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Original Article

Effect of Intrathecal Midazolam added to Bupivacaine on quality and duration of Spinal Anaesthesia in lower abdominal surgeries

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ABSTRACT

Background and Aims: Intrathecal use of various drugs is in vogue nowadays for purpose of prolonging spinal action for postoperative analgesia. The aim of this study was to evaluate the effect of addition of midazolam to bupivacaine when administered intrathecally for lower abdominal surgeries. **Methods:** In the present study, a total of 100 patients of either sex in ages 20-50 years of ASA grade1 and 2 posted for various lower abdominal surgeries were recruited. All cases were randomly allocated to two groups in double blind manner. Group A (control group) received inj. Bupivacaine 0.5% heavy 3.5 ml+ 0.4 ml normal saline intrathecally, whereas Group B (study group) received bupivacaine 0.5% heavy 3.5 ml + 0.4 ml midazolam 0.5% (2 mg) intrathecally. Onset of sensory and motor block was noted and time to achieve maximum blockade was recorded. Duration of sensory block was assessed by time taken for regression of spinal blockade to S2 segment. Degree of analgesia was assessed as 1-4 (excellent to poor), and degree of motor block assessed by Bromage scale. Vitals like pulse, BP, RR, SpO_2 monitoring, and other complications like postoperative nausea and vomiting (PONV), sedation were noted. Postoperative analgesia was assessed using VAS score. Inj. Diclofenac 75 mg IM was given at VAS 5 or more as a rescue analgesic when demanded by patient. **Results:** Results were analyzed using standared t-test. Duration of effective analgesia was 136.38 ±10.76 minutes in control group (Group A) and 216.60±10.71 minutes in study group (Group B) (p value< o.oo1). Adverse effects were comparable in between the two groups. **Conclusion:** Addition of midazolam to bupivacaine for intrathecal use is a good alternative to improve the duration and quality of spinal anaesthesia.

Key words –Intrathecal midazolam, postoperative analgesia, spinal additives, VAS, local anesthetics, pain

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INTRODUCTION

It is divine to allay pain…. **Gallen**

Spinal anaesthesia is a mainstay of many lower limb and lower abdominal surgeries. But the limiting factor for spinal anaesthesia is less duration of analgesia in postoperative period requiring early analgesia interventions. These interventions may, if delayed, not only cause discomfort and apprehension in patient but may also increase patient morbidity and cost of care. To improve the duration of spinal action many drug additives are under study but ideal drug search is still the Holy Grail.

Intrathecal use of various drug additives with local anaesthetic agent is simple and effective method to provide analgesia for postoperative pain. With an advantage of minimal use of drugs and lesser side effects without compromising the spinal action [2].Use of opioids is fascinating but not without side effects like nausea, vomiting, sedation, respiratory depression and itching(3). Midazolam is a potent Benzodiazepine (BZD) with a sedative and anxiolytic property[1]. However, many studies in past have demonstrated BZD receptors in spinal cord in animals and in humans.[2,4] Many studies explained antinociceptive properties when midazolam was injected intrathecally[5]. The mechanism of action is also well explained.[6,7] Authors in many studies have demonstrated and approved its safety in human and animal studies.[14,15] On this basis, present study was undertaken to evaluate the effect of intrathecal administration of midazolam with local anaesthetic agent.

MATERIAL AND METHODS:

In this randomized, prospective double blind study 100 patients of either sex between age group of 20 to 50 years posted for various lower abdominal surgeries were recruited. Patients were randomly allocated to two groups of 50 each by computer method.

All the patients were thoroughly evaluated before surgery and valid written informed consent obtained after explaining the procedure and VAS to the patient. All routine and special lab investigations were done in all patients.

Inclusion criteria: Adult patients of either gender, aged between 20 - 50years, belonging to ASA Class I or II without any co-morbid diseases, scheduled for elective lower abdominal surgeries were included in the study.

