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Comparative Study of Midazolam on the Characteristics of Intrathecal Bupivacaine – A Prospective Randomized Study

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Abstract:
Introduction: *Spinal Anaesthesia is the most commonly used technique for lower abdominal & lower limb surgeries as it is very economical and easy to administer. A common problem during lower abdominal & lower limb surgeries under spinal anaesthesia is visceral pain, nausea and vomiting. Local anaesthetic agents for spinal anaesthesia are used have various side effects and less duration of action. In order to minimize the side effects and maximize the duration of analgesia, various adjuvants have been used along with local anaesthetics. A number of adjuvants like fentanyl, clonidine, dexmeditomide etc., have been used to improve the quality of subarachnoid block. Midazolam a water soluble benzodiazepine is used to increase the duration of analgesia and facilitate early ambulation and reducing hospital stay of the patient. The aim of the study was to compare the subarachnoid block characteristics with Midazolam to intrathecal Bupivacaine.*
Methodology: *After Institutional ethics committee approved and written informed consent, 100 patients between 16-60 years belonging to ASA I&II were included in the study. Patients were randomly allocated into 2 groups of 50 each. Group-1 received 3ml of 0.5% hyperbaric bupivacaine with 0.5ml of 0.9% Saline. Group-2 received 3ml of Hyperbaric Bupivacaine with 0.5m l (2.5mg) of preservative free midazolam. Total volume made upto 3.5ml to achieve subarachnoid block.*
Sensory block characteristics, motor block characteristics, Haemodynamic characteristics, adverse effects, duration of analgesia, statistical analysis and results were noted in all groups. Statistical analysis was done with one way analysis of variants. Duration of sensory blockade was significantly longer in group-II than in group-I. (P value < 0.001). Duration of Motor blockade was also higher in group-II only to some extent (P value < 0.01). The first request of analgesia was significantly longer in group-II than group-I.
Conclusion: *Addition of Midazolam to intrathecal bupivacaine produces better quality of analgesia and without gross haemodynamic disturbances comparative to bupivacaine alone.*
Key Words*: Analgesia, Bupivacaine, midazolam, Postoperative, Subarachnoid blockade.*

I. Introduction

Spinal Anaesthesia is the most commonly used technique for lower abdominal surgeries including orthopaedic surgeries, as it is very economical and easy to administer and safe. Howeverusing local anesthetics alone for subarachnoid block associated with relatively short duration ofaction. Addition of adjuvants like fentanyl, ketamine,clonidine etc, to intrathecal bupivacaine significantly prolongs the duration of spinal anaesthesia and also improved quality of spinal blockade in various clinical studies[1,2]. A common problem during lower abdominal and orthopaedic surgeries under spinal anaesthesia is visceral pain, nauseaand vomiting[3]. This problem can be overcome by the addition of anti-emetics preoperatively and the addition of adjuvants to improve the quality of block.

II. Methodology

After institutional ethics committee approval written informed consent 100 patients of ASA Grade-I & II belonging to both sexes were scheduled for lower abdominal andorthopaedic surgeries included in the prospective randomized controlled study.

Exclusion Criteria:

1. ASA Grade >III
2. Patients below 16 years and above 60 years of age.

3. Patients with H/O severe systemic diseases, metabolic disorders, neurological, congenital & cardiovascular disorders.
4. Patients with H/O allergy to study drugs i.e., bupivacaine, midazolam.
5. Patients with H/O any contra indications to spinal anesthesia.
6. Pregnancy.

Two investigators involved in the study. The observer and anesthesiologist who did intra operative and post operative monitoring were blinded to study. Patients were randomized into 2 groups50 each into Group A & B.

Baseline parameters like HR,PR,NIBP,SPO_2 were recorded in all the 2 groups. After shifting the patient to operating room routine monitors like NIBP, SPO_2 and ECG were applied to the patient. Anemergency resuscitation equipment were kept ready. 18G I V cannula was secured and all patients were preloaded with 10ml per Kg oflactated Ringer's solution. The patients were placed either in the left lateral or right lateral position, under strict aseptic precautions the lumbar puncture was carried out in midline through L_3-L_4 interspace with 25G quink babcocks needle. Group A(n=50) patients received 0.5% hyperbaric bupivacaine(3ml) with 0.9% normal saline(0.5ml). Group B(n=50) patients received 0.5% hyperbaric bupivacaine(3ml) with midazolam 2.5mg (0.5ml)

In all the groups the total volume administered was made upto 3.5ml to achieve subarachnoid block. Intra operatively bradycardia was treated with 1mg of I V atropine. Hypotension was treated with rapid boluses of I V fluids and incremental doses of 6mg of ephedrine. The following parameters were observed.

