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Comparative Clinical Study of 0.5% Hyperbaric Bupivacaine Alone and 0.5% Hyperbaric Bupivacaine with Midazolam Intrathecally for Lower Limb Orthopaedic Surgeries

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Abstract

In order to maximize the quality of anaesthesia by increasing the duration of action and maximising post operative analgesia, a number of adjuvants have been added to spinal local anaesthetics. The present was aimed to study efficacy and analgesic effect of mixture of midazolam-bupivacaine as compared to bupivacaine alone in patients undergoing lower limb orthopaedic surgery under subarachnoid block. Material and Methods: Present study was prospective randomized case control study, conducted patients of either sex aged between 18-60 years, belonging to ASA Grade I and II, undergoing lower limb orthopaedic surgeries. All patients were randomly allocated into two groups (each group consisting of 50 patients) as Group B(control group received 0.5% hyperbaric Bupivacaine alone) and Group M(study group received 0.5% hyperbaric Bupivacaine+1 mg of Preservative free Midazolam (0.2 ml) intrathecally). In group B, mean onset time for sensory blockade was 4.76±0.76 minutes as compared to 3.68±1.06 minutes in the group M, difference was statistically significant. Mean duration of sensory blockade in group B is 88.96±2.98 minutes were as in group M, it is 119.70±8.93 minutes, $p<0.05$ hence statistically significant. Mean duration of maximum motor blockade in B is 161.66±15.58 while in group M, the mean duration of maximum motor blockade is 166.0±12.46 minutes, difference was not statistically significant. In group B, the mean duration of analgesia is 124.86±7.25 minutes as compared to 247±25.74 minutes in group M, p value is 0.000 ($p<0.05$), hence statistically highly significant. Intrathecal preservative free midazolam 1 mg in combination with hyperbaric bupivacaine 0.5% appears effective and a safe option for the enhancement of spinal effect and duration of local anaesthetic agent.

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Key Words

Midazolam, hyperbaric bupivacaine, analgesia, Intrathecal, regional anaesthesia

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INTRODUCTION

Regional Anesthesia for orthopedic lower limb surgeries is thought generally to be safer than General Anaesthesia. It avoids general anesthesia related problems such as poly-pharmacy, airway manipulation, misplacement of endotracheal tube, hypo or hyper ventilation, vomiting, pulmonary aspiration[1,2]. It reduces surgical stress and attenuates the increase in plasma catecholamine and other hormones. Regional Anaesthesia gives intra and postoperative pain relief with full preservation of mental status and normal reflexes. The subarachnoid blockade is a common form of centrineuraxial blockade performed for lower limb orthopaedic surgeries. The ensuing nerve block ensures the patient wellbeing, while motor block facilitates the surgeon's work. The 0.5% hyperbaric bupivacaine is the most commonly used drug. It produces longer duration of anaesthesia with good muscle relaxation and provides effective pain relief in immediate post-operative period. In order to maximize the quality of anaesthesia by increasing the duration of action and maximising post operative analgesia, a number of adjuvants have been added to spinal local anaesthetics[3-5]. The subarachnoid midazolam has been used in humans since 1986 and doses up to 2 mg have been described[3]. The present was aimed to study efficacy and analgesic effect of mixture of midazolam-bupivacaine as compared to bupivacaine alone in patients undergoing lower limb orthopaedic surgery under subarachnoid block.

MATERIALS AND METHODS

Present study was prospective randomized case control study, conducted in department of Anesthesiology, K.G Hospital and Post Graduate Medical Institute, Coimbatore, Tamil Nadu, India. Study duration was of one and half years between April 2017 to November 2018. Study was approved by institutional ethical committee.

Inclusion Criteria:

- Patients of either sex aged between 18-60 years, belonging to ASA Grade I and II, undergoing lower limb orthopaedic surgeries, willing to participate in present study.

