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Comparative Evaluation of Intrathecal Midazolam Added To Bupivacaine, With Bupivacaine Alone For Lower Abdominal And Lower Limb Surgeries: A Prospective, Doubleblind, Randomized Controlled Study.

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Abstract
Objective: *The aim of the study is to assess the addition of intrathecal midazolam and to assess the post operative analgesic effect of addition of midazolam (intrathecal) with bupivacaine as compared with plain intrathecal bupivacaine*
Method: *In this prospective doubleblind, randomized, controlled study, a total of 60 patients (belonging to American society of anesthesiologist ASA I and II physical status between the age group of 25-55 years) scheduled for elective lower limb and lower abdominal surgeries under spinal anesthesia were selected.. The patients were randomly allocated to one of the two groups of thirty patients each*
Group I: received plain hyperbaric bupivacaine
Group II: received plain hyperbaric, bupivacaine with midazolam
The SPO2, heartrate, systolic, diastolic and mean arterial blood pressure were recorded during the surgery. Also sedation score, the time taken for onset of sensory block, complete motor block and their regression time were evaluated.
Results: *Mild to moderate sedation was observed in group II. The time taken for two segment, four segment regression of the sensory block and the regression of the sensory block to L1, were prolonged in group II ($p<0.001$) There were no difference in the heartrate, SPO2, systolic, diastolic and mean arterial blood pressure between the two groups.*
Conclusion: *The addition of preservative free midazolam in the dosage of 0.05mg/kg to intrathecal bupivacaine prolongs the postoperative analgesia in lower abdominal and lower limb surgeries without any adverse effect.*
Keywords: *Hyperbaric bupivacaine, intrathecal midazolam, spinal anesthesia, postoperative analgesia.*

I. Introduction

Spinal anesthesia is most commonly used regional anesthesia technique for lowerlimb and lower abdominal surgeries. It provides effective postoperative analgesia without any complications [18] [19] [20]. Various adjuvants have been added to spinal local anesthetics to prolong the postoperative analgesia such as morphine, clonidine, ketamine, midazolam [6] [7] [8]. Discovery of benzodiazepines receptors in spinalcord triggered the use of intrathecal midazolam for improving the intraoperative analgesia and prolonging the duration of postoperative analgesia, with sparing effect of a postoperative analgesic consumption [9] [10] [21]. Midazolam is a water soluble benzodiazepine with sedative, amnesic, anxiolytic, muscle relaxant and anticonvulsant properties [11] [12] [13] [22] [23] [25]. Intrathecal administration of midazolam produces antinociceptive effects through GABA_A receptors in spinalcord which are in highest concentration in lamina – II or the dorsal horn ganglia. The safety of neuraxial administration of Midazolam in humans has been demonstrated by several studies. Besides analgesia, midazolam is effective in suppressing the reflex response to visceral pain in cesarean sections in humans [14] [16] [17].

A total of 2 mg midazolam (preservative free) intrathecally has been found to be the optimum dose for relieving the pain without any side effects [15]. In this study we evaluated the analgesic efficacy of combination of the intrathecal midazolam with bupivacaine and compared it with bupivacaine alone for the prolonging the postoperative analgesia in patients undergoing elective lower limb and lower abdominal surgeries under spinal anesthesia.

II. Methods And Materials

In this prospective doubleblind randomized controlled study, a total of 60 patient belonging to American society of Anesthesiologist ASA grade I & II physical status, between the age group 25-55 years, scheduled for elective lower abdominal and lower limb surgeries under spinal anesthesia during the year 2014 to 2015 were selected,. After the approval was granted by the institutional ethical committee, written informed

consent was obtained from patients for participation in this study. The patients were evaluated. Those with contraindications to regional anesthesia were excluded from the study.

The patients were randomly allocated to one of the two groups of thirty patients each.

Group I (study drug A patients): Received 2.5 ml of hyperbaric bupivacaine (0.5%) with 8 % dextrose + 0.5 ml of 0.9 % saline

Group II (study drug B patients): Received 2.5 ml of hyperbaric bupivacaine with 8 % dextrose + 0.05mg/kg of midazolam. Active and placebo solutions were prepared by second anaesthesiologist who is uninvolved with the cases. The anesthesiologist performing the block and the postoperative assessment was blinded to the solution administered. Both the groups received no premedication. They were explained about the procedure and the study drug injection in the intrathecal route.