Exclusion criteria: Patients with co-morbid diseases like diabetes, hypertension and any other chronic illness; patients posted for emergency surgeries; patients with height less than 150 cm; patients having spine deformity and absolute contraindications for spinal anaesthesia were excluded from study .

Methodology:-

- During preoperative anaesthesia visit, detailed history of patient taken, thorough physical examination carried out and physical parameters like height and weight recorded. Procedure was explained to the patient.
- Valid written informed consent was obtained.

Routine investigations like CBC, LFT and ECG, CXR PA View and BSL^R if age is more than 40 years were obtained.

All patients were randomly allocated into two groups. By a computer generated table, drug preparations were done by senior anesthetist without labeling and double blinding both user and monitoring anesthetist.

Group A (control group) – consisting of 50 patients, received 3.5 CC of (0.5%) bupivacaine hyperbaric + 0.4 CC of 0.9% Normal saline intrathecally.

Group B (study group) – consisting of 50 patients received 3.5 CC of (0.5%) bupivacaine hyperbaric + 0.4 CC of 0.5% i.e. 2mg of preservative free midazolam intrathecally.

In the operation theatre, patient's baseline vital parameters like blood pressure, pulse rate, respiratory rate and oxygen saturation (SpO_2) were recorded and also monitored, preoperatively.

All patients were preloaded with 10-15 ml/kg of ringer lactate solution and premedicated with Inj. Ranitidine 50mg and Inj. Metoclopramide 10mg IV half an hour prior to the surgery. No sedation was given in premedication.

- Under all aseptic precautions, spinal anaesthesia was given in lateral position with 25 G spinal needle. Time of intrathecal injection of drug and time of onset of sensory blockade was noted. Highest level of sensory blockade and time required to achieve it was recorded. Duration of sensory blockade was assessed by time to S1-S2 segment regression.

Intraoperative analgesia was assessed as:

1= Excellent, 2 = Adequate, 3= Inadequate, 4 = Major discomfort.

Degree of motor blockade was assessed by using Modified Bromage Scale (MBS):

1 = Complete motor block.

2 = Almost complete motor block, able to move feet only.

3 = Able to move the knees.

4 = Able to raise the leg, but unable to keep it raised.

5 = No detectable weakness of hip flexion.

6 = No weakness at all.

Sedation was assessed using Ramsay sedation score:

0- None (patient alert)

1- Mild – (Patient may be sleepy but easy to arouse)

2- Moderate – (Drowsy but still fully arousable)

3- Severe – (Difficult to arouse)

No other sedation or analgesic was given to the patient intraoperatively.

Fall in oxygen saturation less than 95 percent was treated with oxygen supplementation by face mask at 4 L/min.

In postoperative period patients were monitored for complications like nausea, vomiting, shivering, sedation, bradycardia, hypotension, urinary retention and respiratory depression.

In postoperative period analgesia was assessed by using Visual Analogue Scale (VAS), 0 is no pain and 10 is worst unimaginable pain. If the score was more than 5 or patient demanded rescue analgesic, then he/she was given Inj. Diclofenac sodium 75 mg intramuscularly. Time of injection was noted for calculation of total duration of analgesia from time of spinal injection.

Follow up of the patient was done to study any delayed complications. The feedback was obtained from patients before discharge regarding any neurological deficit like tingling, numbness, or weakness in legs, bowel, and bladder dysfunction.
Data was collected in prescribed proforma, meeting the objectives of the study. Students and Chi-square test were applied whenever appropriate.

OBSERVATION:

Table 1: Comparison of onset of Analgesia

	Group	
Parameter	Group A	Group B
Onset Of Analgesia (Min)	2.76	2.50

Characteristics of spinal blockade was recorded every 2 min for first 15 min. In group A, mean time taken for onset of analgesia was 2.66 $\pm$8 min and in group B it is 2.50$\pm$0.6 min, with P value 0.28.

Table 2: Comparison of time to achieve highest level

Mean time in min.	
Group A	Group B
8.58	8.50

Time taken to achieve highest sensory level was also comparable in both groups i.e. mean value is 8.58±0.9 min in Group A and 8.50±1.01min in Group B.

