

Randomized Trial

Comparison of the Effects of Adding Dexmedetomidine Versus Midazolam to Intrathecal Bupivacaine on Postoperative Analgesia

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Background: Dexmedetomidine and midazolam both modulate spinal analgesia by different mechanisms, and yet, no human studies are available to compare them for postoperative analgesia after neuraxial administration.

Objectives: We investigated the addition of dexmedetomidine or midazolam to intrathecal bupivacaine on the duration of effective analgesia and clinical safety profile.

Study Design: Prospective, randomized, double blind, placebo controlled study.

Setting: University teaching hospital.

Methods: The study cohort included a consecutive and prospective series of patients, referred for endourological procedures. The patients were randomly allocated into 3 groups (20 patients each) to receive intrathecally 3 mL of 0.5% hyperbaric bupivacaine in combination with 5 mcg of dexmedetomidine (dexmedetomidine group), 1 mg of midazolam (midazolam group) or 0.5 mL of 0.9% saline (control group). The groups were compared to the regression time of sensory block, duration of effective analgesia (defined as the time interval between administration of intrathecal drug to the time of first analgesic request or a numeric rating scale ≥ 4.0), sedation score, and side effects in the first 24 hours.

Statistics: One way-ANOVA, Kruskal Wallis test, and Chi-square test (χ^2), significance level: $P < 0.05$.

Results: The duration of effective analgesia (time to first analgesic request) was significantly prolonged in the dexmedetomidine group (286 ± 64 minutes, $P < 0.01$) when compared with midazolam group (236.9 ± 64.9 minutes) and the control group (212.7 ± 70.2 minutes). Pairwise comparisons among the 3 groups with Bonferroni adjustment revealed that patients from the dexmedetomidine group were more sedated in comparison to the midazolam and control groups at the end of the first 15 minutes after intrathecal injection [$\chi^2 (2) = 7.157$, $P = 0.028$], with a mean rank sedation score of 35.58 for dexmedetomidine, 25.00 for midazolam, and 30.93 for control. No significant differences in the side effects were observed during the study period. Midazolam did not lengthen the time of the two segment sensory regression or the time to first request analgesia.

Limitation: The study cannot be extrapolated to muscle cutting surgeries under spinal anaesthesia.

Conclusions: The addition of dexmedetomidine (5 mcg) to 3 mL of intrathecal hyperbaric bupivacaine (0.5%) significantly prolongs the duration of effective analgesia in comparison to 1 mg midazolam or placebo (0.9% normal saline) with a comparable incidences of side effects.

Key words: Dexmedetomidine, midazolam, intrathecal, spinal anaesthesia, subarachnoid block, postoperative pain

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One of the basic reasons to add neuraxial adjuvant drugs to intrathecal (IT) or spinal heavy bupivacaine is to prolong the duration of sensory block thereby providing an extended postoperative pain relief. Our clinical experience suggests that patients undergoing endourological procedures of shorter duration usually experience a mild to moderate degree of pain in the immediate postoperative period. This type of pain is usually poorly localized visceral pain and adds to more discomfort than pain to the patient. As most of these endourological procedures are done under spinal anaesthesia, adding a neuraxial adjuvant not only prolongs the duration of postoperative analgesia but is also effective in attenuating this poorly localized visceral pain. Both dexmedetomidine and midazolam are shown to be effective in this regard (1,2). These drugs modulate spinal analgesia by different mechanisms, and yet, no human studies are available to compare them for postoperative analgesia after neuraxial administration.

Dexmedetomidine is a selective α_2 -adrenoceptors agonist that modulates antinociception by inhibiting peripheral norepinephrine release, thus terminating the propagation of pain signals. At the same time post synaptic activation of α_2 -adrenoceptors in the central nervous system inhibits sympathetic activity and may result in hypotension and bradycardia. Midazolam, a benzodiazepine derivative, modulates antinociception through gamma-amino butyric acid (GABA) receptors present in the dorsal horn of the spinal cord and through the activation of spinal δ -opioid receptors. In contrast to sympatholytic effects of dexmedetomidine, IT midazolam keeps the function of sympathetic nervous system intact (3,4), but may result in excessive sedation due to its GABA mimetic and opioid induced analgesia.

A literature search revealed no human clinical trials comparing the addition of dexmedetomidine or midazolam to hyperbaric bupivacaine, although various studies have been conducted by using each of these drugs separately as an adjunct to hyperbaric spinal bupivacaine and concluded that these 2 drugs prolonged the duration of effective analgesia in the postoperative period.

