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Research article

EFFECTS OF INTRATHECAL MIDAZOLAM IN SPINAL ANAESTHESIA: A PROSPECTIVE DOUBLE BLINDED CASE CONTROL STUDY

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ABSTRACT

Background: Increasing the duration of action and maximizing postoperative analgesia has always been a domain of interest in spinal blocks. Many adjuvants have been tried along with local anaesthetic agent to achieve the same. The following study was conducted to compare sensory and motor characteristics with 2mg midazolam in subarachnoid block. **Aim:** To evaluate the efficacy and analgesic effect of the mixture of 2 mg midazolam and 15 mg (3 ml) hyperbaric bupivacaine as compared to bupivacaine alone in patients undergoing infra-umbilical surgery under spinal block. **Material and Methods:** In this observational prospective case control study 100 patients (ASA class I and II), aged 18 to 55 years, undergoing elective infra-umbilical surgeries under spinal block were randomly divided into Group I- patients were administered 0.5% hyperbaric Bupivacaine (3 ml) + 0.9% Normal saline (0.4 ml) intrathecally and Group 2- patients were administered 0.5% hyperbaric Bupivacaine (3 ml) + 2mg preservative free Midazolam (0.4 ml) intrathecally. The onset and duration of sensory and motor block, hemodynamic variables, and side effects during the surgery and recovery were compared among the groups. **Results**: 2mg of preservative free midazolam used as an adjuvant to bupivacaine intrathecally reduces onset time of sensory and motor blockade, also time taken to reach T-10. It also increases time taken for two segmental recession and mean duration of analgesia. **Conclusion**: It can be inferred that Inj. Midazolam 2 mg in combination with Inj. bupivacaine 0.5% hyperbaric can be safely administered intrathecally for better postoperative analgesia.

KEYWORDS: Intrathecal Midazolam, Post-operative Analgesia, Bupivacaine, Spinal Anesthesia.

INTRODUCTION

Regional anaesthesia, for below umbilical surgeries, is held generally to be safer than general anaesthesia. Regional anaesthesia avoids general anaesthesia related problems. General anaesthesia may pose problems like poly-pharmacy, airway manipulation, misplacement of endotracheal tube, hypo or hyper ventilation, vomiting, pulmonary aspiration. Regional anaesthesia attenuates increase in plasma catecholamine and other hormones by reducing surgical stress. Regional anaesthesia gives intra and postoperative pain relief and at the same time preserves mental status and normal reflexes. For below umbilical surgeries, the subarachnoid blockade being the common form of neuraxial blockade performed, it ensures the patient wellbeing and facilitates the surgeon's work. Commonly used drug is 0.5% hyperbaric bupivacaine which produces longer duration of anaesthesia along with good muscle relaxation and effective pain relief in initial post-operative period.

Increasing the duration of action and maximizing postoperative analgesia has always been a domain of interest in subarachnoid blocks. Many adjuvants have been tried along with local anesthetic agent to achieve the same. Intrathecal opioids provide good postoperative analgesia but are associated with adverse effects of itching, nausea, urinary retention, sedation, ileus and life-threatening respiratory depression [1]. Other adjuvants like clonidine, neostigmine and ketamine have been tried but are not used in routine clinical practice owing to their adverse effects [2,3,4]. Midazolam potentiates the effect of local anaesthetics improving the

quality of sensory and motor blockade, also increases the duration of post-operative analgesia without causing side effects of bradycardia, hypotension, post-operative nausea-vomiting, pruritus, urinary retention, sedation and neurotoxicity [5-11]. Considering only a limited number of studies assessing the efficacy of intrathecal midazolam combined with bupivacaine in humans [12,13], following study was conducted to compare sensory and motor characteristics between 3.0mL of 0.5% hyperbaric bupivacaine alone and a combination of 3.0mL of 0.5% hyperbaric bupivacaine with 2mg midazolam in spinal block.