1. Sensory block was assessed by using Pinprick method. Onset time and duration of sensory blockade was recorded.
2. Motor block was assessed by using bromage scale (Table-I). Onset time and duration of motor blockade was noted between 2 groups.
3. Haemodynamic parameters like HR, BP were noted between the 2 groups.
4. Time to first request of analgesia (the duration of post operative analgesia) was compared between the 2 groups.
5. Adverse effects were also noted between the groups. The possible adverse effects like hypotension, bradycardia, nausea, vomiting, sedation, pruritis, urinary retention, respiratory depression etc., were noted.

Table – 1Bromage Scale

	BROMAGE SCALE
0	Free movement of legs and feet, with ability to raise extended leg
1	Inability to raise extended leg and knee flexion is decreased but full flexion of feet and ankle is present
2	Unable to flex knees but some flexion of feet and ankle is possible
3	Unable to move feet, legs or toes

III. Statistical Analysis:

Demographic data was analysed by using fischer's exart test. Sensory and motor characteristics analysed by using one way analysis of variants of student-t test. Time to first request of analgesia was assessed by using student-t test. It was expressed in Mean, Standard deviation, Absolute numbers and percentage. P>0.005 was considered significant.

Table – 2Age And Sex Distribution In Both The Groups

Age in years	GROUP – I		GROUP - II	
	Male	Female	Male	Female
16-25	5	4	6	4
26-35	5	4	5	4
36-45	8	3	7	3
46-55	7	5	6	4
>55	7	2	8	3
Total	32	18	32	18

The mean age of the patient in Group –I was 40.8±14 and in Group – II was 41.1± 14.3. Age incidence between two groups and age distribution between two groups were comparable. In the both the groups male patients were 64% and female patients were 36%. The sex ratio in both the groups is equal.

Table -3Distribution Of Height Of The Patients In Both The Groups

Height in Centimeters	GROUP – I		GROUP - II		TOTAL
	Male	Female	Male	Female	
145-150	1	1	2	1	5
150-160	6	12	7	13	38
160-170	2	5	21	4	32
>170	3	0	2	0	5

Table -4Distribution Of Weight Of The Patients In Both The Groups

Weight in Kgs	GROUP – I		GROUP - II		TOTAL
	Male	Female	Male	Female	
46-50	1	2	1	3	7
51-55	3	7	3	5	18
56-60	10	3	6	5	24
61-65	8	3	10	3	24
66-70	8	3	9	2	22
71-75	2	0	3	0	5

The height and weight of the patients in Group-I and Group-II are comparable.

Table -5Perioperative SBP (Systolic Blood Pressure)Of The Patients At Different Time Intervals.

Time in minutes	Group – I	Group – II	Significance
	Mean±SD	Mean±SD	
0	124.04±11.75	125.48±9.94	p>0.05
5	119.28±10.66	120.16±8.9	p>0.05
10	114.74±9.14	115.04±8.80	p>0.05
20	113.06±8.78	112.64±9.08	p>0.05
30	116.72±7.94	114.88±8.74	p>0.05
45	118.44±8.03	117.88±8.76	p>0.05
60	118.84±8.40	119.96±8.75	p>0.05
120	120.32±9.30	120.92±8.57	p>0.05

There was a fall in SBP in both the groups during first 20 minutes after intrathecal injection and there was gradual recovery after 20 minutes. This difference of recovery in SBP between the groups at different time intervals studied was statistically insignificant(P>0.05).

Table –6Perioperative DBP (Diastolic Blood Pressure) At Different Time Intervals

Time in minutes	Group – I	Group – II	Significance
	Mean±SD	Mean±SD	
0	79.90±5.21	78.28±6.29	p>0.05
5	76.88±5.30	76.32±5.90	p>0.05
10	74.76±5.11	74.08±5.50	p>0.05
20	74.24±5.19	73.16±5.37	p>0.05
30	74.36±5.12	73.76±5.51	p>0.05
45	74.88±5.25	73.44±5.38	p>0.05
60	75.12±5.28	74.76±5.49	p>0.05
120	80.20±5.38	79.96±5.67	p>0.05

There was a fall in DBP in both the groups during first 20 minutes after intrathecal injection and was gradual recovery after 20 minutes. This difference of recovery in DBP between the groups at different time intervals studied was statistically insignificant.(P>0.05).

