VOLUME - 11, ISSUE - 05, MAY - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medical Science

COMPARATIVE STUDY OF INTRATHECAL HYPERBARIC BUPIVACAINE 0.5% VERSUS MIDAZOLAM PLUS HYPERBARIC BUPIVACAINE 0.5% MIXTURE FOR INFRAUMBILICAL SURGERIES.

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ABSTRACT

Background: Sub arachnoid block is a commonly used anesthesia technique for all infra umbilical surgeries & there is search for agents and techniques which would prolong local anesthetic action without its deleterious effects. The present study was designed to compare effect of 0.5% of hyperbaric bupivacaine intrathecal versus 0.4ml of intrathecal midazolam with 0.5% of hyperbaric bupivacaine for infra umbilical surgeries. **Material And Methods:** Present study was single-center, a double-blind trial, conducted in patients of age group 18-60 years with ASA grade I/II posted for elective infraumbilical surgery. 60 patients were divided into Group I received 3ml of 0.5% Bupivacaine heavy and 0.4 ml of 0.9% saline & Group II received 3ml of 0.5% Bupivacaine heavy and 0.4 ml of midazolam (2mg). **Results:** The mean duration of maximum sensory blockade, maximum motor blockade was more in group II as compared to group I & difference was statistically significant ($p<0.05$). Mean duration of surgery was less in group II as compared to group I & difference was statistically significant ($p<0.05$). Duration of Motor blockade, duration of sensory blockade, time for two segment regression, time of rescue analgesia was more in group II as compared to group I & difference was statistically significant ($p<0.05$). Patients complained of pain faster in Group I than in Group II, VAS score. **Conclusion:** Midazolam still finds a place in regular clinical use as an intrathecal adjuvant with hyperbaric bupivacaine due to its hemodynamic stability and better post-operative analgesia with no significant adverse effects.

KEYWORDS : Intrathecal Midazolam, VAS score, rescue analgesia, intrathecal adjuvant, hyperbaric bupivacaine

INTRODUCTION

Sub arachnoid block is a commonly used anesthesia technique for all infra umbilical surgeries. The most commonly used drug for spinal anesthesia is hyperbaric bupivacaine 0.5% but, a major disadvantage of single injection spinal anesthesia is it's limited duration of action.[1] Various adjuvants were used to prolong the duration of action like large array of opioids ranging from morphine, fentanyl and sufentanyl to hydromorphone, buprenorphine and tramadol has been used with varying success. However, their use has been limited by their adverse effects like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use.[2]

Other adjuvants used are epinephrine, clonidine and dexmedetomidine, steroids (dexamethasone)[3], anti-inflammatory agents (parecoxib and lornoxicam), ketamine, magnesium sulphate[4] and neostigmine[5] have also been used with mixed success. The concern regarding the safety profile of these adjuvants is due to its potential neurotoxicity and neurological complications which necessitate further research in this direction.

Current research is directed towards a search for agents and techniques which would prolong local anesthetic action without its deleterious effects.[3] A relatively water soluble benzodiazepine, midazolam is used both in critical care and operating room.[6]

The present study was designed to compare effect of 0.5% of hyperbaric bupivacaine intrathecal versus 0.4ml of intrathecal midazolam with 0.5% of hyperbaric bupivacaine in respect to duration of sensory and motor blockade, duration of post operative analgesia and hemodynamic stability.

MATERIAL AND METHODS

Present study was single-center, a double-blind trial, conducted in department of Anesthesia, at M G M hospital, Navi – Mumbai, India. Study duration was of 2 years (December 2017 To November 2019). Study was approved by institutional ethical committee.

Inclusion Criteria

- Age group 18-60 year with normal cardio respiratory status, ASA grade I/II posted for elective infraumbilical surgery, willing to participate in study

Exclusion Criteria

- History of bleeding disorders
- Allergy to local anesthetics
- Patient with heart disease
- PregnancyStudy procedure was explained to patients in local language prior to surgery & a written informed consent to participate in present study was taken. All patients who fulfilled the inclusion criteria and had of intraoperative shivering under spinal anesthesia were randomized using computer generated chart with allocation ratio of 1:1 into either of the two groups.

