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Efficacy of Clonidine (30µg) and Midazolam (2mg) as Intrathecal Adjuvants to Bupivacaine on Block Characteristics and Post-Operative Analgesia

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ABSTRACT
Discovery of Benzodiazepine receptors in spinal cord in 1986 by Faull and Villiger, triggered the use of intrathecal Midazolam for analgesia. Midazolam is known to produce anti nociception and potentiate the effect of local anesthetics when given in neuraxial blockade. Many workers have studied the effect of Midazolam to Bupivacaine with variable results on the duration and quality of spinal block. A prospective randomised study was conducted to compare the clinical effects of intrathecal Midazolam and Clonidine as Adjuvants to spinal Bupivacaine in patients undergoing infra-umbilical surgeries under spinal anaesthesia in Department of Anaesthesiology after approval from the Ethics Committee and patient consent. Mean time of total duration of analgesia was 305±43 minutes in group BC and was 416.3±22.6 minutes in group BM, the p value was <0.01 and was significant. There was significant difference at 4 and 6 hours p<0.01. No significant difference was found between the groups during 2, 8, 12, 24 hours of VAS p>0.05.

INTRODUCTION

Spinal anesthesia with Bupivacaine has been extensively used for lower abdominal and lower limb surgeries[1]. However on many occasions intra operatively degree of motor block and quality of analgesia seem to be much desired. The same is true with post-operative analgesia also. This drawback can be rectified by adding adjuvants to Bupivacaine. Such an addition will not only improve the duration and quality of sensor-motor block but also provides hemodynamic stability and lower the risk of local anaesthetic toxicity since local anaesthetic requirement is reduced[1,2]. In this background, many adjuvants to spinal Bupivacaine have been tried intrathecally like Opioids (Morphine, Fentanyl, Sufentanil, Alfentanil, Pethidine) and Non-Opioids (Clonidine, Midazolam, Neostigmine, Ketamine, Methylprednisolone etc.)[3]. Discovery of Benzodiazepine receptors in spinal cord in 1986 by Faull and Villiger[4,6], triggered the use of intrathecal Midazolam for analgesia. Midazolam is known to produce antinociception and potentiate the effect of local anesthetics when given in neuraxial blockade. Many workers have studied the effect of Midazolam to Bupivacaine with variable results on the duration and quality of spinal block[4]. Intrathecal Clonidine is another alternative adjuvant to Bupivacaine evaluated extensively. Clonidine (alpha-2-adrenergic agonist) has analgesic effect at spinal level mediated by post synoptically situated alpha-2-adrenergic receptors in dorsal horn of spinal cord[4,9]. Various doses of intrathecal Clonidine have been used in literature from 15-70µg[5,6]. We undertake a study to evaluate the relative efficacy of Clonidine (30µg) and Midazolam (2mg) as intrathecal adjuvants to Bupivacaine on block characteristics and post-operative analgesia.

MATERIALS AND METHODS

A prospective randomised study was conducted to compare the clinical effects of intrathecal Midazolam and Clonidine as Adjuvants to spinal Bupivacaine in patients undergoing infra-umbilical surgeries under spinal anaesthesia in Department of Anaesthesiology after approval from the Ethics Committee and patient consent. A total of 90 patients were enrolled between January 2020 to June 2021 for the study with the following inclusion and exclusion criteria. Sample size was calculated based on the study conducted by Joshi[1] considering the mean difference for duration of analgesia between Bupivacaine Midazolam (BM) and Bupivacaine Clonidine (BC) group as 60 minutes with a standard deviation of 132 and 53. The sample size was calculated with 80% power and alpha of 1.5 (95% confidence interval) and was found to be 90 with 45 cases in each group.

Inclusion Criteria:

- Patients willing to give informed written consent.
- Patients with 18-60 years of age either sex.
- ASA physical status I and II.
- Operations below umbilicus.

Exclusion Criteria:

- ASA physical status grade III and IV.
- Patients with pre-existing spinal disorder, neurological disorders, endocrine disorders, cardio -respiratory or other systemic disease.

Following ethics committee, informed consent was obtained from the patients. Detailed pre-anaesthetic check-up was done. Patients fulfilling the required essential criteria were selected and 90 patients were randomly allocated to following 2 groups:

- **Group BC (45 No.):** Spinal Bupivacaine with Clonidine.
- **Group BM (45 No.):** Spinal Bupivacaine with Midazolam.

Patient allocation was made based on computer generated numbers and sealed envelope method. The study solution for spinal anaesthesia was prepared separately by a person not involved in the patient care. Patients and Anaesthesiologists were blinded to both the study groups.