TABLE -7 Perioperative Heart Rate At Different Time Intervals

Time in minutes	Group – I	Group – II	Significance
	Mean±SD	Mean±SD	
0	81.32±7.35	81.16±7.18	p>0.05
5	82.48±6.78	82.12±6.78	p>0.05
10	83.36±7.00	82.20±6.57	p>0.05
20	83.70±6.32	82.40±5.60	p>0.05
30	81.64±7.13	81.34±5.66	p>0.05
45	81.44±7.12	81.04±5.63	p>0.05
60	82.32±7.13	81.24±5.64	p>0.05
120	82.84±7.13	80.60±6.39	p>0.05

There was an increase in heart rate in both the groups during first 20 minutes and then gradual decrease towards normal. The heartrate was slightly lower in group – II at all time intervals. The difference between the groups at different time intervals studied was statistically insignificant.(p>0.05)

Table – 8Onset Of Sensory Blockade (Seconds) In Eithergroups

Group – I	Group – II	Significance
Mean±SD	Mean±SD	
149.16±11.30	170.84±13.83	P<0.001

The onset of Sensory blockade was 149.16±11.30 sec in Group-I and 170.84±13.83 sec in Group-II was delayed in Group-II. The difference between the groups was statistically highly significant.(P<0.001)

Table – 9Onset Of Motor Blockade (Seconds) In Eithergroups

Group – I	Group – II	Significance
Mean±SD	Mean±SD	
217.40±38.80	239.96±11.83	P<0.001

The onset of Motor blockade was 217.40±38.80 sec in Group-I and 239.96±11.83 sec in Group-II was delayed in Group-II. The difference between the groups was statistically highly significant.(P<0.001)

Table – 10Regression Of Sensory Levels To L_2 Dermatome In Minutes

Group – I	Group – II	Significance
Mean±SD	Mean±SD	
140.48±7.28	165.48±5.03	P<0.001

The time to regression of sensory level to L_2 dermatome in Group-I was 140.48±7.28 min and in Group-II was 165.48±5.03 min. The regression time was more in group-II than in group-I. The difference between the groups was statistically highly significant (P<0.001).

Table – 11Time For Complete Motor Recovery In Minutes

Group – I	Group – II	Significance
Mean±SD	Mean±SD	
180.04±5.15	181.12±5.20	P>0.05

The time for complete motor recovery was 180.04±5.15 min in Group-I, 181.12±5.20 min in Group-II. The recovery time for motor blockade was similar in both the groups. The difference between the groups was statistically insignificant(P>0.05).

Table – 12Time Of First Request Analgesics By The Patients In Either Group In Minutes

Group – I	Group – II	Significance
Mean±SD	Mean±SD	
206.96±8.31	361.30±8.25	P<0.001

The time of first request analgesics by the patients in Group-I was 206.96±8.31 min and 361.30±8.25 min in Group – II, which was longer in Group – II than in Group – I. The difference between the groups was statistically highly significant (P<0.001).

Table – 13 Adverse Effects

Adverse Effects	**Group – I**	**Group – II**
Nausea Vomiting	2	1
Hypotension	4	4
Shivering	3	2
Pruritus	0	0
Seizures	0	0
Respiratory depression	0	0

IV. Discussion

Regional Anaesthesia, particularly spinal anaesthesia is most commonly used technique worldwide for lower abdominal and orthopaedic surgeries. Using local anaesthetics alone will provide less duration of analgesia. In order to improve the quality of analgesia as well as to provide extended postoperative analgesia, various adjuvants are being added to intrathecal local anaesthetics. Of which midazolam have gained prominence due to their multiple beneficial effects like prolonged postoperative analgesia, stable

haemodynamics, reducing postoperative analgesic requirements, facilitate early ambulation and reduced hospital stay. The procedure should not cause complications, simple, easy and not time consuming. Should be prevent discomfort due to multiple pricks of IM/IV injections and relieve more work load on nursing staff.

The principle mechanism by which intrathecalmidazolam provides analgesia is through the GABA-Benzodiazepine system in the spinal cord and there is ample evidence to show the GABA receptors in the spinal cord are involved in nociceptive mechanisms.