III. Procedure And Results

A 18 gauge intravenous cannula was inserted. Patients were preloaded with 500 ml of lactated ringers solution. Standard monitoring was used, (ECG, NIBP, pulse oximetery) during surgery. Base line blood pressure and the heart rate were recorded. The patients were placed in the lateral decubitus position for lumbar puncture. Under strict aseptic precautions, lumbar puncture was performed through a midline approach using 25 gauge spinal needle at L2-L3 (or) L3-L4 intervertebral space. Once free flow of cerebral spinal fluid was obtained, the local anesthetic with the drug was injected at a rate of 1 ml/30 sec. After the injection, the patient was returned to the supine position and retained in that position, for at least 20 minutes before being positioned for surgery. The dermatomal levels of sensory anesthesia were evaluated by pinprick every minute for the first 20 minutes and then at 10 minutes interval until analgesia to pinprick recovered to L 1 segment.

The highest sensory level was noted. The following parameters were evaluated and noted.

a) Time from injection to attainment of highest level of sensory blockade.
b) Time for two segment regression of sensory blockade
c) Time for four segment regression of sensory blockade
d) Time for regression of the sensory blockade to the L1 segment.
e) Time for onset of complete motor blockade. This was assessed and graded at the same time intervals as sensory blockade using the bromage scale.
f) time for recovery of motor blockade to L 2 (hip flexion)
g) central effects – sedation was studied and graded as described by filos et al. using four point sedation score.
h) Intra operatively the blood pressure and heart rate were monitored at I minute interval for the first 10 minutes and later every 10 minutes for one hour.
i) Patients were monitored for 12 hours postoperative.
j) Postoperative analgesia was evaluated using standard 10 cm linear visual analogue scale (VAS)
k) All parameters were computed through the statistical analysis. The mean standard deviation, standard error of the mean, and critical ratios were made for comparing the study drug groups. The significant values were calculated through CR and the significant levels were identified from the Ready – Reckoner table, where the critical ratio follows, a normal distribution, whose 5 % level is 1.96 and 1 % level is 2.576

1) When the observed value of critical ratio is less than 1.96 then the probability of getting this observed value (or) greater than this value by chance is more than 5 % ($p>0.05$) . the level of significance is nil.
2) When the observed value of critical ratio is between 1.96 and 2.576, then it is the normal distribution.
3) When the observed value is greater than 2.576 but less than 3.291, then the probability of getting this observed value (or) greater than this value by chance is less than 1% (ie) $P < 0.01$, The level of significance is high.
4) when the observed value is greater than 3.291, then the probability of getting this observed value (or) greater than this value by chance, is less than 0.1% (ie) $P <0.001$. Then it is very Highly significant. All parameters were statistically analyzed using the students't' test for unpaired observations between the groups.
5) A "P" Value > 0.05 was taken to be statistically not significant (NS), a "P" value of <0.05 as statistically significant (S), A "P" value of < 0.01 as statistically Highly significant (HS) and a "P" value of <0.001 as statistically very high significant (VHS)

3.1. Age, Weight and Gender

Age distribution was shown in Table 1. The mean age of the patients in the Group I was 41.3 ± 10.59 years, while that in Group II 41.4 ± 10.7 YEARS. The mean weight of the patients in the Group I was 62.2 ± 3.55 kg as compared to that in Group II was 62.7 ± 3.2 years (Table 2). The mean height of the patients in the group I was 163.3 ± 5.96 cm as compared to that in group II was 165.1 ± 4.9 cm. There was no statistically

significant difference in the two groups with respect to age and weight. There was no difference between male and female distribution between two groups (Table 3)

Table 1. Age distribution

Age in years	Group I	Group II
25 - 34	9 (30.0 %)	10 (33.3 %)
35 - 44	8 (26.7%)	7 (23.3 %)
45 - 54	7 (23.3 %)	9 (30.0 %)
55 - 64	6 (20.0 %)	4 (13.4 %)