A total of 60 patients were divided into

- Group I (30 PATIENTS) received 3ml of 0.5% Bupivacaine heavy and 0.4 ml of 0.9% saline
- Group II (30 PATIENTS) received 3ml of 0.5% Bupivacaine heavy and 0.4 ml of midazolam (2mg)

Patients were pre-loaded with 10ml/kg of crystalloids for 15minutes. Subarachnoid block was given between L3-L4 space with 25G/26G Quincke Spinal needle under aseptic precautions after free and clear flow of CSF in sitting/lateral posture. Drug was given as per group allocation.

The pulse rate, blood pressure, central venous pressure, SpO2, and EtCO2 were monitored intraoperatively & postoperatively at 30 min, 1, 2, 3 and 4 hourly. Postoperatively, patients were shifted to recovery room & visual analog scale (VAS) score was recorded at 30 min, 1, 2, 3 and 4 hourly. Patients were not given any other analgesics such as nonsteroidal anti-inflammatory drugs.

Hemodynamic parameters, visual analog scale (0-10), level of sensory block (assessed by pinprick), and were monitored for 24 h postoperatively and need for rescue analgesia, side effects, and interventions if any were noted. Hemodynamics,

Spinal characteristics, and adverse effects were monitored.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Quantitative variables were compared using Independent t test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test/Fisher's exact test. A p value of < 0.05 was considered statistically significant.

RESULTS

The mean age in the GROUP II was 41.13±15.96 yrs as compared to 37.6±8.41 yrs in Group I and the difference was statistically not significant (P value – 0.288). There was no statistically significant difference between the groups in gender distribution, ASA grade.

Table 1: General Characteristics

Characteristics	Group II (mean ± SD/ %)	Group I (mean ± SD/ %)	P value
Mean Age (Years)	41.13 ± 15.96	37.6 ± 8.41	0.288
Gender			
Female	11 (36.67%)	12 (40.00%)	0.791
Male	19 (63.33%)	18 (60.00%)	
ASA grade			
I	18 (60.00%)	23 (76.67%)	0.165
II	12 (40.00%)	7 (23.33%)	

The mean duration of maximum sensory blockade, maximum motor blockade was more in group II as compared to group I & difference was statistically significant ($p<0.05$). Mean duration of surgery was less in group II as compared to group I & difference was statistically significant ($p<0.05$). Duration of Motor blockade, duration of sensory blockade, time for two segment regression, time of rescue analgesia was more in group II as compared to group I & difference was statistically significant ($p<0.05$)

Table 2: Anesthesia Characteristics

Anesthesia characteristics	Group II	Group I	P value
Time taken for max sensory blockade (mins)	4.8 ± 1.24	3.37 ± 0.85	<.0001
Time taken for max motor blockade (mins)	8.37 ± 1.07	5.13 ± 0.73	<.0001
Duration of surgery (in mins)	73.33 ± 12.48	88.37 ± 18.19	<0.001
Duration of motor blockade (in mins)	183.33 ± 14.4	141.27 ± 14.96	<.0001
Duration of sensory blockade (in mins)	223.5 ± 15.04	172.03 ± 19.93	<.0001
Time to two segment regression (mins)	105.33 ± 7.65	55.8 ± 10.66	<.0001
Time of rescue analgesia (mins)	300.87 ± 17.07	151.33 ± 17.02	<.0001

Intra-operative heart rate was lower in Group I at 0- 30 minutes as compared to Group II and was statistically significant at 0 to 30 minutes after subarachnoid block.