This study was designed to assess the comparative analgesic efficacy and safety in terms of hemodynamic stability and sedation produced by IT dexmedetomidine (5 mcg) to midazolam (1 mg) when used as an adjunct to hyperbaric bupivacaine in patients undergoing endourological procedures under planned spinal anaesthesia.

Methods

After obtaining approval from the institutional ethical committee and written informed consent, 60 American Society of Anesthesiologists (ASA) physical status I/II patients aged 18 – 60 years who were scheduled for elective endourological procedures under planned spinal anaesthesia were screened to participate in this prospective, randomized, double-blind placebo control study. Patients were included if they were willing to participate in the study and able to understand and use a numeric rating scale (NRS) to evaluate their own pain intensity. Patients with contraindications to central neuraxial block or sensitivity to study drugs and who were on chronic analgesic therapy were excluded from the study. Patients were premedicated with 0.5 mg alprazolam on the night before surgery.

The patients were randomly allocated into one of the 3 groups of 20 patients each using a computer generated randomization schedule and sealed opaque envelope technique. Patients in the dexmedetomidine group received 3 mL of 0.5% hyperbaric bupivacaine combined with 5 mcg of dexmedetomidine (2 units of 100 mcg/mL preservative-free dexmedetomidine loaded in a 40 unit insulin syringe), patients in the midazolam group received 3 mL of 0.5% hyperbaric bupivacaine and 1 mg of midazolam (8 units of 5 mg/mL preservative-free midazolam loaded in a 40 unit insulin syringe) while patients in the control group received 3 mL of 0.5% hyperbaric bupivacaine and 0.5 mL of 0.9% saline in the IT space. The total volumes of IT injections were made 3.5 mL by adding the appropriate amount of preservative-free 0.9% saline.

The IT injections labeled as “study drug” were prepared by an anesthesia resident who was not involved in the patients’ care and coded to maintain the double-blind nature of the study. The investigator performing the block and making observations of the study parameters was blinded to the drug administered intrathecally.

The IT injections were given at the L3-L4 or L4-L5 intervertebral space using a 25-gauge, Quincke spinal needle in the lateral decubitus position. The IT injection was given after confirming the free flow of cerebrospinal fluid (CSF) through the spinal needle. All patients received supplemental oxygen at the rate of 5 liters/minute through a face mask. An infusion of lactated ringer’s solution at the rate of 2 mL/kg/h was administered during anesthesia and the rate of infusion was altered depending upon the hemodynamic response. Blood pressure was recorded at every 2 minutes for the first 15 minutes

and thereafter every 15 minutes until the end of surgery. Hypotension was defined as a decrease in systolic blood pressure by more than 20% of the base line or below 90 mm Hg. Bradycardia was defined as an absolute decrease in heart rate below 55 beats per minute. Hypotension was treated with additional intravenous fluid (4 mL/kg) repeated 2 times and if this failed to reverse the hypotension then an additional bolus of intravenous (IV) ephedrine (0.1 mg/kg) was repeated at the discretion of the attending anesthesiologist. Bradycardia was treated with IV atropine 0.6 mg at repeated dose. The lowest recorded systolic blood pressure and heart rate for each patient was used for statistical analysis.

The spinal block characteristics were assessed with parameters like sensory onset time (time interval between the completion of IT drug injection to the onset of complete loss of pinprick sensation at T8), highest dermatome level of sensory blockade and the time to reach this level from the time of injection (peak sensory block), and duration of sensory block (defined as the time interval from completion of IT drug injection and 2-segment regression of sensory block by pinprick method). The motor level was assessed according to Bromage score (5): (0: no motor loss, 1: inability to flex the hip, 2: inability to flex the knee joint, 3: inability to flex the ankle). The motor block onset time is defined as the time interval between the completion of IT injection to the onset of Bromage 1 score.

Severity of pain was measured by NRS. Patients were asked to rate their pain from a scale of 0 = no pain to 10 = worse pain possible. The NRS was assessed immediately postoperatively and thereafter at 2, 4, 6, 8, 12, and 24 hours of the postoperative period. Intravenous tramadol 2 mg/kg was given when the NRS was ≥ 4 or upon patient request. The time of the first request for analgesia was recorded. Duration of effective analgesia was defined as the time interval between administration of the IT drug to the time of first analgesic request or a NRS ≥ 4 .

The level of sedation of the patients was assessed by the Ramsay sedation score (1: anxious, agitated, and restlessness; 2: oriented and cooperative; 3: responds to command only; 4: brisk response to loud voice and light glabellar tap; 5: sluggish to no response to light glabellar tap or loud auditory stimulus; 6: no response even to pain) (6). Postprocedural complications such as hypotension, bradycardia, respiratory depression (respiratory rate < 8 per minute), shivering, nausea, and vomiting were also recorded when they occurred during the study period.