Table 2. Age and weight in the two groups studied

Group	Age in YearsMean ± SD	Weight in KgMean ± SD	Height in cm Mean ± SD
Study drug A Patients Group I	41.3 SD ± 10.59	62.2 ± 3.55	163.3 ± 5.96
Study drug B Patients Group II	41.4 SD ± 10.7	62.7 ± 3.2	165.1 ± 4.9

Table 3. Distribution of number % of male and female patients in each group

Group	Male	Female %
Group I	70 %	30 %
Group II	80 %	20 %

3.2. Highest level of sensory blockade

The highest level of sensory anaesthesia attained by each patient was noted and marked on a dermatomal chart. (Figure 1)

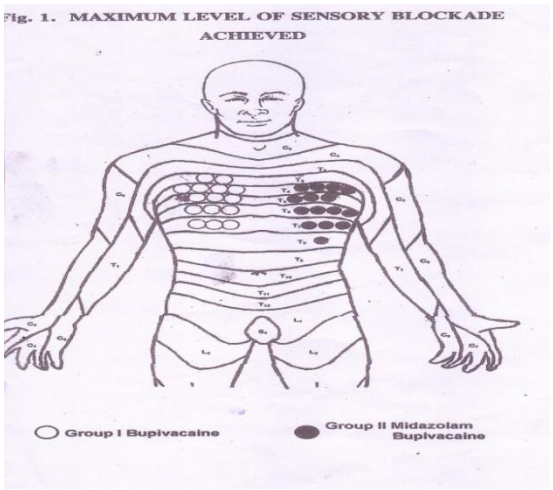

Figure 1. Level of sensory anesthesia

3.3. Time From Injection To Attainment Of Highest Sensory Blockade

The mean time from injection to attainment of highest sensory blockade in Group I (bupivacaine) was 14 minutes, while that in the Midazolam (group II) was 14.5 minutes (Table 4). Inter group comparison did not show a statistically significant difference in the time from injection to attainment of highest sensory blockade between the two groups (Table 5).

Table 4. Time taken for attainment of highest sensory blockade

Group	Mean	SD	SEM
Group I	14.0	3.15	0.57
Group II	14.5	3.36	0.62

Table 5.Inter group comparison of time taken for attainment of highest sensory blockade

Group	(CR) t	P	Significance
Group I / Group II Midazolam	0.60	> 0.05	NS

NS -> Nil Significant

As may be seen in the Table 5, the results show that the comparison of two groups for attainment of highest sensory Blockade is not significant as this critical ratio is 0.60 which is less than table value 1.96 (0.05) (5 % level). Therefore it is not significant.

3.4. Time For Two Segment Regression Of Sensory Blockade

The mean time for two segment regression of the sensory blockade in the group I was 71.5 minutes while that in the Midazolam group II was 122.9 minutes (Table 6). Inter-group comparison of the two segment regression of the sensory blockade showed a statistically Very Highly Significant difference between the Group I and II (P < 0.001). In table 7, inter-group comparison of two segment regression shows that the critical ratio is 19.58 which is greater than 3.29 in Ready–Reckoner table. It is very highly significant (P< 0.001).

Table 6. Inter-group comparison of the two segment regression of the sensory blockade

Group	Mean	SD	SEM
Group I	71.5	9.05	1.64
Group II	122.9	11.3	2.06

Table7. Inter-group comparison of the two segment regression of the sensory blockade

Group	(CR) t	P	Significance
Group I / Midazolam II	19.58	< 0.001	VHS

VHS -> Very Highly Significant

3.5. Time Four Segment Regression Of Sensory Blockade

The mean time for four segment regression of the sensory blockade in the group I was 118.4 minutes while that in the group II (Midazolam group was 187.5 minutes (Table 8). Inter group comparison of the four segment regression of the sensory blockade showed a statistically very highly significant difference between the group I and II (P< 0.001). Here the critical ratio is 14.7 which is greater than 3.29 in Ready – Reckoner table (P < 0.001). So, it is very highly significant (Table 9).