Exclusion Criteria:

- Patients with ASA Grade III and IV physical status.
- Patients not willing for regional anaesthesia.
- Patients with a Known sensitivity to study drugs.
- Patients with a known contraindication to spinal anaesthesia: Bleeding disorders, Severe hypovolemia, Systemic Anticoagulation (risk of spinal haematoma), gross spinal abnormality, localized skin sepsis.
- Neurological involvement or disease like an intracranial space occupying lesion.
- Patients with psychiatric disorders, Pregnancy.
- Patients using any drug that modifies pain perception .
- Patients in extremes of age.
- Patients on chronic analgesic therapy. peripheral neuropathy.

Study was explained to participants in local language and written informed consent was taken. During preoperative anaesthesia visit, detailed history of each patient in the study was taken Data such as age, sex, weight, hospital registration number, date of admission was noted. Thorough physical examination was carried out and general condition of the patient recorded. Baseline parameters such as pulse rate, blood pressure, respiratory rate was recorded. The cardiovascular, respiratory and central nervous system were thoroughly examined. Airway assessment was done. The back and vertebral column of the patients were examined to rule out any spinal deformity and local infection.

The following investigations were done in all the patients such as Hemoglobin, Urine analysis, Random Blood sugar, Blood urea and Serum creatinine, Coagulation profile and Standard 12-lead ECG and chest X-ray chest P/A view for the patients above 40 years of age.

All patients included in the study were premedicated with Table *et al.* prazolam 0.5mg on the night before surgery to relieve anxiety. Tablet Ranitidine 150mg on the night before surgery. Patients were kept nil orally from 10 PM onwards. The procedure of subarachnoid block was explained to the patient and the patient was informed to communicate with anesthesiologist if he/she perceives pain or discomfort during the procedure and during surgery. All patients were randomly allocated into two groups (each group consisting of 50 patients) through a computer-generated Randomization and drug preparations were done by a senior Anaesthetist without labelling and double blinding both user and monitoring anaesthetist. Group B(control group): Patients were administered 0.5% hyperbaric Bupivacaine (2.5 ml)+0.2 ml of intrathecally. Group M(study group): patients were administered 0.5% hyperbaric Bupivacaine (2.5ml)+1 mg of Preservative free Midazolam (0.2 ml) intrathecally. On arrival of the patients in the operating room, monitoring was established with electrocardiography display, pulse oximetry and noninvasive blood pressure. The baseline pulse rate, blood pressure, rate of respiration, oxygen saturation and ECG were recorded in each patient before the subarachnoid block. An intravenous line with 18 G intravenous cannula was secured and preloaded with 15-20 ml/kg of Ringer lactate solution.

The patients were then put in lateral position with head, neck, spine, hip and knees flexed and back arched. The hip and shoulder were maintained in vertical plane and patient was brought to the edge of the table. Under strict aseptic precautions, lumbar puncture was performed at L3-4 interspace with 23G Quincke needle, after preparing with local infiltration of 2mL of 2% lignocaine. After free flow of cerebrospinal fluid, control(B) group received 2.5mL of 0.5% hyperbaric bupivacaine plus 0.2mL of CSF and the midazolam group(M) received 2.5mL of 0.5% hyperbaric bupivacaine plus 1 mg of midazolam in 0.2mL. The drug was injected slowly over a period of 10 seconds. The patient was turned to supine position after injection. The following data were collected such as onset of sensory analgesia, maximum level of sensory analgesia, duration of sensory blockade, quality of motor blockade, duration of maximum motor blockade, total duration of analgesia and intra-operative vitals (pulse rate, blood pressure, respiratory rate, oxygen saturation) at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90 and 120minutes intra-operatively and every hour till 4 hours post-operatively. The level of sedation was assessed every 15 minutes till the end of first hour followed by every half an hour till 12 hours following arrival in the postoperative ward. The patients were observed for 24 hours and any post-operative side effects such as nausea, vomiting, headache, shivering, sedation, respiratory depression, drowsiness ,urinary retention and neurological deficits were noted. The collected data was analyzed by using Statistical Product and Service Solutions (Statistical Package for Social Science, SPSS) Software for windows version 19 Inc and entered into a proforma in Microsoft Excel 2007 sheet for SPSS and subjected to statistical analysis The interval data were expressed as Mean and Standard Deviation. The Student's t-test was used for comparing the two groups. Chi-Square test was used for analysis of statistical data. P value<0.05 was considered significant for statistical difference.