Table 3: Highest sensory level

Highest sensory level	Group A		Group B	
	N	%	N	%
T4	19	38	16	32
T6	29	58	32	64
T8	2	4	2	4
Grand Total	50	100	50	100

In both groups highest sensory level achieved was in between T4 to T6.

Table 4: Comparison of motor block score (MBS) in both groups.

Bromage Score	Group A (Control)	Group B (Study)
One	**27**	**29**
Two	**20**	**21**
Three	**3**	**0**
Four	**0**	**0**
Total	**50**	**50**

Modified Bromage scale (MBS) was used to assess the characteristics of motor block in both groups.

Table 5: Intraoperative sedation score

Sedation Score	Group A(Control)	Group B (Study)
0	31	**33**
1	19	**17**
2	0	**0**
3	**0**	**0**

In Group A, 31 patients and in Group B, 33 patients had sedation score of 0, i.e. they were wide awake. In Group A, 19 patients and in Group B, 17 patients had sedation score of 1, i.e. they were sleeping but easily arousable. None of the patient in both groups showed higher sedation score.

Table 6: Comparison of quality of sensory block

Score	Group A (Control)	Group B (Study)
1 Excellent	13(26%)	**26(52%)**
2 Satisfactory	25(50%)	**24(48%)**
3 Fair/ Inadequate	11(22%)	**0**
4 Poor	**1(2%)**	**0**

The quality of sensory blockade was adequate (i.e. score of 1 and 2) in 76% patients in Group A while in Group B, 26 (52%) had excellent sensory blockade and 24 (48%) patient had satisfactory blockade. None of patient had inadequate or poor sensory blockade. In Group A, 1 patient required supplemental analgesia with IV Ketamine 0.5 mg/kg.
P-value = 0.001 i.e., highly significant.

Figure 1

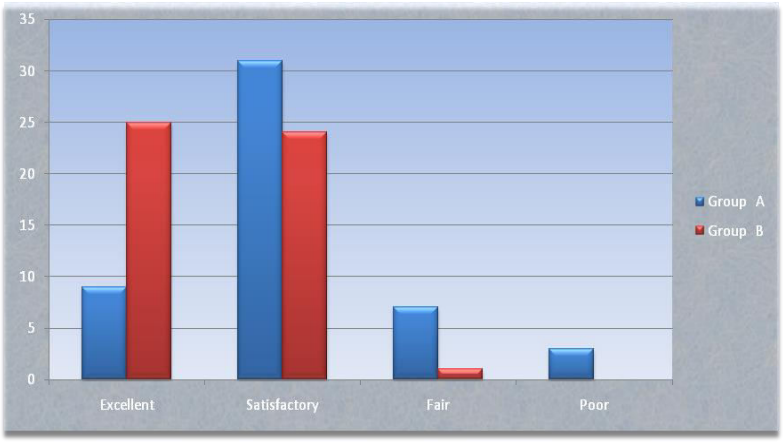


Table 7: Comparison of quality of motor block

Score	Group A (Control)	Group B(Study)
1 Excellent	9(18%)	**25(50%)**
2 Satisfactory	31(62%)	**24(48%)**
3 Fair/ Inadequate	7(14%)	**1(2%)**
4 Poor	**3 (6%)**	**0**

In Group B, almost all patients i.e 25 (50%) patients had excellent motor block and 24 (48%) had satisfactory block. In Group A, only 9 (18%) had excellent motor block but 31patients (62%) had satisfactory blockade. P-value is 0.001 which is highly significant.

