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INTRAVENOUS DEXMEDETOMIDINE VERSUS INTRAVENOUS MIDAZOLAM AS ADJUNCT TO INTRATHECAL BUPIVACAINE: A CLINICAL COMPARISON

Anaesthesiology

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ABSTRACT

Background and Aim: Trials are underway to find an ideal adjunct to spinal anaesthesia. This study was aimed to compares the efficacy of intravenous dexmedetomidine and intravenous midazolam on the duration of sensory-motor block, postoperative analgesia, sedation levels and adverse effect in patients undergoing lower abdominal surgeries under spinal anaesthesia. **Material and Methods:** 90 patients, were randomly allocated into three groups (n=30). Group D received Dexmedetomidine 0.5µg/kg, Group M 0.05 mg/kg Midazolam and Group C Saline, intravenously over 10 mins before spinal anaesthesia with 3 ml of Bupivacaine 0.5%. Maximum upper level of sensory blockade, sensory-motor regression time, time to first postoperative analgesia, sedation score and side effects were recorded. Statistical analysis was done using Statistical Package for Social Sciences Version 15.0 using analysis of variance/Chi-square test/ Kruskal–Wallis test (level of significance $P < 0.05$). **Result:** Sensory block was higher with dexmedetomidine than with Midazolam or saline (T6 vsT8); ($p<0.001$). Sensory and motor regression time was significantly prolonged in dexmedetomidine group (171.33 ± 43.57 and 237.83 ± 70.99 min) compared to midazolam (138 ± 27.28 and 189.33 ± 39.28 min) and saline (132 ± 28.09 min and 168 ± 38.24 min); ($P < 0.001$). Dexmedetomidine, increased time to first request for postoperative analgesia ($P < 0.001$ compared to midazolam and saline). Ramsay sedation score was higher in dexmedetomidine, and Midazolam group compared to saline group ($P < 0.001$). **Conclusion:** Intravenous dexmedetomidine significantly prolongs the duration of sensory and motor block of bupivacaine spinal anaesthesia. It also provides excellent sedation and additional analgesia.

KEYWORDS

Dexmedetomidine, Midazolam, Intravenous, Bupivacaine, Spinal anaesthesia.

INTRODUCTION

Spinal anaesthesia has traditionally been employed since ages to produce sensory analgesia for the surgeries below the level of umbilicus. Bupivacaine is the most used local anaesthetic. However, local anaesthetic agents if used alone have relatively shorter duration of action and early postoperative analgesic requirement.

Different adjuvants have been used to prolong spinal anaesthesia, with the possible advantages of delayed onset of post-operative pain and reduced analgesic requirements [1,2], but the adverse effects produced by them limit their use and prompt further research to find an ideal adjuvant.

Dexmedetomidine, a highly selective α_2-adrenoreceptor agonist, has been used safely as premedication in patients undergoing surgical procedures under regional anaesthesia. Its effects are not limited to sedation but also include anxiolysis, better intraoperative analgesia, and prolonged postoperative analgesia with haemodynamic stability and minimal adverse effects [3,4].

Midazolam, a short-acting water-soluble benzodiazepine has been noted to enhance the analgesic effects of local anaesthetics. It possesses antinociceptive properties with minimal side effects [5,6].

Though the role of intravenous Dexmedetomidine and intravenous Midazolam is well established as premedication before general anaesthesia and for sedation in regional anaesthesia, there is still dearth of studies regarding the effect of intravenous dexmedetomidine and/or intravenous Midazolam premedication on the duration of sensory and motor block during spinal anaesthesia.

With this background, present study was undertaken to assess the effects of intravenous dexmedetomidine prior to spinal anaesthesia on duration of sensory and motor block as well as on sedation and post-operative analgesia in patients undergoing lower abdominal surgeries, in comparison to intravenous midazolam.

MATERIAL AND METHODS

After obtaining ethical committee approval for the study protocol and obtaining written informed consent from each patient, we conducted this prospective randomized, double blinded study. Ninety patients of American Society of Anaesthesiologist (ASA) physical Status I and II, in the age group of 18-60 years, scheduled for lower abdominal surgeries under spinal anaesthesia were included. Patient with known allergy to any of the study drugs, ASA Grades III-V, patients on β-blocker and Ca^{2+} channel blocker, pregnant patients, obese patients, and patients with contraindication to spinal anaesthesia were excluded from the study. Patient having history of alcohol or drug abuse and patient on opioids or sedatives in week prior to surgery were also excluded from the study.

