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Role and efficacy of intrathecal bupivacaine (0.5) with the multiple doses of midazolam (1 mg to 2 mg) while lower limb surgeries

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Abstract
Background: Spinal anaesthesia, which is one of the techniques for infraumbilical surgeries, is most commonly criticized for limited duration of postoperative analgesia. Discovery of spinal receptors like alpha 2 adrenergic, cholinergic, opioid, NMDA and gamma aminobutyric acid (GABA) and benzodiazepine receptors trigger the use of drugs like neostigmine, clonidine, opioids ketamine, midazolam for their synergistic effect with intrathecal local Anaesthetics.
Materials and methods: It was a double blind, prospective, randomised study patients with ASA 1 and 2 was taken. Exclusion criteria were patients with cardiac problem, respiratory problem, coagulation disorders, mental disorders and contraindication to regional block. Day before surgery preanesthetic evaluation was carried and procedure was explain to each patient. 0.5 mg alprazolam and ranitidine 150 mg given bedtime the night before surgery patient is kept NPO overnight.
Results: In our study duration of motor block in group 1 and group 2 was 3.22 (hr) ± 0.73 & 3.52±0.77 P value 0.226. Duration of sensory block in group 1 and group 2 was 4.09 (hr) ± 0.88 & 6.69 (hr) ± 1.29 *p*-value<0.001 significant. There is higher duration of pain free period with group 2. So we can say that intrathecal 2mg Midazo lam added to bupivacaine, duration of postoperative analgesia was significantly prolonged than 1 mg midazolam.
Conclusion: The duration of effective analgesia when midazolam is added to intrathecal bupivacaine is significantly prolonged thereby proving that midazolam is a useful adjunct to intrathecal bupivacaine for post-operative analgesia. Effect of intrathecal midazolam is dose dependent 2mg midazolam prolongs the action of bupivacaine with good sedation and no unwanted side effects.

Keywords: Analgesia, spinal Anestheisa, intra Thecal Bupivacain, midazolam, lower limb surgeries

Introduction
Spinal anesthesia achieved a widespread popularity as a simple and effective method of producing conduction block for surgery in the presence of some ready available drugs, complete aseptic technique, and careful practice; subarachnoid block provides adequate anesthesia for patients undergoing infraumbilical surgery Central neuraxialblocks (CNB) reduces the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding, respiratory depression and postoperative pain relief [1]. But CNB with local anaesthetic has limited duration of analgesiab [2]. Discovery of spinal receptors like alpha 2 adrenergic, cholinergic, opioid, NMDA and gamma aminobutyric acid (GABA) and benzodiazepine receptors trigger the use of drugs like neostigmine, clonidine, opioids ketamine, midazolam for their synergistic effect with intrathecal local anesthetics [2, 3]. Local anesthetics with opioid has effective action but produces respiratory depression, urinary retention, nausea and pruritis [4]. Benzodiazepine receptor (benzodiazepine GABA-A receptor Complex) within the spinal cord which lead to enhance activity of GABA or inhibitory neurotransmitter [5]. There are studies for analgesics benefits of midazolam in early postoperative period following cesarean section and hemorrhoidssurgery [6, 7]. In these studies to 2mg Midazolam is used there is no study which compares analgesic efficiency of midazolam with 1 mg and 2 mg doses [8, 9]. So your study is aimed to do comparative study of analgesic efficacy of intrathecal bupivacaine with midazolam of 1 mg and 2 MG in patient undergoing lower Limb surgeries. The study is designed to compare the analgesic efficacy of intrathecal bupivacaine with the midazolam 1 mg and 2 MG in patients undergoing lower

Limb surgeries. Here we are assessing the onset of action, duration of sensory and motor block, quality of block and undesirable Side Effects like bradycardia, hypotension, nausea, vomiting and sedation.