Table 3: Comparison Of Heart Rate At Various Durations

Interval (minutes)	Group II (Mean ± SD)	Group I (Mean ± SD)	P value
0	91.6 ± 10.18	72 ± 5.07	<.0001
2	90.63 ± 9.42	73.07 ± 4.23	
4	89.53 ± 8.47	74.3 ± 5.23	
6	88.27 ± 9.1	75 ± 4.89	
8	86.8 ± 8.51	75.87 ± 5.17	
10	86.7 ± 8.3	76.47 ± 4.38	
15	84.77 ± 9.07	77.17 ± 4	
20	83.57 ± 8.59	76.7 ± 4.08	
25	81.9 ± 8.4	77.7 ± 5.14	
30	79.87 ± 8.22	78.03 ± 5.24	
45	79.67 ± 8.33	79.03 ± 5.8	
60	78.37 ± 8.6	79.1 ± 5.77	
75	79.21 ± 8.35	79.1 ± 6.02	
90	78.8 ± 8.87	78.23 ± 5.46	
105	80.33 ± 4.93	78.93 ± 4.83	

There was no statistical significance of SBP in Group II and Group I after subarachnoid block from 0-30 minutes and 90 – 150 minutes. Statistical significance was noted between 45 -75 minutes with lower side in Group II.

Table 4: Comparison Of SBP At Various Durations

Systolic Blood pressure interval (in minutes)	Group II (Mean ± SD)	Group I (Mean ± SD)	P value
0	133.8 ± 9.25	130.8 ± 11.39	0.268
2	129.67 ± 9.53	128.07 ± 9.42	0.516
4	126 ± 11.85	127.17 ± 7.75	0.653
6	122.4 ± 14.34	124.13 ± 7.61	0.561
8	120.8 ± 14.16	121.97 ± 7.26	0.689
10	120.4 ± 12.97	120.27 ± 9.44	0.964
15	118.9 ± 12.34	118.2 ± 8.38	0.798
20	118.63 ± 10.58	118.53 ± 10.58	0.971
25	118.87 ± 10.14	117.47 ± 12.02	0.628
30	118.47 ± 9.61	119.03 ± 10.71	0.830
45	116.2 ± 8.28	120.53 ± 7.74	0.041
60	115.67 ± 7.77	121.93 ± 6.7	0.001
75	114.48 ± 8.92	120.6 ± 9.11	0.012
90	117.33 ± 8.67	119.47 ± 8.91	0.449
105	117.33 ± 9	121.48 ± 7.45	0.243

The mean diastolic pressure was lower in Group II as compared to Group I during the intraoperative period.

Table 5 : Comparison Of DBP At Various Durations

Diastolic Blood pressure interval (in minutes)	Group II (Mean ± SD)	Group I (Mean ± SD)	P value
0	75.27 ± 7.49	78.8 ± 6.94	0.063
2	73.53 ± 7.51	77.2 ± 6.21	0.044
4	69.9 ± 7.89	75.87 ± 5.66	0.001
6	69.8 ± 7.45	72.8 ± 6.34	0.098
8	67.87 ± 6.87	71.87 ± 7.24	0.032
10	67.87 ± 7.37	72 ± 6.5	0.025
15	67.77 ± 7.36	71.4 ± 4.11	0.022
20	67.67 ± 7.74	71.6 ± 5.88	0.031
25	68.23 ± 6.97	72.73 ± 6.27	0.011
30	67.67 ± 6.56	73.93 ± 7.51	0.001
45	67.07 ± 5.82	73.4 ± 6.28	0.0002
60	66.6 ± 5.66	74.2 ± 6.46	<.0001
75	67.1 ± 5.99	72.87 ± 6.45	0.001
90	65.6 ± 5.46	73.13 ± 5.58	0.0001
105	65.67 ± 4.08	73.78 ± 5.5	0.002

The pulse was lower in Group II when compared to Group I & difference was statistically significant ($p<0.05$).

Table 6: Comparison Of Post Operative Heart Rate At Various Durations (Post Op)systolic Blood Pressure Was Lower In Group Ii When Compared To Group I And & Difference Was Statistically Significant ($p<0.05$).