Statistical Analysis

The primary end-point of this study was the time to regression of 2-sensory dermatomes from peak sensory block level and duration of effective analgesia. The secondary end-points were the safety profile of the drugs in terms of predefined adverse cardiovascular events, nausea, vomiting, and level of sedation during the study period.

Our power analysis was based on a previous study (7) result indicating the mean duration of sensory block as 223.9 minutes with standard deviation 34.7 minutes while using 3 mL of hyperbaric bupivacaine (0.5%) intrathecally. Assuming a onetime standard deviation (34.7 min) increase in duration of sensory block by adding dexmedetomidine or midazolam intrathecally to bupivacaine with an α value of 0.05 and β value of 80%, a sample size of 16 patients in each group was calculated. The sample size was increased by 25% (i.e., 20 patients in each group) to account for any possible dropouts.

Data were expressed as mean (standard deviation), number, and frequencies. Normality of the data was tested by Shapiro-Wilk test. The comparison of normally distributed continuous variables between the groups was performed using one-way analysis of variance (ANOVA) and, if appropriate, followed by the Bonferroni test for post hoc analysis to see the significance between each pair of groups. Nominal categorical data between study groups were compared using the chi-squared test or Fisher's exact test as appropriate. The Kruskal Wallis test was used to compare the values obtained for ordinal categorical data (sedation scores) among the 3 groups and if found significant, follow-up tests were conducted to evaluate pairwise differences among the 3 groups, controlling for Type I error across tests by using the Bonferroni approach. A P value of < 0.05 was considered statistically significant. The statistical analysis was carried out using SPSS version 16 for Windows software program (SPSS Inc., Chicago, IL).

RESULTS

There were no dropouts from the study after randomization, and out of 60 attempted IT injections, 56 injections were made with the first attempt and 4 injections were made with the second attempt. A repeat attempt was defined as removal or changing the direction of the spinal needle from or within the skin surface.

The demographic data and duration of surgery were comparable among the 3 study groups (Table 1).

Table 1. Patient characteristics and duration of surgery in dexmedetomidine, midazolam, and control groups. Values are mean (standard deviation) or numbers (n).

Variables	Dexmedetomidine (n = 20)	Midazolam (n = 20)	Control (n = 20)	P-value
Age (years)	41.3 (11.3)	47.0 (13)	44.1 (9.8)	0.304
Female/Male (n)	4/16	2/18	1/19	0.322
Weight (kg)	64.2 (13.7)	63.3 (10)	62.3 (8.1)	0.852
Duration of surgery (minutes)	65 (12.3)	63 (10.0)	62 (8.1)	0.671

Table 2. Effect of IT dexmedetomidine, midazolam, and saline when used as an adjuvant to hyperbaric bupivacaine on characteristics of spinal blockade, duration postoperative analgesia, and analgesic requirement.

Variables	Dexmedetomidine (n = 20)	Midazolam (n = 20)	Control (n = 20)	P-value
Block heights	T6(T6-T8)	T6(T6-T8)	T6(T4-T6)	0.225
Onset of sensory block (min)	2.3 (1.2)	2.8 (1.7)	2.4 (0.8)	0.424
Time to peak sensory block (min)	8.6 (2.8)	8.8 (5.3)	8.1 (1.8)	0.844
Onset of motor block (min)	3.4 (2.5)	5.0 (3.5)	3.5 (1.8)	0.114
Time to 2 segment regression (min)	131.9 (35.2)*#	99.3 (38.1)	73.6 (33.8)	0.001
Time to first analgesic request (min)	286 (64) *#	171 (77)	167 (73)	0.001
Number of analgesic request in 24 h	0.45 (0.5)	0.50 (0.5)	0.55 (0.5)	0.826

Values are mean (standard deviation) or numbers (n). * $P < 0.05$ in comparison to midazolam group; # $P, 0.01$ in comparison to control group.

The characteristics of spinal sympathetic blockade and postoperative analgesic request were depicted in Table 2. The peak sensory levels reached, time to onset of sensory block, motor block, and peak sensory block were not significantly different among the groups. Time to 2-segment regression of sensory analgesia and duration of effective analgesia (time of the first rescue analgesic requirement) was significantly longer in the dexmedetomidine group (131.9 ± 35.2 minutes, 286 ± 64 minutes) in comparison to the midazolam group (99.3 ± 38.1 minutes, 171 ± 77 minutes) and the control group (73.6 ± 33.8 minutes, 167 ± 73 minutes) ($P = 0.001$) with no significant difference between the midazolam and control group. There were no significant differences between the number of doses of analgesic requests after administration of the first analgesic on request.

