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Comparative Study to Evaluate the Effect of Intravenous Dexmedetomidine and Intravenous Midazolam to Prolong Intrathecal Bupivacaine Anaesthesia

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ABSTRACT

Subarachnoid block is one of the most frequently used anaesthetic techniques. The addition of adjuvants to local anesthetics might prolong spinal anaesthesia, decrease the dosage of local anaesthetic, delayed-onset of postoperative pain and reduced analgesic requirements. Present study was aimed to compare effect of intravenous dexmedetomidine versus intravenous midazolam to prolong intrathecal bupivacaine anaesthesia at a tertiary hospital. Present study was single-center, prospective, comparative study, conducted in Patients between 18 years and 60 years, ASA I and II, undergoing traumatic lower limb surgeries, renal calculi removal, TURP as elective procedures under spinal/intrathecal anaesthesia, willing to participate in present study. Patients were allocated into one of the three groups, 25 patients each, as group M (midazolam group), group D (dexmedetomidine group) and group NS (normal saline group). 75 ASA I and II patients were included in the study. There was no statistically difference with respect to age, height, weight, duration of surgery and ASA status ($p>0.05$) and the three groups were comparable. The results displayed that there is a significant difference in time to reach highest sensory levels, two segment regression among the three groups. The mean and Standard deviation of visual analogue score and time for analgesia among three groups were compared. There was a significant difference with respect to VAS. It is lesser in Dexmedetomidine group compared to midazolam and normal saline group ($p<0.05$) Time to first request for postoperative analgesia was later in the Dexmedetomidine group than in the Midazolam and Normal saline groups ($p<0.05$). The number of patients requiring rescue analgesia was lesser in Group D than in Group M and Group NS. The incidence of hypotension was found higher in group NS than in group M and D, but there was no significant difference. Intravenous dexmedetomidine provided better spinal block quality by prolonging the sensory block when compared to midazolam.

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Key Words
Dexmedetomidine, midazolam, spinal block quality, bupivacaine

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INTRODUCTION

Subarachnoid block is one of the most frequently used anaesthetic techniques. Spinal anaesthesia is distinguished by its ease to performance with a definite end point, rapid onset of action, excellent anaesthetic efficacy and motor blockade. Spinal analgesia is a well-known technique used in lower abdominal, urological, and lower extremity procedures and a variety of agents, like epinephrine, phenylephrine, adenosine, magnesium sulfate and clonidine, have been used as adjuncts to local anesthesia for prolonging the duration of spinal analgesia via the intrathecal route.

The addition of adjuvants to local anesthetics gained an extensive reputation due to the belief that they might prolong spinal anaesthesia, decrease the dosage of local anaesthetic, delayed-onset of postoperative pain and reduced analgesic requirements. Despite the abundance of various adjuvants, there is a continuing dispute whether this practice adds to the clinical advantage or just complicates the procedures and introduces risks for medication error.

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist. It has been used for premedication and as an adjunct to general anaesthesia, as it provides preoperative sedation, analgesia, and hemodynamic stability and reduces requirements for intraoperative inhalational agents and postoperative analgesics[1,2,3]. Also, it has been used safely as premedication or as a sedative agent in patients undergoing surgical procedures under regional anaesthesia[4,5]. Present study was aimed to compare effect of intravenous dexmedetomidine versus intravenous midazolam to prolong intrathecal bupivacaine anaesthesia at a tertiary hospital.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative study, conducted in department of anaesthesiology, at SCB Medical college and Hospital Cuttack, Odisha, India. Study duration was of 2 years (September 2015 to October 2017). Study approval was obtained from institutional ethical committee.

Inclusion criteria:

- Patients between 18 years and 60 years, ASA I and II, undergoing elective procedures under spinal/intrathecal anaesthesia, willing to participate in present study

Exclusion criteria:

- Patient refusal
- Any contraindications to spinal anaesthesia
- Emergency surgeries
- Coagulopathy
- Hemodynamically unstable patients
- Allergy to any of the study drugs
- Use of any sedative or opioids one week prior to the surgery
- Chronic liver disease, Chronic kidney disease, Cardiovascular disease, Neurological disease, Respiratory or cardiovascular disease
- Preexisting neurological deficits in the lower extremities

Study was explained to patients in local language and written consent was taken for participation and study. After intravenous insertion of an 18-G catheter in the operating room, all patients received 500 mL of lactated Ringer's solution intravascular volume loading before spinal anaesthesia. Monitors included electrocardiography, non-invasive blood pressure measurement, pulse oximetry to measure peripheral oxygen saturation (SpO^2).