Post operative pulse rate (minutes)	Group II	Group I	P value
30 mins	78.6 ± 8.39	81.1 ± 5.24	0.348
1 hour	78.43 ± 8.07	82.33 ± 5.25	0.045

2 hours	78.33 ± 7.97	85.2 ± 5.47	0.001
3 hours	81.53 ± 7.48	87.87 ± 4.93	0.001
4 hours	80.27 ± 7.82	86.03 ± 5.56	0.002

Table 7 : Comparison Of SBP At Various Durations (Post Op)

Post operative SBP interval (minutes)	Group II	Group I	P value
30 mins	117.33 ± 7.21	125.2 ± 5.62	<.0001
1 hour	119.13 ± 7.82	127.8 ± 6	0.0001
2 hours	120.87 ± 8.06	131.6 ± 6.82	<.0001
3 hours	123.67 ± 6.79	134.47 ± 7.16	<.0001
4 hours	120.8 ± 6.03	129.67 ± 7.07	<.0001

Diastolic Blood Pressure was lower in Group II when compared to Group I and & difference was statistically significant ($p<0.05$).

Table 8: Comparison Of DBP At Various Durations (Post Op)

Post operative DBP interval (minutes)	Group II	Group I	P value
30 mins	70.33 ± 6.19	76.07 ± 5.98	0.001
1 hour	70.53 ± 6.08	78.6 ± 5.8	<.0001
2 hours	70.27 ± 6.05	80.2 ± 5.34	<.0001
3 hours	70.13 ± 6.3	82 ± 6.13	<.0001
4 hours	69.47 ± 6.21	79.13 ± 6.03	<.0001

Mean arterial pressure was lower in Group II when compared to Group I and & difference was statistically significant ($p<0.05$).

Table 9: Comparison Of MAP At Various Durations(Post Op)

Post operative MAP interval (minutes)	Group II	Group I	P value
30 mins	86 ± 5.21	92.44 ± 4.22	<.0001
1 hour	86.73 ± 5.16	95 ± 4.33	<.0001
2 hours	87.13 ± 5.3	97.33 ± 4.46	<.0001
3 hours	87.98 ± 4.91	99.49 ± 5.26	<.0001
4 hours	86.58 ± 4.48	95.98 ± 3.97	<.0001

VAS (Visual Analogue score) at 30 minutes was found to be zero in both the groups, At 1 hour – VAS score of 1 was achieved by 90% of Group I and VAS score of 2 was achieved by 10% of Group I. At 2 hours, VAS score was still 0 in Group II compared to Group I, At 3 hours, VAS score of 1 was seen in 60% and VAS score of 2 was seen in 40% of patients in Group B patients.

Table 10: VAS score

	VAS score	Group II	Group I	Total	P value
30 mins	.00	100%	100%	100.00%	
1 hour	.00	100%	0%	50.00%	
	1.00	0%	90%	45.00%	<0.0001
	2.00	0%	10%	5.00%	
2 hour	.00	100%	0%	50.00%	
	1.00	0%	20%	10.00%	
	2.00	0%	43%	21.67%	
	3.00	0%	10%	5.00%	<0.0001
	4.00	0%	20%	10.00%	
	5.00	0%	7%	3.33%	
3 hour	1.00	60%	0%	30.00%	
	2.00	40%	23%	31.67%	
	3.00	0%	20%	10.00%	<0.0001
	4.00	0%	37%	18.33%	
	5.00	0%	20%	10.00%	
4 hour	.00	57%	0%	28.33%	
	1.00	43%	0%	21.67%	<0.0001
	2.00	0%	10%	5.00%	
	3.00	0%	57%	28.33%	
	4.00	0%	33%	16.67%	

The number of patients requesting for their first dose of rescue analgesia in Group I was 10 % at 2 hours, 20% at 3 hours, 13.33% at 4hours as compared to no need of rescue analgesia till 4 hours of post surgery in Group II, which was statistically significant.