Table 8: Intra-operative complication

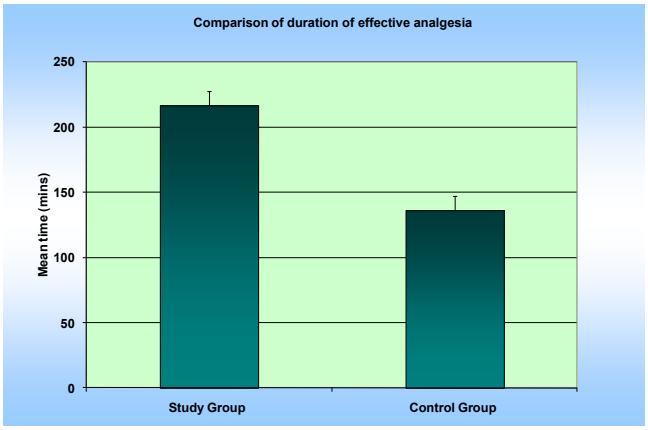
Intra-operative complication	Control Group		Study group	
	N	%	N	%
Bradycardia	1	2	2	4
Hypotension	2	4	2	4
Shivering	4	8	3	6
Respiratory depression	0	0	0	0

P value- 0.92 'Chi- Square' test was applied, p value significant if p<0.05 and highly significant if p<0.01
No significant difference was found in both groups.
2 patients in both the groups had hypotension.1 patient in Group A and 2 patients in group
B had episodes of bradycardia which was treated with Inj Atropine 0.6 mg.IV.4 patients in Group A and 3 patients in Group B had shivering, which was treated with warm IV fluids and warm drapes

Table 9: Comparison of Duration of sensory blockade

Parameters	Control Group		Study group		P value
	Mean	SD	Mean	SD	
Time for 2 segment regression (mins)	87.08	6.90	132.26	13.51	0.001
Time for S2 segment regression (mins)	**178.18**	14.27	**246.36**	8.90	0.001
Duration of effective analgesia (mins)	**136.38**	10.76	**216.60**	10.71	0.001

Figure 2



Duration of sensory blockade was assessed by time for 2 segment regressions and time for S2 segment regression. In Group A, mean time for 2 segment regression was 87.0±6.9 min as compared to 132.2 ± 13.5 min with Group B which was statistically significant. Also, time for S2 segment regression was comparatively higher in Group B i.e. 246.3 ± 8.9 min than in Group A i.e. 178.1 ± 14.2 min. It suggests that duration of sensory blockade is more in patients who received midazolam intrathecally.

Table 10: Post-operative complication

Post-operative complication	Control Group		Study group	
	N	%	N	%
Bradycardia	2	4	1	2
Hypotension	0	0	1	2
Nausea	2	4	2	4
Shivering	2	4	1	2
Vomiting	2	4	2	4
Respiratory depression / Urinary retention	0	0	0	0

Post operative complications were comparable between both groups, were treatable easily and not life threatening

Duration of effective analgesia was taken from time of intrathecal injection to the first supplementation of rescue analgesic on demand by patient or VAS >50.

In Group A, first supplementation of rescue analgesic was required at mean value of 136.3±10.7 min while in Group B this mean duration is 216.6±10.7 min, which is statistically highly significant ($P < 0.01$).

In both groups incidence of postoperative complications is less. Bradycardia was observed in 2 (4%) of patients in group A and 1 (2%) of patient in Group B. Hypotension was seen in 1 (2%) of Group B patient and none in Group A. Other complications like shivering and vomiting was seen in 2 (4%) patient in Group A while 1 (2%) and 2 (4%) in Group B respectively

Signs of respiratory depression were absent in all patients. Urinary retention was not observed in any of patient in postoperative period as every patient is catheterized as protocol.

DISCUSSION:

Intrathecal midazolam with local anaesthetic was studied widely since decades. Its use in clinical practice was increasing after proven safety in human[14,15]. As explained the mechanism of antinociceptive action of midazolam is through the BZD receptors in spinal cord [4,5] which was confirmed by various in vivo and in vitro, animal and microscopic studies[3].