MATERIAL & METHOD

Study design: A prospective double blinded case control study
Study location & period: This study was conducted at Pravara Rural Hospital of Pravara Institute of Medical Sciences over a period of one year from Jan 2015 to Jan 2016.
Ethical approval: Approval from institutional ethical committee and written informed consent from patients were obtained prior to study.
Inclusion criteria: 100 patients (ASA class I and II), aged 18 to 55 years, undergoing elective infra-umbilical surgeries were included in this prospective double blinded case control study.
Exclusion criteria: Patients not willing for regional anesthesia, with a known contraindication, sensitivity to study drugs, having psychiatric disorders, pregnancy or using any drug that modifies pain perception were excluded from the study.
Pre-medication: It was done with tab. Alprazolam 0.5 mg and tab. Ranitidine 150 mg orally the previous night for patients in both the groups and were advised to be nil orally from 10 pm. All patients were explained about the visual numeric scale (VNS) of pain assessment. On the day of surgery intravenous access was secured with 18-gauge venous cannula and preloading with 10 ml/ kg of lactated Ringer's solution was done.
Sampling method: The patients were randomly allocated into two groups through computer generated randomization.
Group I: Patients were administered 0.5% hyperbaric Bupivacaine (3 ml) + 0.9% Normal saline (0.4 ml) intrathecally.
Group 2- patients were administered 0.5% hyperbaric Bupivacaine (3 ml) + 2mg preservative free Midazolam (0.4 ml) intrathecally.
Method: Patient and the anesthesiologist who performed spinal block and made observations to the solution administered. The study solution was prepared by an anesthesiologist not involved in the administration of spinal anesthesia. A lumbar subarachnoid block was performed under strict aseptic precautions with patient in left lateral position, with a pillow under the head on a flat table. The L3-4 inter-space was used for lumbar tap after local skin infiltration with inj. 2% Xylocaine (2 ml). Sab arachnoid block was given using 26 Gauge Quincke needle through midline approach. After obtaining clear flow of CSF, drug was injected slowly using 5ml syringe, after negative aspiration for blood. Supine position was given to patients immediately after drug administration. The time of injection of the drug was recorded as 0 minute.

During surgery, all patients were given oxygen at 2L/min via nasal cannula and intravenous Ringers lactate solution for maintenance. Electrocardiography, pulse rate, NIBP, respiratory rate and SpO2 were monitored continuously and charting done every 5mins till first 1 hr and then every 15mins till surgery lasted and post operatively and every 15mins for 2hrs. Sensory and motor block were assessed at 5, 10, and 15 minutes after spinal anesthesia and then every 15 minutes during operation and until 1 h of recovery period by pin-prick testing bilaterally along the midclavicular line using a 26-gauge hypodermic needle. The umbilicus was considered as T10 dermatomal level. Time taken for sensory block to reach level T10 after spinal anesthesia was recorded. Time taken to reach highest level and time for two segmental recession was also noted.

Motor block was assessed using a 6-point modified Bromage scale (MBS) (1 = complete motor block; 2 = almost complete block, the patient is able to move feet only; 3 = partial motor block, where patient is able to flex the knees but unable to raise the leg; 4 = detectable weakness of hip flexion, where patient is able to raise the leg but is unable to maintain it; 5 = no detectable weakness of hip flexion; 6 = no weakness at all)[14]. Time of onset and duration of motor blockade was noted for all the patients. Any complication or adverse effects were noted and managed accordingly. Inj. Ephedrine 5 mg intravenously in increments and rapid infusion of intravenous fluids was given to maintain mean arterial blood pressure within 20% of baseline. Drop in pulse rate below 50/min was considered bradycardia and managed with injection Atropine 0.6mg intravenously. Inj. Ondansetron 4mg intravenously was given for Nausea & vomiting. Shivering was treated with warm drapes and warm intravenous fluids. Patients were shifted to the postoperative ward and observed till the first administration of analgesic (Inj. Diclofenac sodium 1.5mg/kg intramuscularly was given at the VNS score of 5 or on patients demand). Time for voiding post operatively was noted to assess the recovery of autonomic (sympathetic) activity, at the first successful trial of voiding. Patients were followed till discharge for delayed complications like urinary retention, transient neurological symptoms, post-dural puncture headache.