Table 11: First Dose Of Rescue Analgesia

First Dose Of Rescue Analgesia Interval (minutes)	Group II	Group I	P value
30 mins	Nil	Nil	--
1 hour	Nil	Nil	--
2 hours	0%	20%	0.024
3 hours	0%	40%	0.0001
4 hours	0%	27%	0.005

DISCUSSION

Prolongation of duration of spinal block is desirable for both long procedures and postoperative pain relief. It is easy to perform, less cumbersome, inexpensive and offers a high level of patient satisfaction. Previously different drugs have been used to prolong the duration of action like clonidine, epinephrine, neostigmine, dexmedetomidine, opiods.

Intrathecal midazolam causes antinociception by endogenous neurotransmitters acting at spinal cord delta opioid receptors.[7] The highest density of GABA-like immune-reactivity, GABA receptors, and benzodiazepine receptors was localized as a dense band within lamina II of the dorsal horn (especially inner lamina II) with moderately high densities in laminae I and III. So it was concluded that action of intrathecal midazolam is by GABA and BZD receptors.[8] Midazolam, Benzodiazepine analgesia administered by centroneuroaxis route was found to enhance the effects of local anesthetics given in spinal anesthesia post operatively. It increases the duration and quality of spinal block.[9]In our study, Intrathecal midazolam with Bupivacaine i.e., Group II was found to have better post- operative analgesic ($P < 0.05$) with far less rescue analgesic consumption in 24 h. In our study, Group II required less rescue analgesia because postoperative analgesic action was up to 4-6 hours and patients using bupivacaine with normal saline i.e., Group I required more analgesia. In the current study, we found prolonged sensory and motor blockade with Group II as compared to Group I.

In a similar study by Shadangi et al.,[10] duration of sensory blockade was prolonged in the midazolam group (90.8 versus 115.8 min, p-value is 0.001), while the duration of motor blockade was comparable (151.8 versus 151.3 min, p-value is 0.51). The duration of effective analgesia was significantly longer in the midazolam group compared to the control group (121.3 versus 221.1 min, p-value is 0.001).

Anas Amer M Ajam et al.,[11] compared the effect of adding 1 and 2 mg midazolam to hyperbaric bupivacaine and concluded that the longer duration of analgesic was found using midazolam adjuvant with bupivacaine compared to free adjuvant group in women underwent spinal anesthesia where we found similar results in our current study.

In our study, the mean time taken for two segment regression in Group II was 105.33 ± 7.65 min which was longer than in Group I 55.8 ± 10.66 min with $P<0.001$. It was highly significant in our study. Batra et al.,[12] conducted study on postoperative analgesia following intrathecal administration of midazolam with hyperbaric bupivacaine in combination; in patients undergoing knee arthroscopy which showed time to regression of sensory analgesia to L5-S2 level was longer in midazolam - bupivacaine group as compared to bupivacaine group. Duration of sensory blockade The total duration of sensory blockade i.e. time for regression to S1 dermatome was significantly prolonged in Group II 223.5±15.04 minutes as compared to control group I 172.03±19.93 (p value <

0.0001) in our study. Bharti et al.,[13] reported in their study that intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anesthesia in patients undergoing lower abdominal surgery. The duration of sensory block (i.e., time to regression to the S2 segment) was significantly longer in the midazolam group than the bupivacaine group (218min versus 165min,) and duration of motor block was also prolonged in midazolam group than in the control group (on 180min versus 250min,). Similar results were found in studies conducted by Batra et al.,[12] Yun et al.,[14] Kim and Lee et al.,[15] & Gupta et al.,[16]

In our study time taken for motor blockade to reach the modified Bromage scale 0 was significantly prolonged in Group II (183.33±14.4) minutes when compared to Group I (141.27±14.96) minutes (p value < 0.0001). Prolonged motor blockade was also found in other studies conducted by Bharati et al.,[12] (on 250min versus 180min). Anirban chottopadhyay et al.,[17] also found that prolonged motor blockade increases the duration of analgesia (median 320min versus 220min) and motor block (median 255min versus 195min).