Two patients from the dexmedetomidine group and one patient from the midazolam group had a sedation score of 4 at one time point in contrast to none from the control group. A Kruskal-Wallis H test showed that there was a statistically significant difference in sedation score between the different add-on therapies at 15 minutes [$\chi^2 (2) = 7.157, P = 0.028$, with a mean rank sedation score of 35.58 for dexmedetomidine, 25.00 for midazolam, and 30.93 for control] and at 30 minutes [$\chi^2 (2) = 6.140, P = 0.046$, with a mean rank pain score of

34.83 for dexmedetomidine, 27.63 for midazolam, and 29.05 for control) after IT injection, but were comparable at the end of surgery ($P = 0.349$) (Table 3). Pairwise comparison with Bonferroni adjustment indicated a higher median sedation score for the dexmedetomidine group in comparison to the midazolam group at the end of 15 minutes (adjusted significance, $P = 0.023$) and 30 minutes (adjusted significance, $P = 0.058$) with no significant difference between the midazolam-control or dexmedetomidine-control group. Incidences of hypotension, bradycardia, shivering, nausea, and vomiting were similar among the groups (Table 4).

All patients had peripheral oxygen saturation of more than or equal to 99% by pulse oximeter in room air throughout the study period.

Discussion

Both midazolam and dexmedetomidine are relatively newer additions to the list of adjuvants used in IT anaesthesia and may act synergistically with IT bupivacaine to prolong the duration of postoperative analgesia. However, both the drugs differ in their mechanism of action in mediating antinociception when introduced intrathecally (2,8,9). To the best of our knowledge, this is the first study comparing midazolam and dexmedetomidine as neuraxial adjuvants with 0.5% hyperbaric bu-

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Table 3. Comparison of Sedation Score* among dexmedetomidine, midazolam, and control groups. Values are mean rank or numbers (n).

Variables	Dexmedetomidine (n = 20)	Midazolam (n = 20)	Control (n=20)	P-value
15 min	35.58**	25.00	30.93	0.028
30 min	34.83	27.63	29.05	0.046
At the end of surgery	32.50	29.50	29.50	0.379

*Ramsay's sedation score (1: anxious, agitated and restlessness, 2: oriented and cooperative, 3: responds to command only, 4: brisk response to loud voice and light glabellar tap, 5: sluggish to no response to light glabellar tap or loud auditory stimulus, 6: no response even to pain).

** P = 0.023 in comparison to midazolam after Bonferroni adjustment.

Table 4. Incidences of adverse effects. Values are number of patients (n).

Variables	Dexmedetomidine (n = 20)	Midazolam (n = 20)	Control (n = 20)	P-value
Bradycardia	5	3	3	0.641
Hypotension	7	8	5	0.592
Shivering	1	0	1	0.596
Nausea/Vomiting	0	0	1	0.596

pivacaine in spinal anesthesia. The current study results showed that the addition of 5 mcg dexmedetomidine or 1 mg midazolam as an adjunct to 3 mL of 0.5% hyperbaric bupivacaine prolonged the duration of effective analgesia in the postoperative period compared to bupivacaine alone. Moreover, dexmedetomidine appears to be more analgesic efficient than midazolam as evidenced by a longer duration of effective analgesia or the time to first analgesic request/administration.

IT midazolam (10-15) and dexmedetomidine (16-21) influence the characteristics of spinal block in terms of prolonging the duration of sensory analgesia, time to 2-segment regressions and time to first post-operative analgesic request in a dose-dependent manner with comparable hemodynamic stability. However, their effect on onset of sensory and motor block is not consistent. Few studies found any statistically significant difference in time to the onset of sensory and motor block in comparison to control after adding either 2 mg midazolam (10,22) or 5 – 15 mcg of dexmedetomidine (21,23,24) intrathecally to spinal bupivacaine. A study by Sanwal et al (25) showed that it's the dose of bupivacaine and not the dose of midazolam that determine the time to onset of sensory or motor block. In our study, we used an equal amount of hyperbaric bupivacaine (15 mg) and all 3 groups were comparable regarding the time to onset of sensory and motor block and time to reach peak sensory block and the height of block.