Statistical analysis: All data were entered into a proforma in excel sheet for SPSS and subjected to statistical analysis. Student's t test and One-way analysis of variance (ANOVA) was used for normally distributed parametric data. Repeated variables were analyzed with repeated measure of one-way ANOVA. Post hoc multiple comparison test was done using the Tukey-Kramer method. Statistical analysis was performed with statistical software (Statistical Package for Social Science

[SPSS] version 19.0 for Windows, SPSS, Inc.). A P value < 0.05 was considered statistically significant.

RESULTS

The mean age in Group I was 35.94 ± 12.08 years with a minimum age of 18 years and maximum age of 55 years. The mean age group in Group II was 36.1 ± 12.32 years with a minimum age of 18 years and maximum age of 55 years. The age difference between the groups is not statistically significant. Majority of cases in both groups were males - 58% in Group I and 56% in Group II were male patients. The mean duration of surgery was 105.98 ± 23.86 minutes in Group I, 112.46 ±29.60 minutes in Group II. No significant statistical difference was found between the two groups with respect to age, sex of the patients and duration of surgery (p > 0.05).

Table No. 1. Demographic Profile and Duration of surgery

	Group I	Group II	P value
Mean age (years)	35.94	36.1	0.8169
Sex (m/f)	29/21	28/22	0.8399
Duration of surgery (mins)	105.98	112.46	0.2311

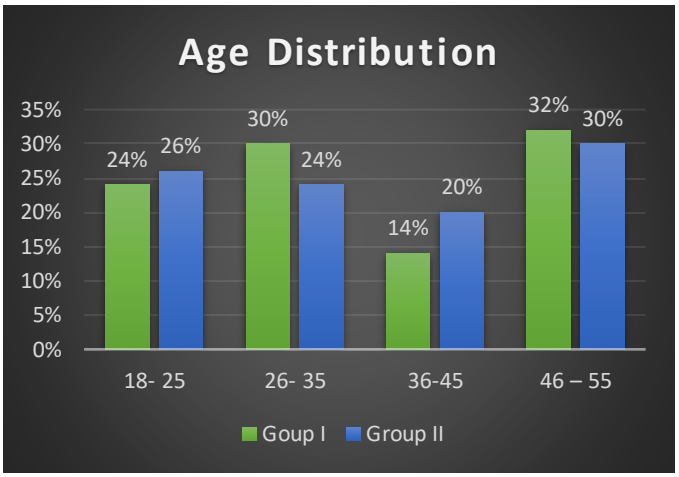

Figure 1. Age Distribution

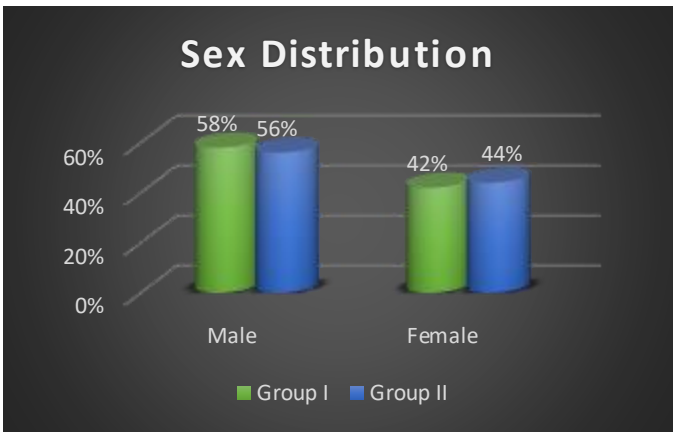

Figure 2. Sex Distribution

Majority of patients (28%) in Group I underwent lower limb surgery followed by lower abdominal and gynaecology surgeries. Majority of patients (28%) in Group II underwent urological surgery. The difference in surgical procedure in both the groups was statistically not significant. (P=0.8043)