RESULTS AND DISCUSSIONS

Table 1: Time of Onset of Sensory Block(Min)

Parameter	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
TOSB	3.5	0.7	2.4	0.5	<0.01 **

Highest level of sensory block is depicted among the Groups. 15 patients (group BC) and 11 patients (group BM) had sensory block up to T4. 20 patients (group BC) and 23 patients (group BM) had sensory block up to T6. 10 patients (group BC) and 11 patients (group BM) had sensory block up to T8(p=0.647).

Table 2: Highest Level of Sensory Block

Parameters	Group BC		Group BM		
	No. of patients	%	No. of patients	%	p-value
T4	15	33.3%	11	24.4%	
T6	20	44.4%	23	51.1%	
T8	10	22.2%	11	24.4%	
Total	45	100.0%	45	100.0%	0.647

Time for 2-segment regression was 109.4±3.6 hours and 110.5±4.4 hours in group BC and BM respectively, the p value=0.204 and was not significant.

Table 3: Time for 2-Segment Regression(Min)

Parameter	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
Two-segment regression	109.4	3.6	110.5	4.4	.204

Mean time of duration of sensory block was 153.1±10.0 minutes in group BC and was 202.6±16.7

minutes in group BM, the p value was <0.01 and was significant.

Table 4: Total Duration of Sensory Block(Min)

Parameter	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
TDSB	153.11	10.02	202.67	16.77	<0.01

Mean time of onset of motor block was 4.98±0.75 minutes in group BC and was 3.42±0.58 minutes in group BM, the p value was <0.01 and was significant.

Table 5: Time of Onset of Motor Block(Min)

Parameter	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
TOMB	4.98	0.75	3.42	0.58	<0.01 **

Mean time of duration of motor block was 318.8±9 minutes in group BC and was 295.6±13.4 minutes in group BM, the p value was <0.01 and was significant.

Table 6: Total Duration of Motor Block(Min)

Parameter	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
TDMB	318.8	9.0	295.6	13.4	< 0.01 **

Mean time of total duration of analgesia was 305±43 minutes in group BC and was 416.3±22.6 minutes in group BM, the p value was <0.01 and was significant.

Table 7: Total Duration of Analgesia (Min)

Parameter	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
Total duration of Analgesia	305.0	43.4	416.3	22.6	<0.01 **

There was significant difference at 4 and 6 hours p<0.01. No significant difference was found between the groups during 2,8,12,24 hours of VAS p>0.05.

Table 8: VAS

VAS	Group BC		Group BM		
	Mean	SD	Mean	SD	p-value
2 hrs	0.4	0.6	0.4	0.5	.725
4 hrs	3.0	0.9	1.8	0.6	<0.01
6 hrs	5.1	0.8	3.5	0.5	< 0.01
8 hrs	4.1	1.1	4.0	0.8	.602
12 hrs	3.7	0.9	3.7	0.8	.962
24 hrs	3.2	0.8	3.3	0.8	.583