Materials and Methods

After approval from the hospital ethics committee, a prospective randomized double blind placebo study was carried out on 50 (ASA1 and 2) adults aged between 30 and 80+years, either sex 25 in each group as in Table 1 and Table 2, Figure 1 scheduled to undergo elective surgical procedures on lower abdomen, lower extremity, or urological procedures under subarachnoid block. Comparative study of analgesic efficacy of intrathecal bupivacaine with midazolam of 1 mg and 2 MG in patients undergoing lower Limb surgery was carried in Aadhar Hospital Hisar Haryana after local ethical committee and written informed consent from 50 patients scheduled for elective lower limb orthopaedic surgeries. It was a double blind, prospective, randomised study patients with ASA 1 and 2 was taken. Exclusion criteria were patients with cardiac problem, respiratory problem, coagulation disorders, mental disorders and contraindication to regional block. Day before surgery preanesthetic evaluation was carried and procedure was explain to each patient. 0.5 mg alprazolam and ranitidine 150 mg given bedtime the night before surgery patient is kept NPO overnight.

In the operating room, 18 G cannula secured in left upper limb. All patients were pre-medicated with 150mg ranitindine and 4mg ondansetron. Preloading done with 10ml/kg of ringer lactate prior to subarachnoid block. Baseline monitors were connected to record heart rate (HR), non-invasive blood pressure (NIBP), ECG, oxygen saturation (sp02). After recording the baseline parameters, patient is put in sitting position and under sterile aseptic precautions, lumbar puncture done at L4-L5 level with 26G Quincke's needle. After free flow of CSF, drug is injected slowly into the subarachnoid space. Patient is immediately place supine and onset of action assessed by pinprick, senasation at T6 level.

Patients were randomly allocated into two equal groups 25 patients in each group. Group 1 received 2.8 ml of 0.5% hyperbaric bupivacaine with 0.1 ml of preservative free midazolam and 0.1 ml of distilled water Group 2 received 2.8 ml of 0.5% bupivacaine with 0.2 ml of preservative free midazolam.

The onset of sensory block (time taken for complete loss of pin prick sensation at T10 level)

Duration of sensory block (time taken for sensory block to regress below T12)

Onset of motor block (time taken to achieve bromage Motor Scale 3)

Duration of motor block (bromage score 0) Duration of effective analgesia (time for rescue analgesia intraoperatively IV fentanyl and postoperatively IM diclofenac, IV paracetamol, IV tramadol) Surgery started following confirmation of subarachnoid block Intraoperatively hypotension, fall in BP>20% in SBP from the baseline) treated with IV fluids and Mephentermine 6mg. Bradycardia treated with 0.6mg atropine when PR<60/min. Sedation score recorded.

Sedation score 0 = awake
1 = sleeping comfortably easily arousable 2 = deep sleep but arousable
3 = deep sleep not arousable

The obtained results were subjected to statistical analysis. Independent 't' test was used. P value determined
P value>0.05 taken in significant<0.05 significant
<0.01 highly significant
<0.001 very highly significant

Post-operatively, patient observed for 24 hours. Rescue analgesia was given with IV tramadol, IM diclofenac. Duration of sensory block was taken from starting of surgery till patient complains of pain and ask for rescue analgesia

Statistical methods

Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made, Assumptions: 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher exact test used when cell samples are very small.

Results

Bupivacaine is a local anesthetic of the amide type, chemically related to mepivacaine; bupivacaine, like other local anesthetics, causes a reversible blockade of impulse propagation along nerve fibers by preventing the inward movement of sodium ions through the nerve membrane. Bupivacaine has a rapid onset and a medium to long duration. No difference in demographic distribution of patients. No difference in onset of action duration of motor block and side effects. Onset of sensory block in group 1 onset of sensory block in group 1 and Group 2 was 2.35 (min) □□0.65 & 2.30□0.57 respectively *P* value of 0.845, which is not significant. Duration of motor block in group 1 and group 2 was 3.22 (hr) □0.73 & 3.52□0.77 *P* value 0.226. Duration of sensory block in group 1 and group 2 was 4.09 (hr) □0.88 & 6.69 (hr) □□1.29 *p*-value<0.001 significant. There is higher duration of pain free period in Table 4, 5, 6, 7.