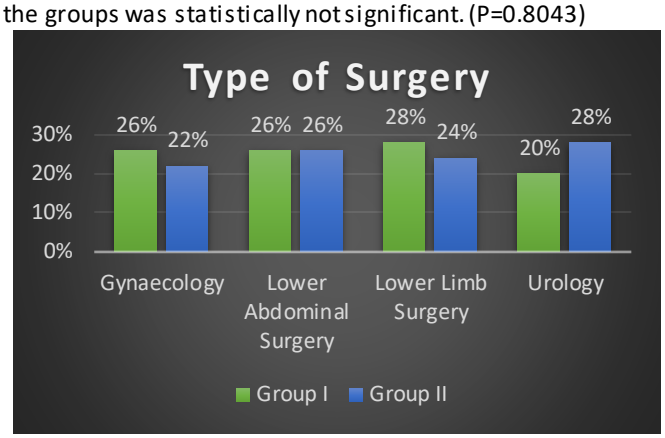

Figure 3. Type of surgery

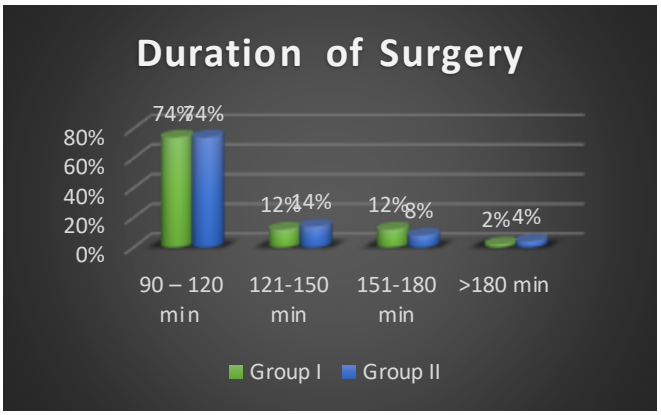

Figure 4. Duration of surgery

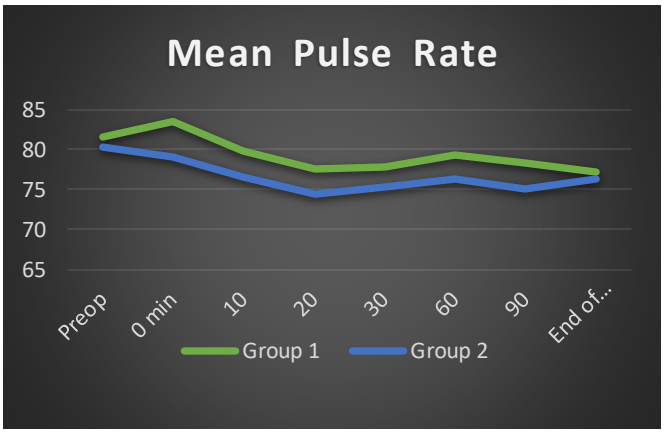

Figure 5. Mean Pulse rate variation

Table 2. Type of surgery

	Group I		Group II		TOTAL
Type of Surgery	No.	%	No.	%	
Gynaecology	13	26	11	22	24
Lower Abdominal Surgery	13	26	13	26	26
Lower Limb Surgery	14	28	12	24	26
Urology	10	20	14	28	24
TOTAL	**50**	**100**	**50**	**100**	**100**

Changes in pulse rate (p=0.461), respiratory rate (p= 0.4137) and mean arterial pressure were comparable in both groups and was found to be statistically insignificant (p=0.4137).