Patients were allocated into one of the three groups, 25 patients each, based on a computer-generated random numbers table:

- **Group M:** Midazolam group
- **Group D:** Dexmedetomidine group
- **Group S:** Normal saline group

Each group was premedicated 5 min before spinal anaesthesia. The study drugs pre-mixed to a total volume of 5 mL in the 5 mL syringe and administered intravenously over a 10 min period as a single dose. Five minutes after the end of the infusion, the patient was placed in the lateral position and dural puncture was performed at the L3-4 interspace using a standard midline approach with a 25-G Quincke needle. Bupivacaine 0.5% 3 mL was injected intrathecally, and the patients was received oxygen 4 L min^{-1} via a facemask throughout the procedure. Both the patient and the anaesthesiologist were blinded to the treatment group, and all recordings was performed by an anaesthesiologist blinded to group allocation.

Sensory blockade, Motor block was assessed immediately after block assessment Heart rate (HR), mean blood pressure (MAP), oxygen saturation (SpO^2), and respiratory rate (RR) was recorded

before premedication, 2 min after end of premedication, immediately before and after dural puncture, and every 5 min for 120 min after spinal anaesthesia. The occurrence of any complication in the preoperative and postoperative periods will be noted, particularly in relation to respiratory or cardiovascular problems, nausea or vomiting, and headache.

The data will be analysed statistically using SPSS version 24 (SPSS Inc., Chicago, IL, USA). The ANOVA test will be used to assess differences among the 3 groups with respect to non-parametric variables. If this will reveal significant differences, the BONFERRONI test will be used to analyse differences between groups in pairs. Categorical data will be analysed using the chi square test. A p-values <0.05 will be considered to indicate statistical significance.

RESULTS

75 ASA I and II patients who had satisfied the criteria of inclusion and exclusion were included in the study. The mean and standard deviation of age, height and weight among three groups were compared, there was no statistically difference with respect to age, height, weight, duration of surgery and ASA status (p>0.05) and the three groups were comparable (Table 1).

The mean and Standard deviation of baseline heart rate, baseline mean arterial pressure, baseline spo2 among three groups were comparable, there was no statistically significant difference among the three groups are ANOVA was used to analyse the mean difference of time to reach highest sensory level, time for two-segment regression and time to reach from Bromage 3 to Bromage 1 between three groups (Table 2). The results displayed that there is a significant difference in time to reach highest sensory levels, two segment regression among the three groups. The pair wise comparison of groups showed that group D is significantly different from other two groups for two segment regression and Highest sensory level. The time taken for HSL in group D is lesser than group M and group NS. The time taken for 2 DR is more in group Dexmedetomidine in comparison to Midazolam and normal saline group. The motor block (Bromage 3 to Bromage 1) among the three groups are not statistically significant (Table 3).

Pair wise comparison analysis was done by using BONFERONI test, which shows there is a statistical significance in Group D compared to Group M and Group NS (Table 4).

The mean and Standard deviation of visual analogue score and time for analgesia among three groups were compared. There was a significant difference with respect to VAS. It is lesser in Dexmedetomidine group compared to midazolam and normal saline group (p<0.05) Time to rst request for postoperative analgesia was later in the Dexmedetomidine group than in the Midazolam and Normal saline groups (P<0.05). Fewer patients in the Dexmedetomidine group required an analgesic (Diclofenac Na) during the rst 24hr after spinal block than in the midazolam (p<0.05) and saline (p<0.05) groups (Table 5 and 6).

Table 1: Age, sex and weight distribution

Parameters	Group D (n = 25)	Group M (n = 25)	Group NS (n = 25)	p-value
Age (years)	54.72±3.18	55±2.97	55±2.53	0.926
Weight (kg)	78.9±9.4	80.8±5.24	78.8±9.4	0.970
Height (cm)	169.6±5.85	169.2±6.15	169.6±5.9	0.600
Duration of surgery (min)	38.72±3.506	39.68±3.301	40.52±4.293	0.239
ASA (I/II)	14/11	11/14	12/13	0.563