RESULTS AND DISCUSSIONS

The Following Observations were Made During the Study: The minimum age was 19 years and maximum age was 60 years. The mean age group B is 39.40±11.59 years(SD) and group M is 36.62±10.75 years. There were 34 male patients and 16 female patients in group B. The group M had 33 male patients and 17 female patients.

Table 1: General Characteristics

Characteristics	Group B	Group M
Age group (in years)		
Below 30	14	15
31-40	18	15
41-50	12	12
51-60	4	6
Mean age(yrs) ± SD	39.40 ± 11.59	36.62 ± 10.75
Gender		
Male	34	33
Female	16	17

In group B the range for onset of sensory blockade is 4-6 minutes with mean onset time being 4.76±0.76minutes. In the group M the range for onset of sensory blockade is 2-6 minutes with a mean onset time of 3.68±1.06 minutes. The t value is 5.977 and p value being .000(p<0.05), hence statistically significant.

Table 2: Time for Onset of Sensory Blockade

	Onset of Sensory Blockade		
Group	Range	Mean	SD
B	4-6	4.76	0.72
M	2-6	3.68	1.06
t = 5.977	p = 0.000 (p<0.05)		

Mean duration of sensory blockade in group B is 88.96±2.98 minutes were as in group M, it is 119.70±8.93 minutes, p<0.05 hence statistically significant

Table 3: Duration of Sensory Blockade(Two Segment Regression)

	Duration of Sensory Blockade(minutes)		
Group	Range	Mean	SD
B	85- 98	88.96	2.98
M	106- 140	119.70	8.93
t= -23.079	p=0.000	statistically significant	

Mean duration of maximum motor blockade in B is 161.66±15.58 with a range being 135-210 minutes. In group M, the mean duration of maximum motor blockade is 166.00±12.46 minutes with a range being 148-210 minutes. As p value is 0.127 it is statistically not significant.

Table 4: Duration of Maximum Motor Blockade

	Duration of maximum motor blockade(minutes)		
Group	Range	Mean	SD
B	135 - 210	161.66	15.58
M	148 - 192	166.00	12.46
t=	1.813	P value 0.127	Not significant

In group B, the mean duration of analgesia is 124.86±7.25 minutes with a range of 110-142 minutes. In group M, the mean duration of analgesia is 24±25.74 minutes with a range of 190-302 minutes. The duration of analgesia has been increased from 124.86 minutes to 247.82 minutes. The p value is 0.000 (p<0.05), hence statistically highly significant.

Table 5: Duration of Analgesia

	Duration of analgesia (minutes)		
Group	Range	Mean	SD
B	110 - 142	124.86	7.25
M	190 - 302	247.82	25.74
t= -32.509	P value 0.000	statistically significant	

Time of first voiding was recorded and compared between the two groups as a measure of sympathetic recovery. The mean duration of first voiding time is 285±38.50 minutes in group B and 293.68±35.54 in group M. Since p value is >0.05, this is statistically not significant.

Table 6: Time of First Voiding

	Duration of first voiding(minutes)		
Group	**Range**	**Mean**	**SD**
B	225 - 400	285.56	38.50
M	236- 410	293.68	35.54
t= -1096		p= .276	Not significant

The Visual Analogue score for effectiveness of pain relief is shown in the two groups. In group B, the mean score is 3.8±0.5 and in group M, it is 3.7±0.5. The t value is 1.0 and the p value is 0.32, hence there is no statistical significance between them.

Table 7 : VAS

		VAS (scores)	
Group	**Range**	**Mean**	**SD**
B	3-5	3.8	0.5
M	3-5	3.7	0.5
t= 1.0	p= 0.32		significant

In group B, 3 patients had bradycardia, 3 patients had hypotension, and 2 patients had nausea and vomiting. In group M, 2 patients had bradycardia, 3 had hypotension and 3 patients had nausea. Here p=1.86 and hence there is no statistical difference between the groups.