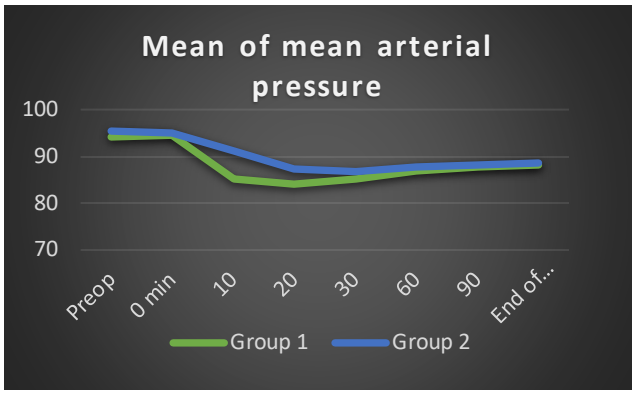

Figure 6. Mean Arterial Pulse variation

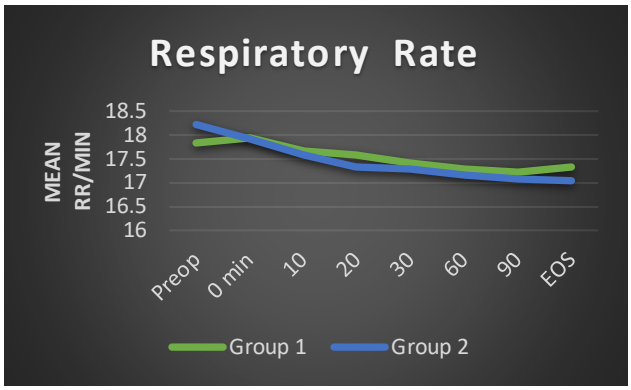

Figure 7. Respiratory Rate variation

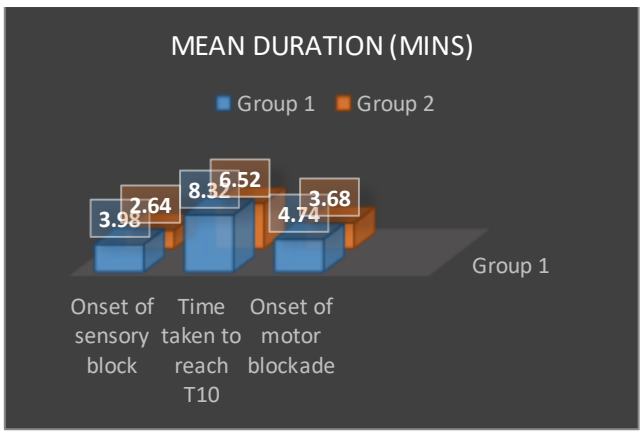

Figure 8. Mean duration for onset of sensory and motor blockade and time taken to reach T10

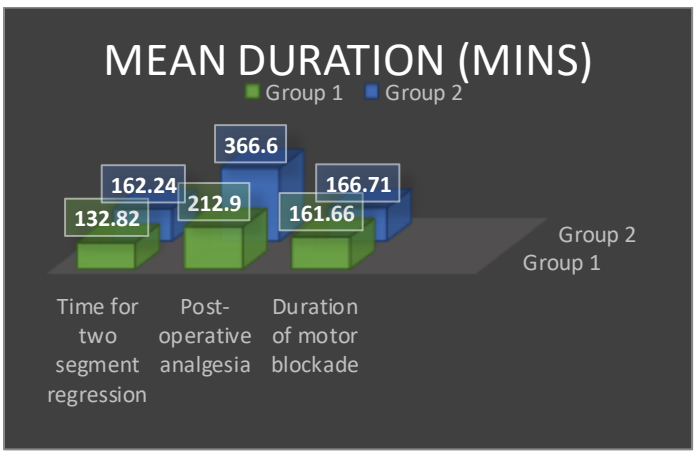

Figure 9. Mean duration for two segmental regression, post operative analgesia and motor blockade.