This prospective study was conducted to compare intrathecal bupivacaine and bupivacaine with midazolam in lower abdominal and lower limb surgeries. The patients were selected at random to avoid any kind of bias and to allow comparability of results obtained.

Intrathecal administration of midazolam relieved post operative pain of somatic origin. This study was well correlated with **Goodchild CS; Noble j (1987 Mar)**[4].

Edwards M, Serro JM, Gent JP, Good child CS (1990)[5] studied the mechanism by which midazolam causes spinally mediated analgesia. Our study was well correlated with this study.

Valentine, J.MJ; Lyons, GL Bellamy, M.C.(1996)[6] studied the effect of intrathecal midazolam on postoperative pain. 52 patients scheduled for elective caesarean section under spinal anaesthesia were randomly allocated to receive either bupivacaine(B), bupivacaine with diamorphine(BD), bupivacaine with midazolam or all three(BMD) by intrathecal injection. Post operatively no differences in Visual analogue score (VAS), sedation, post operative nausea and vomiting could be demonstrated between groups. No side effects attributable to midazolam were identified. Intrathecal midazolam appears safe and has clinically detectable analgesic properties. Our study was well correlated with the study.

Batra.YK; Jain.K; Chari.P; Dhillon MS; Shaheen.B; Reddy-GM (1999)[7] to evaluate the post operative analgesic effect of intrathecal midazolam and bupivacaine mixture in patients undergoing knee arthroscopyprovided better post operative analgesia without any adverse effects well correlated with our study.

Sen A, Rudra A, Sarkar SK, Biswas B (2001 Dec.)[8] conducted a study about intrathecal midazolam for postoperative pain relief in caesarean section deliveries. It produces highly significant post operative pain relief. Our study well correlated with the study.

Kim M.H; Lee Y.M. (January 2001)[9] showed the intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy well correlated with our study.

Amr M.Abdelfatah, MD; Ahmed A.Fawaz, MD; Hesham M.AL-Azazi, MD(2003)[10] studied the post operative analgesic effect of intrathecal fentanyl versus midazolam in knee arthroscopy. Midazolam bupivacaine mixture appears to be superior to fentanyl-bupivacaine mixture by its reduced magnitude of undesirable effects, correlates with our study.

Bharti N, Madan R, Mohanty PR, Kaul HL (2003)[11] studied the effect of addition of midazolam to intrathecal bupivacaine on the duration and quality of spinal blockade, significantly improves the duration of quality of spinal anaesthesia and provides prolonged perioperative analgesia without significant side-effects well correlated with our study.

Yegin Sanli S, Dosemeci L, Kayacan N, Akbas M, Karsli B (2004)[12] conducted as study to evaluate the analgesic and sedative effects of intrathecal midazolam with bupivacaine in spinal anaesthesia in patients undergoing perianal surgery produces more effective and longer analgesia with mild sedative effect well correlates with our study.

Prakash Smitha; Joshi N; Gogia AR; Prakash Sunil; Singh R(2006)[13] conducted a study on analgesic effect of intrathecal midazolam with bupivacaine. It provides moderate prolongation of post operative analgesia when used as an adjuvant to bupivacaine. Our study was well correlated with this study.

Mi Ja Yun; Yoon Hee Kim; Jin Hee Kim; Kyoung Ok Kim; Aa Young Oh; Hee P Park (2007)[14] examined the effect of 1 or 2 mg of intrathecal midazolam added to bupivacaine on the duration of spinal anaesthesia to T10 in orthopaedic patients. Addition of 2mg midazolam to bupivacaine prolonged the duration of spinal block to T10 well correlated with our study.

Mohammed Saeed Abd EI Aziz (2009)[15] conducted a study on intrathecal midazolam as adjuvant to bupivacaine 0.5% in orthopaedic surgeries increases the analgesic effects and lowers side effects well correlates with our study.

Shadangi BK; Garg R; Pandey R; Das T (2011)[16] conducted a prospective randomized case control study on effects of intrathecal midazolam resulted in prolonged post operative analgesia without increasing motor block in lower limb and gynaecological procedures.

V. Conclusion

Addition of 2.5mg of midazolam with 0.5% hyperbaric bupivacaine produces better quality of analgesia, longer duration of analgesia reduced post operative analgesia requirements without gross hemodynamic disturbances compared to bupivacaine alone in lower abdominal and lower limb surgeries.

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