Table 2: Baseline heart rate, mean arterial pressure, Spo2

Parameters	Group D (n = 25)	Group M (n = 25)	Group NS (n = 25)	p-value
Baseline HR (min)	80.16±6.053	81.32±6.902	79.76±6.559	0.681
Baseline MAP (mm of Hg)	90.44±5.316	92.08±3.872	89.88±8.007	0.406
Baseline SPO^2 (%)	98.32±3.966	99.12±0.726	99.04±1.136	0.440

Table 3: Higher sensory level, two dermatome regression and motor duration

Parameters	Group D (n = 25)	Group M (n = 25)	Group NS (n = 25)	p-value
Higher sensory level (mins)	4.16±1.143	7.52±0.872	7.68±0.748	0.000
Two dermatome regression (mins)	146.40±13.503	97.20±14.295	88.40±14.629	0.000
Motor duration (mins)	181.60±11.431	176.40±9.074	176.80±10.693	0.154

Table 4: Pair wise analysis

PARAMETER	D -M	M–NS	NS–D
Higher sensory level (mins)	0.000	1.000	0.000
Two dermatome regression (mins)	0.000	0.093	0.000

Table 5: Overall 24hr visual analogue scale, time for first analgesia

Parameters	Group D (n=25)	Group M (n=25)	Group NS (n=25)	p-value
24 hr Visual analogue scale	2.24±0.436	2.72±0.678	2.72±0.614	0.005
Time for first analgesia (mins)	201.08±14.54	126.20±18.333	120.56±13.232	0.000

Table 6: Pair wise significance:

PARAMETER	D-M	M–NS	NS–D
Visual analogue scale	0.015	1.000	0.015
Time for first analgesia	0.000	0.609	0.000

Pair wise significance analysed using BONFERONI test

Table 7: Rescue analgesia in first 24 hours and side effects

Parameters	Group D (n = 25)	Group M (n = 25)	Group NS (n = 25)	p-value
Patients received rescue analgesia	6(24%)	15(60%)	16(64%)	
Side effects				
Hypotension	3 (12%)	0	5 (20%)	0.070
Bradycardia	2 (8%)	0	1 (4%)	0.353
Sedation (5/6)	2 (8%)	5(20%)	0	0.050

The number of patients requiring rescue analgesia was lesser in Group D than in Group M and Group NS (Table 7). The incidence of hypotension was found higher in group NS than in group M and D, but there was no significant difference between the three groups in the occurrence of hypotension. Excessive sedation (Ramsay sedation score of 5) was observed in two patients of the Dexmedetomidine group and in ve patients of the midazolam group. Bradycardia was found to be 8% in Group D, where group Midazolam reported no such cases. Side effects such as dyspnoea, shivering, nausea, headache, TNS and backache were not found in any groups.

DISCUSSION

Many studies demonstrate that intravenous administration of dexmedetomidine prolongs the duration of subarachnoid block. However, these studies have a difference in their mode of administration of dexmedetomidine[6,7]. It is recommended to administer dexmedetomidine over no<10 min, as rapid administration might produce tachycardia, bradycardia, and hypertension. Bolus administration of midazolam 0.05 mg kg^{-1} was reported to give enough sedation and amnesia without any adverse effects on hemodynamic and respiration in patients aged 30-70 years under spinal anaesthesia. Therefore, midazolam 0.05 mg kg^{-1} was administered to the patients in this study.

In our study, the three groups displayed no significant difference in the maximum block height. The maximum block height attained was T4 and the minimum attained was T10. This is in accordance with previous studies[8]. Whizar-Lugo *et al*.,[8] obtained a maximum sensory level of T4, where they have used 1 mcg kg^{-1} of dexmedetomidine over 20 min. Reddy *et al*.,[9] achieved a maximum sensory level of T4 ±1 with dexmedetomidine group on infusing 0.5 mcg kg^{-1} of dexmedetomidine over 10 min before SAB with 3 cc of 0.5% bupivacaine.

In the current study, group D displayed statistically significant difference in the time for maximum sensory block. It was found that the time taken for HSL in group dexmedetomidine is lesser than midazolam and normal saline groups Synergistic interaction between dexmedetomidine and local anaesthetics has been observed in previous studies. Memis *et al*.[10] reported that the addition of 0.5 µg kg^{-1} dexmedetomidine to lidocaine for intravenous regional anaesthesia shortened sensory and motor block onset times and prolonged sensory and motor block recovery times without causing side effects. The underlying mechanism of this effect remains unclear. The supra-spinal, direct analgesic, and/or vasoconstricting actions of dexmedetomidine are suggested to be involved in this mechanism.