After wheeling the patient into operation theatre, monitors were attached to the patient and baseline parameters including heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), peripheral O_2 Saturation (SpO_2) and electrocardiogram (ECG) were recorded. Intravenous (IV) line was secured with 18 G cannula and all patients were preloaded with 1000 ml of Ringer's Lactate (RL) solution. Using a computer-generated randomization, the patients were randomly allocated into Group D (dexmedetomidine group), group M (midazolam group) and group C (control group) of 30 patients each. Group D (n=30) received IV Dexmedetomidine 0.5µg/kg diluted to 5ml with normal saline (NS) over a period of 10 min, Group M (n=30) received IV Midazolam 0.05 mg/kg diluted to 5ml with NS over a period of 10 min and Group C (n=30) received IV NS 5 ml over a period of 10 min. Five minutes after the administration of respective drugs, the patient was placed in left lateral position and under aseptic precaution, lumbar puncture was performed at L3-L4 or L2-L3 interspace (in case the lumbar puncture failed at L3-L4 interspace) using a standard midline approach with a 25-G Quincke spinal needle. 3 ml of Bupivacaine 0.5% was injected intrathecally, and patient received oxygen 4L/min via venturi's face mask throughout the procedure. The anaesthesiologist and the patients were blinded to the treatment group, and all recordings were performed by an anaesthesiologist blinded to group allocation.

Sensory and motor block was assessed every 2 min for first 10 min after completion of intrathecal injection of drug and thereafter every 10 min during surgery and postoperatively till the duration of block. The level of sensory blockade was assessed by pinprick method using 26G hypodermic needle along mid-axillary line bilaterally. The level of the sensory block (highest dermatomal level of sensory blockade by needle pinprick method) and recovery time for sensory blockade (defined as 2 dermatome regression of anaesthesia from the maximum level) was also recorded.

Motor block was assessed immediately after sensory block assessment using Modified Bromage Scale [7]. Score 0=No paralysis. Score 1=Unable to raise extended leg. Score 2=Unable to flex knee. Score

3=Unable to flex ankle.

Motor block duration (time for return to grade 0 on the Modified Bromage Scale) was recorded.

The level of sedation was assessed before spinal anaesthesia and assessment was repeated every 10 min for 120 min using Ramsey Sedation Scale [8]. Score 1=Anxious, agitated, or restless. Score 2= Cooperative, oriented and tranquil alert. Score 3=Responds to commands. Score 4=Asleep, but with brisk response to light glabellar tap or loud auditory stimulus. Score 5=Asleep, sluggish response to light glabellar tap or loud auditory stimulus. Score 6=Asleep, no response. Excessive sedation was defined as a score greater than 4/6.

HR, MAP, RR and SpO_2 was recorded before premedication, 2 min after end of premedication, immediately before dural puncture, immediately after dural puncture, and every 5 min thereafter for 120 min after spinal anaesthesia. Hypotension was defined as decrease in MAP below 20% of baseline or systolic pressure of < 90 mmHg and was treated with incremental doses of IV mephentermine 3 mg and additional lactated ringer's solution as appropriate. Bradycardia was defined as HR < 50 beats/min and was treated with bolus of atropine 0.6 mg intravenously. Respiratory depression was defined as RR < 12 breaths per min or SpO_2 < 95% and was treated by oxygen supplementation and respiratory support if required.

Postoperative pain was assessed using Visual analogue scale (VAS) with calibrations from 0 – 10 (0 - No pain, 10 - worst imaginable pain). Postoperative pain was assessed hourly for first 6 hours and then 4 hourly in a 24 hours assessment period. Patients with a VAS of 3 or more received Diclofenac 75mg intravenously. The time for the first request for analgesia after surgery was recorded as duration of post-operative analgesia.

Occurrence of adverse effects in the perioperative period was noted, particularly in relation to respiratory or cardiovascular problems, nausea or vomiting and headache and managed symptomatically.

