, Gupta PK, Pandey MN, Agarwal S, Arora A. Prolongation of subarachnoid block by intravenous dexmedetomidine for subumbilical surgical procedures: A prospective control study. Anesth Essays Res 2014;8:175-8.
20. Abdallah FW, Abrishami A, Brull R. The facilitatory effects of intravenous dexmedetomidine on the duration of spinal anesthesia: A systematic review and meta-analysis. Anesth Analg 2013;117:271-8.
21. Niu XY, Ding XB, Guo T, Chen MH, Fu SK, Li Q. Effects of intravenous and intrathecal dexmedetomidine in spinal anesthesia: A meta-analysis. CNS Neurosci Ther 2013;19:897-904.