Table 8. Inter-group comparison of the four segment regression of the sensory blockade

Group	Mean	SD	SEM
Group I	118.4	20.25	3.70
Group II	187.5	16.24	2.96

Table 9. Inter-group comparison of the four segment regression of the sensory blockade

Group	(CR) t	P	Significance
Group I / Midazolam II	14.7	<0.001	VHS

VHS -> Very Highly Significant

3.6. Time For Regression Of Sensory Blockade To L1 Segment

The mean time for regression of the sensory blockade to L1 segment in the group I was 183.9 minutes while that in group II (Midazolam was 256.5 minutes (Table 10). Inter-group comparison of the regression of the sensory blockade to L1 segment-showed a statistically very highly significant difference between the group 1 and II P <0.001) (Table 11). Here the table 11 inter-group comparison shows a critical value of 17.49 which is greater than 3.29 in Ready – Reckoner table, the P value is (<0.001), so, it is very highly significant.

Table 10. Time for regression of sensory blockade to L1 segment

Group	Mean	SD	SEM
Group I	183.9	19.5	3.56
Group II	256.5	12.7	2.32

Table 11. Inter-group comparison of time for regression of sensory blockade to L1 segment

Group	(CR) t	P	Significance
Group I / II	17.49	< 0.001	VHS

VHS -> Very Highly Significant

3.7. Time For Onset Of Complete Motorblock

The mean time for onset of the complete motor blockade in the group I was 6.26 minutes while that in group II (Midazolam) was 6.3 minutes (Table 12). Inter-group comparison showed no statistically significant difference in the time of onset of complete motor blockade between the groups I / II. (P > 0.05) (Table 13). Here the critical ratio is 0.07, which is lesser than 1.96 in the Ready – Reckoner table. So the probability of observing

this value by chance, a value equal to (or) greater than 1.96 by chance is more than 5% (P > 0.05 so, it is not significant.

Table 12. Onset of complete motor blockade

Group	Mean (min)	SD	SEM
Group I	6.26	2.15	0.39
Group II	6.30	1.90	0.30

Table 13. Inter-group comparison of the onset of complete motor blockade

Group	(CR) t	P	Significance
Group I / II	0.07	>0.1 (0.05)	NS

NS -> Not Significant

3.8. Mean time taken for recovery of motorblock

The mean time for regression of the motor blockade in group I was 122.2 minutes and in group II was 120.3 minutes (Table 14). Inter-group comparison showed no statistically significant difference in the time taken for recovery of the motor blockade, between the two groups (Table 15).

Table 14. Mean time taken for recovery of motorblock

Group	Mean	SD	SEM
Group I	122.2	12.34	2.25
Group II	120.3	11.48	2.09

Table 15. Mean time taken for recovery of motorblock

Group	(CR) t	P	Significance
Group I / II	0.65	> 0.05	NS

NS -> Not Significant

3.9. Sedation

Most of the patients in the Midazolam group were sedated intraoperatively while only two patients were sedated in the Group I. The sedation score achieved in these patients was 2 (ie) these patients were drowsy, but responsive to verbal stimulus. None of the patients had a sedation score of 3 or 4. The data was analysed and shown in the following table 16 and 17.

Table 16. Sedation score

Group	Mean	SD	SEM
Group I	1.06	0.260	0.047
Group II	2.70	0.466	0.085

Table 17. Sedation score

Group	(CR) t	P	Significance
Group I / II	17.6	<0.001	VHS

VHS -> Very Highly Significant

3.10. Maximum change in heart rate (Δ HR Max)

The baseline heart rate and lowest heart rate achieved during the study period were tabulated as shown in Appendix 3 A and 3 B. The maximal change in the heart rate (Δ HR Max) from the baseline was then derived and the mean and standard deviation of Δ HR Max calculated in Group I and Group II. The heartrate (Δ HR Max) in Group I was 18.9 ± 5.9 while that in group II was 20.5 ± 6.57 (table 18). The comparison was shown in Table 19.

Table 18: Maximum change in the heart rate (Δ HR)

Group	Mean	SD	SEM
Group I	18.9	5.9	1.1
Group II	20.5	6.6	1.2

Table 19: Inter-group comparison of the maximum change in heart rate

Group	(CR) t	P	Significance
Group I / II	1	>0.05	NS

NS -> Not Significant

3.11. Maximum Change In Systolic Blood Pressure

Inter-group calculated in group I and group II. The Δ SBP max in Group I was 25.2 ± 11.3 while that in group II was 25.4 ± 10.9 (Table 20). The comparison was shown in Table 21.