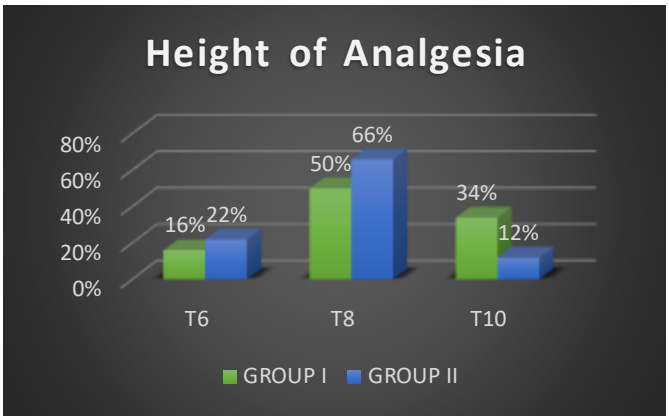

Figure 10. Highest level of sensory blockade achieved

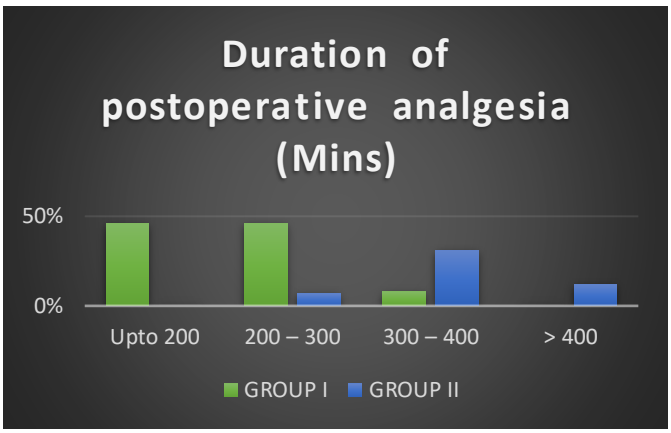

Figure 11. Duration of post operative analgesia

Table 3. Sensory and Motor Block Characteristics.

PARAMETER	GROUP I	GROUP II	P Value
Onset of sensory block	3.98 ± 1.42	2.64 ± 0.74	<0.0001*
Time taken to reach T10	8.32 ± 2.28	6.52 ± 1.75	<0.0001*
Onset of motor blockade	4.74 ± 1.14	3.68 ± 0.58	<0.0001*
Time for two segment regression	132.82 ± 13.59	162.24±18.3	<0.0001*
Post- operative analgesia	212.90 ± 62.78	366.60 ±50	<0.0001*
Duration of motor blockade	161.66 ± 15.58	166.71±12.5	0.1272

Data was presented as Mean ±SD, *Significant

Table No.4: Comparison of time of onset of motor blockade.

Onset of Motor Blockade					
	GROUP I		GROUP II		P value
Time in Mins	No. of patients	%	No. of patients	%	<0.0001
3-4	18	36	49	98	
4-5	19	38	0	0	
>5	13	26	1	2	
Total	50	100	50	100	

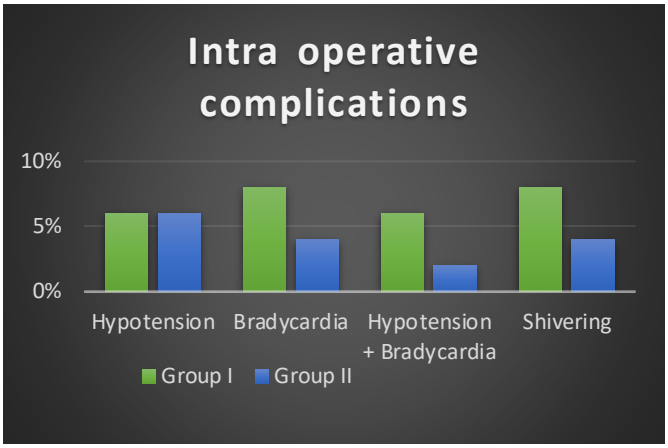

Figure 12. Intra operative complications.

Intra-operative complications were observed more in group I compared to group II for bradycardia, hypotension + bradycardia and shivering. However, the differences were statistically insignificant for all the complications.

Table 6. Mean time for voiding.

Time for voiding			
TIME in mins	**Group I**	**Group II**	**P value**
Minimum	146	195	0.1586
Maximum	340	451	
Mean + SD	255.24 ± 57.04	272.02 ± 61.02	

The mean time for voiding was 272.02 ±61.02 minutes in group II as compared to 255.24 ±57.04 in group I and the difference was statistically not significant (p=0.1586). None of the patient had any complications in post-operative period in either group.