In the current study, it was found out that the time to reach Bromage 1 was not statistically faster for group D (181.60±11.431) on comparison with group M (176.40±9.074) and group NS (176.80±10.693). Al-Mustafa *et al*.[11] reported that the time to reach Bromage 1 was 199.9±42.8 min in dexmedetomidine group and 138±31.3 min in control group. Dinesh *et al*.[12] study showed that time to reach reach Bromage 1 was 220.7±16.5 mins in the dexmedetomidine group and 131±10.5 minutes in the control group. The higher time to reach Bromage 1 in the above study might be due to the usage of higher dose of bupivacaine and higher bolus dose of dexmedetomidine.

Compared with the prolongation of the sensory block, the duration of motor block was not affected by dexmedetomidine. It could be explained that conduction of sensory nerve bre might be more

inhibited than motor nerve bre at the same concentration of dexmedetomidine, as similarly reported with clonidine. The current study found no significant difference in the mean blood pressure and heart rate in all the groups. This is supported by the previous study by Dinesh *et al*.[12]

In the current study, a statistically significant difference was obtained in group D in the time for first request for analgesia which is more on comparison with group M and control. In Kaya *et al*.[13] study, the time for first request analgesic request was 216±43 minutes in dexmedetomidine group and 136±25 minutes in midazolam group. Harsoor *et al*.[14] found that duration of analgesia in dexmedetomidine group was 222.8±123.4 min and 138.36±21.62 in the control group. Reddy *et al*.[9] reported the duration of analgesia as 243.35±56.82 min in dexmedetomidine group and 140.75±28.52 min in the control group.

Based on present and previous studies, the effect of dexmedetomidine is not dependent on the route of administration. Midazolam has been reported to have an antinociceptive effect through the neuroaxial pathway. However, the effects of midazolam on nociception may depend on the route of administration, with analgesia observed after spinal or epidural application, but not after systemic administration of this agent. Also, in our study, intravenous administration of midazolam did not enhance the analgesic effect of intrathecal injection. Finally, the use of dexmedetomidine premedication before spinal anaesthesia seems to offer clinical advantages compared with midazolam premedication, since dexmedetomidine provides additional analgesia.

In our study, even though there were incidence of hypotension of 12% in group D and 20% in group NS as well as incidence of bradycardia almost 8% in group D and 4% in group NS, they were not statistically significant. Mustafa *et al*.[11] presented similar results even with higher doses of dexmedetomidine 1 mcg kg^{-1} bolus over 10 minutes, followed by 0.5 mcg/kg/hr. comparable results of no statistically significant difference in the occurrence of hypotension and bradycardia between the groups were observed in some previous studies. The current study highlights that lesser dose of 0.5 mcg kg^{-1} of dexmedetomidine could reduce the occurrence of hypotension and bradycardia when compared with the studies using higher dosages.

Rapid or bolus intravenous administration of dexmedetomidine produces sudden hypertension and bradycardia until the central sympatholytic effect dominates, resulting in moderate decreases in both MAP and HR from baseline. We observed no biphasic change or signi cant cardiovascular variability in this study consisting mainly of healthy patients. This might be attributed to sympathetic blockade associated with spinal anaesthesia, slow administration of a low dose, and suf cient preoperative hydration. However, further studies are needed to investigate the ef cacy of dexmedetomidine in geriatric patients or medically compromised patient populations.

In previous studies, it has been shown that dexmedetomidine caused no or minimal respiratory depression. However, midazolam is known to cause apnoea and arterial desaturation in sedative doses. There was no respiratory depression in any patients and respiratory parameters (respiratory rate, SpO_2) remained within normal limits throughout our procedure. None of the patients had complaints of nausea, vomiting, and shivering. There were no complaints of headache, backache and TNS in any of the patients postoperatively.

CONCLUSION

Intravenous dexmedetomidine provided better spinal block quality by prolonging the sensory block when compared to midazolam. Addition of intravenous dexmedetomidine before spinal block provided similar relief with delayed-onset of postoperative pain and significantly less analgesic requirements. A single dose of intravenous dexmedetomidine given as premedication prolonged the duration of sensory blockade of bupivacaine induced spinal anesthesia. It also provided sedation and additional analgesia.

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