Table 1: Age distribution

Age in years Total	Group I	Group II
31-40 9(18%)	1(4%)	8(32%)
41-50	1(4%)	7(28%)

8(16%)		
51-60 10(20%)	3(12%)	7(28%)
61-70 12(24%)	10(40%)	2(8%)
71-80 12(24%)	10(40%)	2(8%)
>80 1(2%)	1(4%)	0(0%)
Total 50(100%)	25(100%)	25(100%)
Mean ± SD 59.07±14.46	68.30±11.47	49.20±11.18

P< 0.001**, Significant, Student t test

Table 2: Gender distribution

Gender Total	Group I	Group II
Female 20(40%)	15(60%)	5(20%)
Male 30(60%)	10(40%)	20(80%)
Total 50(100%)	25(100%)	25(100%)

P=0.008**, Significant, Chi-square test

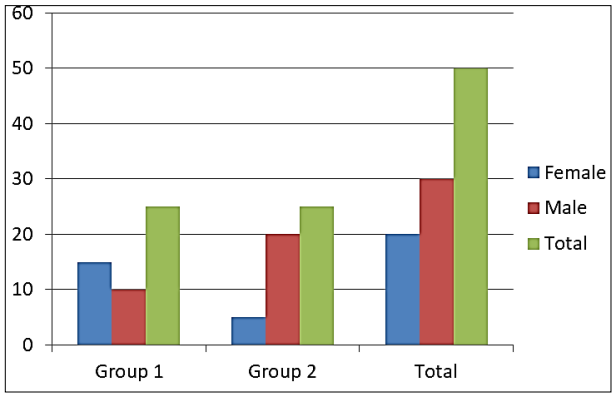

Fig 1: Sex distribution

Table 3: ASA grade distribution

ASA Grade	Group I	Group II
Total		
1 20(40%)	9(36%)	11(44%)
2 25(50%)	12(48%)	13(52%)
3 5(10%)	4(16%)	1(4%)
Total 50(100%)	25(100%)	25(100%)

P=1.000, Not significant, Fisher exact test

Table 4: Weight (Kg) distribution in two groups

Weight (kg)	Group I	Group II	Total
<40	3(10%)	0(0%)	3(5%)
40-50	8(35%)	2(10%)	
10(22.5%)			
51-60	5(15%)	1(5%)	6(10%)
61-70	8(35%)	9(35%)	17(35%)
71-80	1(5%)	13(50%)	
14(27.5%)			
Total	25(100%)	25(100%)	50(100%)
Mean ± SD	55.35±13.23	69.15±9.12	62.15±13.37

P< 0.001**, Significant, Student t test

Table 5: Onset of actions (mins) distribution in two groups

Onset of actions (Mins)	Group I	Group II
Total		
1 4(8%)	3(12%)	1(4%)
2 25(50%)	10(40%)	15(60%)
2.5 2(4%)	2(8%)	0(0%)
3 19(38%)	10(40%)	9(36%)
Total 50(100%)	25(100%)	25(100%)

P=0.741, Not significant, Fisher exact test

Table 6: Comparison of clinical and outcome variables in two groups

Variables	Crow I	Crows II	Total	P
Value				
Age in years	68.30±11.47	49.20±11.18	59.07±14.46	<0.001**
Weight (kg)	55.35±13.23	69.15±9.12	62.15±13.37	<0.001**
Onset of actions (mins)	2.35±0.65	2.30±0.57	2.32±0.61	0.815
Duration of surgery (hrs)	2.62±1.10	2.09±0.65	2.38±0.94	0.090+
Duration of Motor Blockade (hrs)	3.22±0.73	3.52±0.77	3.36±0.75	0.226
Duration of Sensory Blockade (hrs)	4.09±0.88	6.69±1.29	5.32±1.70	<0.001**

Table 7: Sedation distribution in two groups

Sedation	Group I	Group 11	Total
Negative	0(0%)	2(8%)	2(4%)
Positive	25(100%)	23(92%)	48(96%)
Total	25(100%)	25(100%)	50(100%)

P=0.487, Not significant, Fisher exact test

Table 8: Side effects distribution in two groups

Side effects	Group I	Group 11	Total
Negative	25(100%)	25(100%)	50(100%)
Positive	0(0%)	0(0%)	0(0%)
Total	25(100%)	25(100%)	50(100%)

P< 0.001**, Significant, Fisher exact test

Table 9: Frequency distribution of duration of motor blockade and sensory blockade

Variables	Group I	Group 11	Total	*P* value
Duration of motor Blockade (hrs.)				
<3	4(16%)	2(8%)	6(12%)	
3-4.5	20(80%)	20(80%)	40(80%)	0.755
>4.5	1(4%)	3(12%)	4(8%)	
Duration of sensory blockade (hrs.)				
<5	17(68%)	2(8%)	19(38%)	
5-S	8(32%)	13(72%)	26(52%)	<0.001**
>3	0(0%)	5(20%)	5(10%)	