In our study the onset of sensory block was 3.47±0.66 mins in BC group and 2.42±0.54mins in BM group. Saxena[5], found a shorter onset of sensory block (2.54±0.34mins) in Clonidine group (30mcg added to 0.5% hyperbaric Bupivacaine, 13.5mg). Ingley[7] also reported a shorter onset of sensory block (1.08±0.32mins with BM group and 0.66±0.44mins with BC group). But they had used 2.5mg Midazolam and 75 mcg Clonidine. Joshi[9] who used 2mg Midazolam and 30mcg Clonidine also found shorter onset of blockade (1.84±0.98mins in BM group and 2.44±3.87mins in BC group). Agarwal[3] used 15mg Bupivacaine with 2.5mg Midazolam and found a longer onset time (3±1.22mins). Shadangi[1] who used 3ml of 0.5% Bupivacaine with 2mg of Midazolam, found the onset of sensory block to be 4.6±0.7mins. But these authors defined T8 level for checking onset unlike L1 dermatome as in our study. Similarly, Raval[2] used Clonidine 30mcg with 15mg 0.5% hyperbaric Bupivacaine and found the onset of sensory block at T10 to be 6.5±2.33mins. We found that the highest dermatomal level of anaesthesia reached in both groups was T4(25% in Group BM and 33% in Group BC). Majority of patients (44% in Group BC and 51% in Group BM) demonstrated highest sensory level of T6. Prakash[8] found that the maximum level reached with 2mg Midazolam ranged from T3-T5 in which majority of the patients attained a level of T4. Joshi[9] who compared 30mcg Clonidine and 2mg Midazolam found that the maximum level of sensory block ranged from T4-T10 in which majority of patients attained T6 in both groups. Thakur[10] found that the maximum level reached with 30mcg Clonidine ranged from T4-T8 in which majority of the patients attained a sensory level of T6. We found that the time for 2-segment regression was comparable in both groups (109.4±3.6mins in Group BC and 110.5±4.4mins in Group BM. Similar findings are reported with Clonidine by Dobrydnjor[11] (126±17mins), Thaku[10] (110.60±26.22mins), Raval[2] (118.67±25.55mins). However, in study conducted by Prakash[8] using 2mg Midazolam with 2 ml of Bupivacaine, regression time was found to be prolonged (182±30mins). Saxena[12] who used 30mcg Clonidine with 13.5mg of Bupivacaine also reported a prolonged duration (192±14.42mins). The duration of sensory block in our study was 153.1±10.0 minutes in Group BC and was 202.6 ±16.7 minutes in Group BM. Joshi[9] found similar results (169.28±63.69mins in BC group and 210.84±68.44mins in BM group). However, Agarwal[3] using 1mg Midazolam found the duration to be shorter (158.6±32.16mins). Unlike our results with Clonidine, longer duration time has been reported by Dobrydnjov[11] (247±75mins), Thakur[10] (276±40.62mins), Raval[2] (296.88±38.30). We found that the onset of motor block was 4.98±.75mins in BC group and 3.42±0.58mins in BM group. Saxena[12] found shorter onset of motor block (2.30±0.34mins) with 30mcg Clonidine. Joshi[9] also found shorter onset (2.30mins in BC group and 2.08mins in BM group). In the study by Shadangi[1], the onset of motor block was defined as Bromage scale 3(we have chosen Bromage scale 1) and hence obtained delayed onsets-Midazolam 2mg (6.0±0.8mins) and Clonidine 25mcg (8.273±1.941mins). In our study we found that the duration of motor block was 318.2±8.97 minutes in group BC and 295.6±13.4 minutes in group BM. Joshi[9]

also reported longer motor block in Group BC (322.92±135mins) compared to Group BM (293.80±108.69mins). Shadangi[1] reported a duration of 151.3±3.2mins with Midazolam 2mg. These results on motor block suggest better muscle relaxation with Clonidine rather than Midazolam which is a little baffling in the background of the well-known relaxant effect of systemically administered Benzodiazepines. Similar observation on muscle relaxation is shared by Kothari[13]. Further, Dobrydnjov[11] who also found similar potentiating of motor blockade with Clonidine interpreted that this is due to dose related direct a-motoneuron hyperpolarisation by a adrenoceptor agonism. We found that the duration of analgesia was 305±43 minutes in group BC and 416.3±22.6 minutes in group BM. This correlates with the results of Joshi[9] (Group BC-296.60±52.77mins and Group BM-391.64±132.98mins). For Clonidine (30mcg) the duration of analgesia has been variously reported as 242.1±23.3mins to 350.44±34.37mins in studies by Saxena[12], Raval[2]. In our study the mean VAS in BC group at 4 hours (3.04±0.90) and 6 hours (5.09±0.82) were significantly more compared to BM group (1.76±0.61 at 4 hours and 3.51±0.55 at 6 hours), indicating longer post-operative analgesia with Midazolam. Similarly, Joshi[9] found that the mean VAS at 4 hours (3.12±9.92) and 6 hours (6.28±1.45) in BC group were significantly <BM group (1.53±1.58 at 4 hours and 3.12±1.71 at 6 hours). Gupta[14] who used 2.5mg Midazolam also found that the VAS at 4 hours and 6 hours as 3.0±0.96 and 5.20±1.41 respectively. Saxena[12] reported the mean VAS at 3.5 hours to be 3.2±0.47 with Clonidine 30mcg. We found that the total number of rescue analgesics used were 123 in BC group compared to 98 in BM group. The mean number of rescue analgesics were 2.733±0.58 in Group BC and 2.178±0.53 in Group BM. This was similar to the result obtained by Joshi[9] (2.76±0.87 in BC and 2.04±1.01 in BM). Gupta[14] also found similar results (2.17±0.50) with Midazolam. This shows that the Midazolam group fared better in analgesic effect with less dependence on rescue drugs.

CONCLUSION

It is concluded from our study that as intrathecal Adjuvant to 0.5% hyperbaric Bupivacaine (12.5mg), Midazolam(2mg) offers superior enhancement of quality of analgesia compared to Clonidine (30mcg), based on the following observations.

- Duration of sensory block and duration of post-operative analgesia were longer with Midazolam.
- Motor block lasted shorter with Midazolam.
- VAS ≥4 and number of rescue doses in 24 hours were far less in Midazolam group.

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