Table 8: Complications

Complications	**Group B**	**Group M**
Bradycardia	3	2
Drowsiness	-	-
Hypotension	2	3
Nausea and vomiting	2	3
Urinary retention	-	-

The subarachnoid blockade is the common form of centrineuraxial blockade performed for lower limb orthopaedic surgeries. It ensures patient wellbeing, while motor block facilitates the surgeons work. 0.5% hyperbaric bupivacaine produces longer duration of anaesthesia with good muscle relaxation. It provides effective pain relief in initial post-operative period. Adjuvants are drugs that increase the efficacy or potency of other drugs when given concurrently. Neuraxial adjuvants are used to improve or prolong analgesia and decrease the adverse effects associated with high doses of a single local anesthetic agent. In addition to their dose sparing effects, neuraxial adjuvants are also utilized to increase the speed of onset of neural blockade i.e. reduce latency, improve the quality and prolong the duration of neural blockade[3,4]. Midazolam is one such adjuvant, water soluble imidazo-benzodiazepine derivative which has been tried since early 1980. The intrathecal benzodiazepine induced analgesia is spinally mediated. The site of action of benzodiazepine molecules are GABA receptors which are abundant in the dorsal root nerve cells of the spinal cord. The maximum concentration of GABA receptors is found within lamina II of dorsal nerve cells, a region which plays a prominent role in processing nociceptive and thermoceptive stimulations. By acting over the GABA receptors benzodiazepines induce changes in chloride conductance and enhance GABA induced presynaptic inhibition of primary afferent terminals. In present study, the time for onset of sensory blockade for the two groups was not statistically significant when compared. In Group B, it was 4.76±0.76minutes minutes were as in Group M it was 3.68±1.06 minutes, here p value 0.000(p<0.05) is significant. So, the addition of midazolam to bupivacaine has made apparent difference with regard to the time of onset. Vaswani[5,6] in her study reported that the addition of midazolam intrathecally reduced the onset of sensory blockade from 3.00±0.41 minutes in control group(group I) to 2.00±0.25 minutes in midazolam group(Group II) (p<0.001). Similar were the results of the studies conducted by B.K Shadangi[7] as the time of onset of sensory block was 4.8 minutes in Group B versus 4.6 minutes in Group BM, Abhisekh[8] as the time of onset of sensory block was 2.64±0.74 in study group versus 3.98±1.42 in control group Ulhas Misal et al.,9 and colleagues as the mean time of onset of sensory block was 2.76 in control group versus 2.5 minutes in study group. The results of the present study are consistent with the above-mentioned studies with regards to the time of onset of sensory blockade Batra[9,10] showed that the duration of sensory blockade increased from 229.8±41.4 minutes in Bupivacaine group to 267.6±67.38 minutes in Midazolam group with p value <0.05 and thus, being statistically significant. B.K. Shadangi[7] showed the duration of sensory blockade increased from 90. 8 minutes in B group versus 115.8 minutes in BM group;p value 0.001 and hence statistically significant. Abhisekh[8] showed the time for two segment regression was prolonged in the study group BM (162.24±18.3 versus 132.82±13.59 minutes) p value <0.0001 and hence statistically significant. Similar were the results of studies conducted by Anirbhan Chattopadhyay[11] (255 minutes versus 195 minutes), Md. Mohsin[12], B. Vasanthi[13] the time for two segment regression was prolonged in the study group BM(mean 122.9 minutes; p value <0.001), Ulhas Misal9(mean 87.08 versus 132.26 minutes; p value <0.001). In the present study the duration of sensory blockade was prolonged from is 88.96±2.98 minutes in group B to 119.70±8.93 minutes in Group M and it was found to be statistically significant as p<0.05.It can be attributed to the lipophilicity of midazolam and its synergism with local anaesthetics. The benzodiazepines exert their antinociceptive effect at the spinal cord whereas midazolam excerts its action through GABA A., on getting bound, opens ligand gated chloride channels. Chloride conductance is increased leading to hyperpolarisation and presynaptic inhibition of afferent terminal in spinal cord and hence reduction in the neuronal activity.