A sample size of 30 patients per group was calculated based on a previous study [9], for which we assumed a standard deviation (SD) of 30 min in time to sensory regression of two dermatomes, an error of 0.05 and power of 80%.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. Data was expressed as either mean ± SD or numbers and percentage (%). The means of the continuous variables were compared between the three groups using analysis of variance (ANOVA). The Kruskal–Wallis test was used to assess differences among the three groups with respect to nonparametric variables. Categorical data were analysed using the Chi-square test with a "P value" reported at 95% confidence interval. P values < 0.05 was considered statistically significant.

RESULTS

Spinal anaesthesia was successful in all the patients and all patients completed the study. The study groups (Group D, M and C) were found to be comparable with respect to demographic characteristics of the patient such as age, weight, gender, duration of surgery and ASA physical status. (Table 1)

Table 1: Comparison Of Demographic Characteristics Of The Patients

SN	Variables	Group D (n=30)		Group M (n=30)		Group C (n=30)		Statistical significance	
		Mean	SD	Mean	SD	Mean	SD	F	"p"
1.	Age (years)	42.20	9.78	44.90	9.94	38.67	12.60	2.490	0.089
2.	Gender (M: F)	11:19		17:13		12:18		χ^2=2.790 (df=2); p=0.248	
3.	Body weight (kg)	53.33	9.73	56.13	8.45	53.97	11.10	0.671	0.514
4.	Duration of surgery (min)	108.0	21.4	105.0	22.3	107.3	19.8	0.166	0.847
5.	ASA Grade I: II	18:12		17:13		20:10		^{2}=0.655; (df=2); p=0.721	

Characteristics of sensory and motor block are summarized in Table 2 and Table 3.

Table 2: Dermatomal Level Of Sensory Block Achieved In Different Groups

SN	Group	No. of cases	Highest Dermatome level achieved	Lowest Dermatome level achieved	Median
1.	D	30	T5	T8	T6
2.	M	30	T6	T8	T8
3.	C	30	T6	T10	T8

χ^2=28.267 (df=2); p<0.001 (Kruskal Wallis test)

Table 3: Intergroup Comparison Of Time Taken To Achieve Different Landmarks

SN	Landmark	Group D (n=30)		Group M (n=30)		Group C (n=30)		Statistical significance	
		Mean	SD	Mean	SD	Mean	SD	F	"p"
1.	Two Segment Regression of Sensory Bock (min)	171.33	43.57	138.00	27.28	132.00	28.09	11.778	<0.001
2.	Regression of Motor Block to Bromage 0 (min)	237.83	70.99	189.33	39.28	168.67	38.24	14.104	<0.001
3.	Time to 1st Request for Postop. Analgesia (min)	293.67	160.90	137.67	65.31	94.67	32.93	31.588	<0.001

Maximum upper levels of sensory block achieved ranged from T6 to T10 in group C, T6 to T8 in Group M and T5 to T8 in Group D. Median peak value for maximum sensory level achieved was higher with Group D (T6) than with Groups M and C (T8), (p<0.001). Time taken for two segment regression of sensory block, regression of motor block to Bromage score 0 and time to first request of post-operative analgesia was minimum in Group C and maximum in Group D. For all the three parameters, statistically significant intergroup differences were observed (p<0.001). As compared to Group D both Groups C and M had significantly lower mean values for two segment regression of sensory block, regression of motor block to Bromage score 0 and time taken for first request of post-operative analgesia (p<0.001). However, statistically no significant difference in mean values of Groups C and M was observed for any of the parameters.

Ramsay sedation score achieved ranged from 1 to 2 in Group C, 1 to 4 in Group M and 2 to 4 in Group D. The median of the highest sedation score achieved was 2 in Group C whereas in Groups D and M it was 3. Statistically, there was a significant intergroup difference (p<0.001) (Table 4).

Table 4: Median Sedation Score Achieved In Different Groups

SN	Group	No. of cases	Minimum	Maximum	Median
1.	D	30	2	4	3
2.	M	30	1	4	3
3.	C	30	1	2	2

χ^2=47.348 (df=2); p<0.001 (Kruskal Wallis test)

The mean HR and MAP was lower as compared to that at baseline at all the intraoperative intervals in all the three study groups. Statistically significant intergroup differences in Mean HR and MAP were observed. At all the time intervals mean value in Group D was lower compared to Group M and Group C (Figure 1).