Chi-square/Fisher exact test

Table 10: Comparison of study variables in two groups

Variables Value	Group I	Group II	Total	P
Duration of surgery (hrs.)	2.62±1.10	2.09±0.65	2.33±0.94	0.090+
Duration of motor blockade (hrs.)	3.22±0.73	3.52±0.77	3.36±0.75	0.226
Duration of sensory blockade (hrs.)	4 09±0.88	6.69±1.29	5.32±1.70	<0.001**

The time of onset of sensory block, time to achieve maximum sensory block, and level of dermatomal sensory blockade was similar in both the groups and no significant difference was observed. However, the time taken for two segment regression of sensory block, regression of sensory block to S1 dermatome, and the duration of effective analgesia was significantly higher in the Group II This infers that the patients who were administered midazolam along with the bupivacaine had a prolonged sensory blockade than the bupivacaine only group. In Table 2, 3, 8, 9, 10.

Discussion

The inclusion of midazolam in intrathecal bupivacaine was shown to significantly enhance the duration of post-operative analgesia. However, the difference in time of onset of sensory blockade, time taken to achieve maximum sensory block, and the level of sensory block amongst the two groups was not statistically significant. Although different types of surgical procedures have been selected we have avoided bias by random distribution of cases Bupivacaine, a potent drug acting, amide local anaesthetic, blocks the generation, propagation and oscillation of electrical impulses in peripheral and central nervous system. The sodium channel is a key target to local anaesthetic actively. Bupivacaine blocks sodium currents and rapidly inactivates potassium currents in the neurons of spinal dorsal horn [9, 10, 11]. Benzodiazepines produce sedative hypnotic, anxiolytic, anticonvulsant and antinocioceptive effect by interaction with GABAA receptors. These receptors are known to be involved in nociceptive mechanism. The receptors are present in higher concentration in lamina II at dorsal horn ganglia. Yegin *et al*. who studied 44 patients with bupivacaine and midazolam combination. No difference in onset of sensory block [12]. But there are no study done which compares the action of 1 mg & 2 mg midazolam intrathecally. Vlentine *et al*. compared intrathecally bupivacaine, bupivacaine-midazolam, Bupivacainedimorphine & found no side effects due to midazolam [13]. Tucker *et al*. did a cohort study and concluded administration of 2 mg midazolam intrathecal did not course any neurotoxicity [14]. Kim & Lee Prakash *et al*. administered intrathecal bupivacaine, together with midazolam, in either 1mg or 2mg dose showed prolonged duration of action with addition of midazolam [15, 16]. However the mechanism of action of intrathecal midazolam is attributed to the potential role of spinal benzodiazepine receptors in sequential antinociceptive action. Administration of benzodiazepine antagonist (Bicuculline) has been reported to reverse the analgesic effect of intrathecal midazolam suggesting that the antinociceptive actions are mediated via BZD/GABA-A receptor complex which are present in lamina II of dorsal horn ganglia of spinal cord. Intrathecal midazolam is involved in the release of endogenous opioid acting at spinal delta receptors. Its antinociceptive effect has been suppressed by delta selective opioid antagonist naltrindole. Intrathecal midazolam besides causing analgesia has been found to be effective in suppressing reflex response to visceral distension in rabbits and visceral pain in humans in cesarean section. Although our study may be criticized for adopting a low dose of midazolam. This was done with the intention of providing safe and prolonged post-operative analgesia. The duration of motor block was not assessed as our objective was to determine effectiveness of midazolam as an adjunct to intrathecal bupivacaine in post-operative pain relief.

Conclusion

Therefore we conclude here the duration of sensory block is prolonged in group II with mild sedation and no side effects. So that duration of action of intrathecal midazolam is dose dependent. Our study was limited to lower limb surgeries, so we recommend further studies on different types of operations as caesarian sections, hysterectomy, and abdominal surgeries; another recommendation is to compare midazolam and the other adjuvants as opioids with the use of the different approved doses of intrathecal midazolam.

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Conflict of interest: None declared

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