The study of Batra[10] on the patients undergoing knee arthroscopy, reported that the mean ambulation time as a measure of complete recovery from motor blockade was 242±30.9 minutes in the bupivacaine group and 258.3±25.4 minutes in Midazolam group(p >0.05). This study shows that intrathecal midazolam has no significant effect on motor blockade. Similarly, the results of the study done by B.K Shadangi[7] showed comparable findings with regard to the duration of maximum motor blockade between the two groups (151.8 versus 151.3 minutes) p value=0.51., hence not significant. In the present study, the duration of maximum motor blockade in group B is 161.66±15.58 with a range of 135-210 minutes, and 166.00±12.46 minutes in group M with a range being 148-210 minutes. As p value is 0.127 it is statistically not significant. The results of our study are consistent with that of the above-mentioned studies with respect to maximum duration of motor blockade. Midazolam is a potent short acting benzodiazepine in aqueous solution has been reported to provide antinociceptive effect in animals and in humans. B.K Shadangi et al.,7 (mean 221.1 minutes in BM versus 121.3 minutes in B; p value 0.001), Bharti[14] (199 in BM v/s 103 minutes in B., p<0.001), Ulhas Misal[9] (mean 216 in BM versus 136 minutes in B), Abhisekh[8] (366.60 in BM versus 212.90 minutes in B) and Anirbhan Chattopadhyay[11] (median 320 minutes in BM versus 220 minutes in B) showed that the mean duration of analgesia significantly prolonged in patients receiving intrathecal midazolam. In the present study the duration of analgesia was prolonged from 124.86±7.25 minutes in Bupivacaine group to 247±25.74 minutes in Midazolam group. This is statistically highly significant as p value is 0.000. The study of Batra[10] showed no difference in the time of first voiding in control group(252±29.8minutes) and in study group(258.8±25.4) (p>0.05). Kim and Lee10 reported that time to the episode of first self-voiding(control group: 4.99h, BM1group:4.95h, BM2 group:5.31h), was similar in all groups. Also, no statistically significant difference was found in mean time for voiding in study conducted by Abhisekh et al.,8 which was 272.02 minutes in Group II as compared to 255.24 minutes in Group I. The analgesic effect of intrathecal midazolam was segmental, with no alteration in sympathetic tone or reflexes. In present study, the time of first voiding, when compared with the two groups were statistically not significant. The time of first voiding is 285±38.50 minutes in group B and 293.68±35.54 minutes in group M(p=.276) (p<0.05 to be statistically significant). The results of our study are consistent with the study of Batra[10] and Kim[4]. The subarachnoid midazolam is also devoid of complications such as, bradycardia, hypotension, post-operative nausea and vomiting, pruritus, urinary retention, and neurotoxicity[9,10]. There was no statistical difference observed between the two groups with regards to complications, such as hypotension, bradycardia, post-operative nausea and vomiting, respiratory depression, urinary retention and signs of neurotoxicity. Limitations of the study were small sample size, conducted in a single center with small sample size which included stable, ASA Grades I or II patients. Therefore, our findings have external validity and cannot be extrapolated to the general population. The study was underpowered to detect potentially significant differences in secondary outcome variables, the data generated gives us fair idea about the safety and hemodynamic stability of the combination. There was heterogenicity as concerns the nature of the procedures, as these procedures varied. This, therefore meant the difference in the extent of tissue damage and thereby the nociceptive input varied and may have had an effect on the duration of effective analgesia.

CONCLUSION

It has been observed that, the addition of 1mg of preservative free midazolam to 0.5% hyperbaric bupivacaine reduces the onset time of sensory block and prolongs the duration of effective analgesia without increase in the incidence of any significant complications. Intrathecal preservative free midazolam 1 mg in combination with hyperbaric bupivacaine 0.5% appears effective and a safe option for the enhancement of spinal effect and duration of local anaesthestic agent. However, further studies are required in large sample size for confirmation of its beneficial effects and further evaluation of significant complications before introduction into routine anaesthetic practice.

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