Table 20. Maximum change in systolic blood pressure from the baseline (Δ SBP Max)

Group	Mean (mm)	SD	SEM
Group I	25.2	11.30	2.10
Group II	25.4	10.90	2.00

mmHg -> Millimeters of Mercury

Table 21. Inter-group comparison of the maximum change in the systolic blood pressure (Δ SBP max)

Group	(CR) t	P	Significance
Group I / II	0.06	> 0.05	NS

NS -> Not Significant

3.12 Maximum Change In Diastolic Blood Pressure

The baseline diastolic blood pressure and lowest diastolic blood pressure achieved during these period were tabulated as shown in the Appendix 3 A and 3B. Maximal change in the diastolic blood pressure (Δ DBP max).from the baseline was then derived and the mean and standard deviation of ΔDBP max calculated in the Group I and II (Midazoiam). Maximal change in the diastolic blood pressure (ΔDBP max) in the group I was 15.9 ± 7.03 mmHg while that in Group II was 18.00 ± 8.16 mmHg (Table 22). The ΔDBP max revealed no statistical difference (P > 0.1) between the two groups (Table 23).

Table 22. Intergroup comparison of Δ DBP Max revealed no statistical difference (P > 0.1) between the two groups

Group	Mean (mm)	SD	SEM
Group I	15.90	7.03	1.30
Group II	18.00	8.16	1.48

mmHg = Millimeters of Mercury

.

Table 23. Inter-group comparison of the maximum change in diastolic blood pressure (Δ DBP max)

Group	(CR) t	P	Significance
Group I / II	0.89	> 0.05	NS

NS -> Not Significant

3.13 Maximum Change In The Mean Arterial Pressure

The baseline mean arterial pressure and the lowest mean arterial pressure achieved during the study period were tabulated as shown in Appendix 3A and 3B. Maximal change in the mean arterial pressure (Δ MAP Max) from the baseline was then derived and the mean and standard deviation of (Δ MAP Max) in the group I was 18.9 ± 7.30 mmHg while in group II was 20.1 ± 7.28 mmHg (Table 24). The Inter-group comparison of maximal change in mean arterial pressure (Δ **MAP max**) from the baseline was not significant (Table 25).

Table 24. Intergroup comparison of (Δ MAP max) revealed no statistical difference (P>0.1) between the two groups

Group	Mean (mm)	SD	SEM
Group 1	18.90	7.30	1.30
Group II	20.10	7.28	1.30

mmHg = Millimeters of Mercury

Table 25. Inter-group comparison of the maximum change in mean arterial pressure (A MAP Max)

Group	**(CR) t**	**P**	**Significance**
Group I / II	**0.63**	>0.05	NS

NS -> Not Significant

IV. Discussion

In this study, the addition of Midazolam to Bupivacaine intrathecally provided better postoperative analgesia without any adverse effects. The segmental antinociception produced by intrathecal Midazolam is mediated by Benzodiazepine-GABA receptor complex that is involved in other Benzodiazepine actions.

Midazolam has a relatively high affinity for the benzodiazepine receptor roughly two times that of the diazepam. There are separate benzodiazepine and GABA recetor coupled to a common inophore chloride channel. Occupation of both receptors produces memberanehyperpolarisation and neuronal inhibition. Midazolam interferes with reuptake of GABA thereby causing accumulation of GABA. This is consistent with Benzodiazepine- GABA interaction hypothesis, these effects are reversed by administration of benzodiazepine antagonist flumazenil and GABA –A antagonists bicuculline. Intrathecal midazolam also causes the release of endogenous opiod acting on the spinal delta receptors as naltrindole, a delta selective opiod antagonist suppresses the analgesis effect of intrathecal midazolam.

(I) Here in this study, the addition of Midazolam to Bupivacaine did not alter the time taken for the attainment of highest sensory block, time taken for the onset of the motor block and also time taken for the recovery of the motor block to L2 level (hip flexion)

(II) B u t ,

1) it significantly prolongs the time taken for two segment regression of the sensory block, mean value in Group I was 71.5 min, whereas in Group II was 122.9 minutes ($P < 0.001$).
2) Also prolongs the time for the four segment regression of the sensory block. Mean value in Group I was 118.4 min whereas in Group II was 187.5 minutes ($P < 0.001$).
3) Also, the Midazolam with Bupivacaine combination prolongs the time for regression of the sensory block to LI segment, mean time in Group I was 183.9 minutes, whereas in Group IT was 256.5 minutes ($P < 0.001$).