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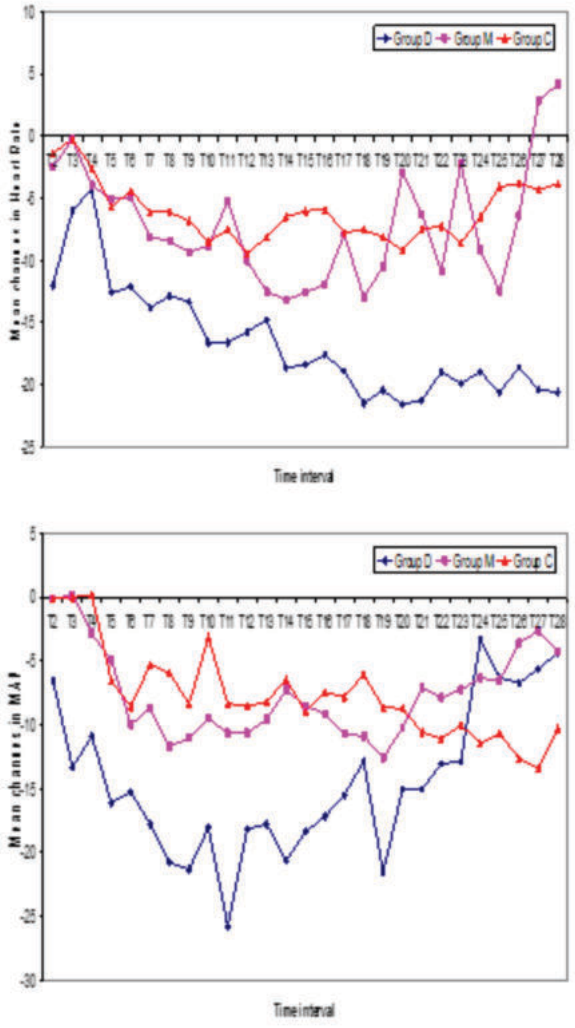

Figure 1: Intergroup Comparison of Mean Heart Rate (Tukey HSD test) and MAP (mmHg) (Paired t-test)

Respiratory parameters (SpO_2 and RR) remained within normal limits throughout intra, and postoperative period and no statistically significant difference was observed among groups.

No side effect or adverse event was reported in any case of Group C. In Group D, bradycardia was reported in 5 (16.7%) and hypotension in 3 (10%) cases. There was 1 case in Group M who reported of headache, nausea, and vomiting. Statistically, significant differences among groups were observed for bradycardia and hypotension. (Table 5)

Table 5: Comparison Of Three Groups For Presence Of Any Side Effect Or Adverse Events

SN	Event	Group D		Group M		Group C		Statistical significance	
		No.	%	No.	%	No.	%	χ^2	P
1.	Bradycardia	5	16.7	0	0	0	0	10.588	0.005
2.	Hypotension	3	10.0	0	0	0	0	6.207	0.045
3.	Headache, Nausea, Vomiting	0	0	1	3.3	0	0	2.022	0.364

All patients in all the three study groups had complete recovery of sensory and motor functions.

No other drug or procedure related complication was noted in any of the study groups.

DISCUSSION

Different adjuvants to local anaesthetics have been tested and tried to prolong the duration of spinal anaesthesia. Clonidine, a α_2 agonist is widely used, and its synergistic use with local anaesthetics is well known [10]. Dexmedetomidine, also an α-2 agonist is a more suitable adjuvant to spinal anaesthesia compared to clonidine as it has more sedative and analgesic effects due to its more selective (8 times) α-2 receptor agonist activity than clonidine [11].

Study by Jaakola et al. demonstrated moderate analgesic effect of IV dexmedetomidine with a ceiling effect at a dose of 0.5 µg/kg [12]. Also, rapid administration might produce tachycardia, bradycardia, and hypertension, therefore it is recommended to administer it over no less than 10 min [13]. Keeping these findings in mind dexmedetomidine, 0.5 µg/kg was given intravenously over 10 min in this study. Previous studies suggest that Midazolam is safe and efficacious adjunct to bupivacaine spinal anaesthesia. Nishiyama et al. [14] reported that the bolus administration of intravenous midazolam 0.05 mg/kg provided enough sedation and amnesia without any adverse effects on hemodynamic and respiration in patients under spinal anaesthesia. Therefore, IV midazolam 0.05 mg/kg was administered to the patients in this study.