The changes seen in mean heart rates in both the groups were statistically significant from 0-30 minutes which was lower in Group B as compared to Group A , but after 30 minutes it was statistically insignificant in this study which is supported by Batra et al.,[12] & Bharti et al.,[13] In contrast to present study, Batra et al.,[12] Bharti et al.,[13] & Gupta et al.,[16] there was no comparable difference between pulse rate , SBP, DBP, MAP intraoperatively.The VAS score is higher in Group I , total number of analgesics used in 4 hours post – operative was more in Group I and the time taken for 1st rescue analgesia is earlier in the Group I with 6 patients asking for rescue analgesia at 2 hours and 12 at 3rd hour and 8 patients at 4th hour when compared to Group II where there was no need of rescue analgesia 4 hours postoperatively which was statistically significant (p value < 0.0001). Therefore, Intrathecal midazolam has a longer duration of analgesia.

This observation was supported by Batra et al.,[12] noted higher VAS score in patients received bupivacaine alone than patients received midazolam and bupivacaine combination. Requirement for rescue analgesic was also delayed in midazolam group. They concluded that intrathecal administration of midazolam along with bupivacaine produces better postoperative analgesia.

This observation was also supported by Agrawal et al.,[18] they noted postoperative pain relief following intrathecal administration of 1mg preservative free midazolam with bupivacaine in patients scheduled for elective lower abdominal, lower limb, and endoscopic urological surgeries. Time to first rescue analgesic in patients who received bupivacaine alone were significantly earlier than the patients who received bupivacaine and midazolam combination (4±3.5 hours versus 17.6±8.87 hours, p<0.0001). They concluded that intrathecal midazolam and bupivacaine provides longer duration of postoperative analgesia as compared to intrathecal bupivacaine alone without prolonging time for dermatomal regression. The authors also reported no episodes of bradycardia, hypotension, pruritus, urinary retention, and sedation related to midazolam.

Gupta et al.,[16] investigated the effect of intrathecal midazolam in lower limb orthopedic surgery. In this study they investigated the postoperative analgesic efficacy of intrathecal midazolam 2.5 mg as an adjunct to bupivacaine for spinal anesthesia in 80 patients undergoing lower limb orthopedic surgery. Mean duration of postoperative analgesia was significantly lower in patients who received bupivacaine alone in comparison to patients who received midazolam-bupivacaine combination (min versus min,). Supplemental analgesic dose requirements with diclofenac were significantly less in midazolam-bupivacaine group (2.17 ± 0.50 versus 3.00 ± 0.39,) and concluded that intrathecal midazolam 2.5 mg provided moderate prolongation of postoperative analgesia when used as an adjunct to bupivacaine.

The side effects like bradycardia, hypotension was not seen in any of the groups. This is supported by the study conducted by Agrawal et al.,[18] conducted a study on postoperative pain relief following intrathecal administration of 1mg preservative free midazolam with bupivacaine where the authors reported no episodes of bradycardia, hypotension, pruritus, urinary retention, and sedation related to midazolam. Similar reports were seen in study conducted by Bharti et al.,[13] where there were no significant side effects.

Limitations of present study were small sample size, single hospital based & elective cases, larger, multicentric studies are required to confirm present study findings.

CONCLUSION

Intrathecal Midazolam supplementation with bupivacaine significantly prolongs the duration of sensory block, motor blockade and the time to segment regression was prolonged whereas there was delayed onset of sensory and motor blockade. Hemodynamic stability wasbetter seen with the use of intrathecal midazolam. Further lesser VAS score was observed with the intrathecal midazolam use with no need of rescue analgesia till 4 hours of post surgery. We conclude that midazolam still finds a place in regular clinical use as an intrathecal adjuvant with hyperbaric bupivacaine due to its hemodynamic stability and better post-operative analgesia with no significant adverse effects.

Conflict of Interest: None to declare

Source of funding: Nil

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