The dose of IT midazolam as an adjunct to bupivacaine in various studies ranges between 1 and 2 mg. Kim and Lee (14) as well as Prakash et al (15) in their

dose finding study used either 1 mg or 2 mg of IT midazolam along with a fixed dose bupivacaine and opined a dose-dependent effect of IT midazolam. Both these studies concluded a prolongation of duration of effective analgesia in the postoperative period in either dose of midazolam but the duration did not reach statistical significance between control group and 1 mg midazolam group [3.8 ± 0.5 h versus 4.3 ± 0.7 h ($P = 0.18$)] in the latter study (15). Whereas studies using a very small dose of dexmedetomidine (3 mcg) could demonstrate significantly longer duration of sensory block and the time to first analgesic request (18,19), a finding also supported by other authors using dexmedetomidine in the range of 5 – 15 mcg (20,21). In our study both 5 mcg of dexmedetomidine and 1 mg of midazolam increased the duration of effective analgesia in the postoperative period but this reached statistical significance only between the dexmedetomidine versus midazolam and control group and not between the midazolam and control group. Sanwal and colleagues (25) demonstrated that addition of IT midazolam (2 mg) to bupivacaine increased the duration of effective analgesia by only 5% (193.6 ± 17.2 to 203.16 ± 23.06 , $P < 0.05$) which is clinically insignificant even though it is statistically significant.

Both midazolam (26) and dexmedetomidine (27) have a supra-spinal mechanism of action but their sedative effect after IT administration has not been reported in depth. The available literature on IT midazolam gives conflicting evidence regarding its sedative potential. Yagnin et al (22) reported a mild but statistically significant sedative effect with IT midazolam 2 mg, whereas,

other authors did not find such difference in comparison to their respective control group (10,12,13,25). Hala et al (21), concluded that higher doses of IT dexmedetomidine (15 mcg) not only prolong the duration of effective analgesia but also result in lower Ramsay sedation scores (median score of 2 – 4). In our study the dexmedetomidine group patients tended to be more sedated in the first 30 minutes after the IT injection. However, all patients were oriented, cooperative, and promptly responded to verbal command at the end of surgery.

The most significant hemodynamic side effects that can be expected with the use of IT α -2 adrenoreceptor agonists are bradycardia and hypotension. Joshi et al (11), in their study, compared 2 mg midazolam to 30 mcg of clonidine added to 15 mg of 0.5% hyperbaric bupivacaine and found a higher incidence of hypotension/bradycardia in the clonidine group compared to the midazolam group (44%/36% versus 16%/0%). Considering the Kanazi et al study (19), we assumed that 5 mcg of dexmedetomidine used in our study would be equipotent to 40 – 50 mcg clonidine when used to supplement spinal bupivacaine. One study demonstrated that the higher dose of bupivacaine is responsible for perioperative hypotension rather than the use of midazolam (25). Our present study results are in accordance to the finding of Joshi et al (11) and the dexmedetomidine group resulted in the highest incidence of hypotension and bradycardia (35%/25%). Although the 3 groups were comparable regarding the occurrence of hypotension and bradycardia, the higher incidence of hypotension and bradycardia could be due to avoidance of preloading, a higher dose of hyperbaric bupivacaine, and defining bradycardia as an absolute decrease in heart rate below 55 beats per minute in contrast to other studies (20,21).

Karbasfrushan et al (13) reported a higher incidence of nausea and vomiting in the bupivacaine-midazolam group compared to the bupivacaine control group where as others did not find any difference in occurrence of postoperative nausea and vomiting in comparison to the control group (11,23). In our study, one patient from the control group, none from the dexmedetomidine group, and none from the midazolam group had nausea/vomiting during the study period.

There were 3 major limitations to our study. First, it did not account for the duration of the motor block. We have limited our observations to sensory block characteristics because the primary aim of the study was to identify whether dexmedetomidine or midazolam was more efficient in providing a longer pain-free period. Second, it enrolled patients undergoing only endourological procedures. Therefore these study results cannot be extrapolated to patients undergoing other infra-umbilical muscle cutting open procedures under spinal anesthesia. The third limitation is the assumption that both 5 mcg of dexmedetomidine and 1 mg of midazolam are equipotent and we suggest further studies to find out the equipotential dose ratio of dexmedetomidine to midazolam.

CONCLUSIONS

To conclude, dexmedetomidine (5 mcg) is more analgesically efficient in comparison to midazolam and 0.9% saline when used as an adjunct to 3 mL of 0.5% hyperbaric bupivacaine and prolongs the duration of effective analgesia in the immediate postoperative period without any significant hemodynamic instability. The mild sedation resulting from IT dexmedetomidine may be beneficial in short-term endourological procedures.

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