DISCUSSION

Onset of sensory blockade in present study was earlier in group II with mean time 2.64 minutes as compared to mean of 3.96 minutes in group I, which concurs with studies by Vaswani et al [10], Nidhi et al [15], S. Sidiq et al [16] and Malavika Kulkarni et al [17] whereas Batra et al [6] observed no difference between the groups regarding onset of sensory block. Time to reach level of T-10 was less for group II with mean of 6.52 minutes in comparison with Group I with mean of 8.32 minutes whereas maximum level achieved is comparable in both groups. Nidhi et al [15] observed similar results in their studies, whereas according to Batra et al [6], S. Sidiq et al [16] and Malavika Kulkarni et al [17] no significant difference was found in both groups. Onset of motor blockade in our study was significantly quicker in group II with mean of 3.68 minutes compared to 4.74 minutes in Group I, which is similar to results observed by Vandana et al [18]. Duration of motor blockade in our study in Group I was 161.66 ± 15.58 minutes and 166.71 ± 12.46 minutes in Group II which is statistically not significant (P value 0.1272). Vandana et al [18] although found the difference significant with duration of motor blockade, none of the other authors have observed this in their studies. In our study mean time for two segmental sensory regression was 162.24 minutes in Group II as compared to 132.82 minutes in Group I, which was statistically significant. MalviKa et al [17] observed significant difference between the midazolam group and normal saline group with regards to regression of sensory block. Nidhi et al [15] observed no significant difference between the groups, whereas Batra et al [4] observed that time to block regression and ambulation were faster with the control group. In our study, we found significant statistical difference in the mean time for rescue analgesia which was 366.60 minutes in Group II as compared to 212.90 minutes in Group I. The duration of analgesia in only 8% of patients was between 300-400 minutes in Group I compared to 62% in Group II. For 24% of patients it was more than 400 minutes and in two patients it was more than 500 minutes in group II. This concurs with the studies of various other authors. Batra et al [6], Nidhi et al [15], Malvika et al [17], S.Sidiq et al [16] all observed midazolam increases mean duration of analgesia. In our study no statistically significant deference was found in mean time for voiding which was 272.02 minutes in Group II as compared to 255.24 minutes in Group I. This concurs with findings of Batra et al [6] and Kim et al [7] while Malvika et al [17] and S.Sidiq et al [16] did not mention it. In our study, hypotension was observed in 6% of patients (3 patients) in both the groups. Bradycardia was observed in 8% (4 patients) of Group I and in 4% (2 patients) in Group II. Hypotension and bradycardia was observed in 6% of group I and 2% of Group II. These observations concur with the observations of Kim et al [7], Batra et al [6], Nidhi et al [15], Bharti et al [11], Valentine et al [13], Bhattacharya et al [9]. In present study, no statistically significant difference was found (p = 0.127) in mean the duration of maximum motor blockade, which was 161.66 ± 15.58 with a range of 135 to 210 minutes in group I, and 166.71 ± 12.46 minutes with a range being 148 to 210 minutes in group II. This is consistent with the study of Batra et al [6]. Thus, midazolam has no effect on motor blockade and helps in early ambulation and day care surgery. All patients were observed post operatively for 72 hours and observed for, urinary retention, transient neurological symptoms, and post dural puncture headache. None were reported or observed in the study group and concurs with the observations of Kim et al [7], Batra et al [6], Nidhi et al [15], Bharti et al [11], Valentine et a [13], Bhattacharya et al [9].

CONCLUSION

It is evident from this study that minimal dose (2mg) of preservative free midazolam used as an adjuvant to bupivacaine intrathecally reduces onset time of sensory and motor blockade, also time taken to reach T-10. It also increases time taken for two segmental recession and mean duration of analgesia which offers advantage during the

shifting and postoperative period giving adequate time for rescue analgesia. It does not alter the hemodynamic profile significantly which fulfills the operative requirements, along with reduced incidence of nausea and vomiting. It shows no respiratory depressant effects unlike opioids. Thus, it offers a simple method with no adverse effects and hence definitely a better adjuvant to local anesthetics for infra umbilical surgeries.

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