Our study suggests that premedication with IV dexmedetomidine significantly increases the maximum upper level of sensory block (T6) compared to Midazolam (T8) and control group (T8) ($p<0.001$). Also, mean time for two-segment regression of sensory block was significantly increased in dexmedetomidine group (171.33 ± 43.57 min) as compared to Midazolam (138 ± 27.28 min) and saline group (132 ± 28.09 min). These findings agree to the observations of other similar studies in which significant prolongation in mean duration of sensory blockade in dexmedetomidine group was reported [4,9,11,15,16].

These effects can be explained based on Supra-spinal, direct analgesic, and/or vasoconstricting actions of dexmedetomidine [17]. Dexmedetomidine has inhibitory effect on the locus ceruleus (A6 group) located at the brain stem. Inhibition of the locus ceruleus results in disinhibition of the noradrenergic nuclei and exerted inhibitory effect on nociception in the spinal cord, which explains the prolongation of spinal anaesthesia after intravenous administration of dexmedetomidine [18].

Although mechanism of motor block is unclear, these similar mechanisms (supraspinal, spinal, and peripheral actions) possibly explain the prolongation of motor blockade [17]. In the present study, dexmedetomidine group had maximum duration of motor block (237.83 ± 70.99 min) followed by Midazolam group (189.33 ± 39.28 min) and then Control group (168 ± 38.24 min). For all the three combinations, motor blockade time was longer than sensory blockade. The results of present study corroborate with the results of Al-Mustafa et al. [15], Kumari et al. [16], Elcicek et al. [19] and Hong et al. [20].

Mean HR and arterial pressure was significantly lower in dexmedetomidine group as compared to Midazolam and control group. These findings are expected as dexmedetomidine decreases sympathetic outflow and circulating level of catecholamines resulting in bradycardia and hypotension [3,12,21]. In this study, there was a significant difference in the number of patients who developed hypotension (10% vs. 0% vs. 0%) and bradycardia (16.7% vs. 0% vs. 0%) in dexmedetomidine, Midazolam and control groups, respectively ($P < 0.001$). Hypotension and bradycardia, both could be managed with injection Mephentermine and Atropine, respectively. The findings of the present study with regards to the HR and MAP matches those with other research studies [16,19].

In this study, Ramsay sedation scores were significantly higher in dexmedetomidine, and Midazolam group (median scores 3) as compared to control group (median scores 2), but like Al-Mustafa *et al*. [15], Kumari et al. [16], and Hong *et al*. [20], no patients in any of the groups was observed to have excessive sedation, thus indicating that dexmedetomidine provides sedation comparable to midazolam. Dexmedetomidine as well as Midazolam are excellent sedating agents, but sedation characteristics of dexmedetomidine differ from other sedatives, as patients remain quiet, cooperative, and easily arousable.

Dexmedetomidine as well as Midazolam showed a better analgesic activity as compared to control, however, only Dexmedetomidine was found to be effective in providing postoperative analgesia in the present study. The time until first request for postoperative analgesic was significantly prolonged in the dexmedetomidine group (293.67 ± 160.90 min) as compared to Midazolam group (137.67± 65.31 min)

and control group (94.67± 32.93min) ($P < 0.001$). These observations are in accordance with the findings of Kaya et al. [9] who also observed that dexmedetomidine increased the time to the first request for postoperative analgesia compared to midazolam and saline. Similarly, kumari et al. [16] and Hong *et al*. [20] noticed that the mean time to first request for postoperative analgesia was longer in the dexmedetomidine group compared to the control group.

Although no major adverse effects were reported in this study, larger studies are required to rule out any short- or long-term side effects.

CONCLUSION

Supplementation of intrathecal Bupivacaine with intravenous Dexmedetomidine significantly prolongs sensory and motor blockade as well as time to post-operative analgesic requirement than adjunctive use of intravenous Midazolam with intrathecal Bupivacaine or spinal anaesthesia using Bupivacaine alone. Also, Dexmedetomidine provided good sedation levels comparable to Midazolam without any significant respiratory depression, haemodynamic instability, and other side effects.

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