Inter-group comparison between the Group I and II showed a statistically very highly significant difference in the time for two segment regression. four segment regression and regression of the sensory block to L1 segment.

(III) Midazolam with Bupivacaine did not show any difference in the highest sensory level attained.

(IV) A high sedation score was achieved in the Midazolam-Bupivacaine group. Mean value, in Group II was 2.7 whereas in Group I was 1.06. Intergroup comparison showed a very high significant difference between group I and II ($P < 0.001$). Only two patients in Group I had a sedation score of 2 (ie) patient drowsy but responsive to verbal stimulus, all other patients in Group I had a score of 1 only (ie) Awake.

Whereas in Group II, (Midazolam-Bupivacaine) most of the patients had the score of 3 (le) patient is drowsy, responsive only to physical stimulus all others had a score of 2, thus minimizing the need for postoperative sedation on the day of surgery.

All the patients in Group I received rescue analgesia in 256.5min. Inj .Diclofenac sodium 75 mg IM was given as rescue analgesia if VAS>3.

But only one patient in Group II received analgesia in this period.. Blood pressure and heart rate showed no difference between the groups. Only two patients in each group developed bradycardia and hypotension, who responded effectively to intravenous Atropine (0.6 mg) or Ephedrine 6 mg respectively. The use of a larger volume for preloading 500 ml of lactated Ringer's solution prior to administration of anaesthesia as performed in our study could probably have resulted in extremely low incidence of bradycardia and Hypotension. Neither motor block nor time to void urine was prolonged with addition of Midazolam to Bupivacaine. There was no incidence of nausea vomiting, itching, urinary retention or post dural puncture headache during follow-up of these patients.

We found that addition of Midazolarn provided an enhancement and increased duration of sensory analgesia without delaying recovery to ambulation and ability to void. This analgesic effect may be attributed to the segmental antinociceptive effects of intrathecal Midazolam.

In this comparative study, the results observed were in consistent with previous studies done on patients undergoing knee arthroscopy by Batra Y.K et al [24], where intrathecal midazolam is added to bupivacaine. **It** is also observed in the previous studies done by Naguib-M [1], who examined the analgesic efficacy of the caudal administration of Midazolam, Bupivacaine, and mixture of both the drugs in 45 children postoperatively undergoing inguinal herniotomy. Time to first analgesic administration paracetamolsuppository was longer in the Midazolam-Bupivacaine group ($P < 0.001$).

The findings are also similar to those seen in previous study by Nishiyama-T et al [2] [3] [4], who studied about the optimal diluent volume for post-operative analgesia and sedation produced by epidurally administered Midazolam after upper abdominal surgery in the dosage of 75-100 mcg / kg.Valentine JM [5], studied the effect of intrathecal Midazolam, on post-operative pain, and found, that intrathecal Midazolam at 0.05 mg/kg had wider analgesic properties. Gulec et al [26], observed a higher sedation score, and longer duration of analgesia 21.5±I.2 hr. in the Bupivacaine-Midazolam group than Bupivacainemorphine group 14.5 ± 1.6 hr., and Bupivacaine group 8.15 ± 1.3 hr. after caudal administration for post-operative analgesia in children undergoing inguinal and urogenital surgery. In

our study, we noticed that adding preservative free Midazolam with hyperbaric 0.5% Bupivacaine intrathecally, provided increased duration of sensory analgesia and with increased sedation score without delaying motor recovery.

V. Summary And Conclusion

In conclusion, the postoperative analgesia is superior and of improved quality when Midazolam is added to spinal Bupivacaine.. It may find a place in regular clinical use as in the dosage of 0.05 mg / kg an adjuvant in selective spinal anaesthesia. with local anesthetics.

Competing interests

We (authors) declare that there is no conflict of interest in terms of financial and personal relationships with other people or organization that could not appropriately manipulate our work.

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