In human studies, it is recommended to use preservative free midazolam intrathecally to improve its safety [8] . In clinical studies various authors used midazolam for spinal blocked with local anaesthetic [9-12] eg. Kim MH 2001 in haemorrhoidectomy, Batra YK in arthroplasty and Prakash etal in LSCS etc. Proper dose selection is important to avoid complications like neural toxicity, systemic effects and optimal duration of drug effect[13]. Commonly recommended dose is 1-2 mg [9,13]. Similarly, in our study 2 mg of preservative free midazolam dose selected. We observed significant improvement in quality and duration of spinal blockade mostly to excellent level sensory and motor blocked was instant and grade 4 respectively in midazolam (study) group and intra operative comfort was more in midazolam group needed no supplementation[5] . Most importantly duration of effective analgesia which was found to be significantly increased 216±10 min compared to bupivacaine alone 136±10 minutes. Our findings corresponds to study of N Bharti etal[15] (199 min) and Nidhi Agarwal [16] (164 ± 67.7 min) but differs from Prakash et al [13] as they found short duration or no action in some patients.

Despite that the number of patients required analgesia in first 24 hrs postoperative period was less in study group. In our study 40% of patients were found to have 36-48 hours of analgesia clearly underlines the drug effectiveness in postoperative period and requiring less residue analgesia. But the uniformity was not seen in all patients that was not explainable. Still possibly that can be of subjectiveness of patient to pain, nature of surgery, duration of tissue handling and experience of surgeon.

Sometimes Bupivacaine alone may not abolish discomfort while handling bowel or peritoneum needs sedation intraoperatively. On contrary we found more comfort in study without any supplementation with analgesics.

Intra and postoperative complications are comparable in both groups. Sedation was observed in midazolam group but S Prsarthy reported sedation and desaturation in some patients…but we found no desaturation.

There were no reported cases of neuronal complications like delayed recovery of blocked , long term effects like numbness, muscle weakness, over the period of study duration and follow up period.

Thus, in this study we found that there was significant improvement in duration of effective analgesia on injection of intrathecal midazolam with bupivacaine without any complications. But the duration enhanced for 3-4 hours and 24 -36 hours analgesia was observed only in 40% patients and not in all patients. However, further studies are required in large sample size for confirmation and to evaluate these complications. Also, other better and safe additives are to be evaluated to maximize the duration of analgesia with spinal action. In conclusion Intrathecal midazolam appears effective and safe option for enhancement of spinal effect and duration of local anaesthestic agent.

REFERENCES:

1. J. G Reves, R.J. Fragen, H.R. Vinik, and D.J. Greenbaltt, “Midazolam: pharmacology and use,” Anaesthesiology, vol.62 no. 3 pp.310-324,1985.
2. R.L.M.Faull and J.W.Villiger, “Benzodizepine receptors in the human spinal cord : a detailed anatomical and pharmacological study, Neuroscience, vol. 17,no. 3,pp791-802,1986
3. J.B.Dahl, I.S. Jeppesen, H.Jorgensen. J.Wetterslev, and S.Moiniche, “Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anaesthesia: a qualitative and quantitative systemic review of randomized controlled trials,” Anaesthesiology, vol.91,no. 6, 1919-1927,1999.
4. C.S.Goodchild and J.Noble, “The effect of intrthecal midazolam on sympathetic nervous system reflexes of man-a pilot study ,” The British Journal of Clinical Pharmacology, vol. 23,no. 3 pp.279-285, 1987.
5. D . Niv, J.G. Whitewam, and L.Loh, “depression of nocicepitive sympathetic reflexes by the intrathecal administration of midazolam,” the British journal of Anaesthesia, vol. 55, no.6, pp. 541-547, 1983.
6. M. Edwards, J.M. Serrao, J.P.Gent, and C.S. Goodchild, “ On the mechanism by which midazolam causes spinally mediated analgesia.” Anesthesiology, vol. 73, no.2 pp. 273-277, 1990.
7. Goodchild CS, Guo Z,Musgreave A, Gent JP. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid recertors. Br. J Anaesth 1996;77:758-63
8. Y.K. Batra, K.Jain, P.Chari, M.S.Dhillon, B.Shaheen, G.M.Reddy. “Addition of intrathecal midazolam to bupivacaine produces better postoperative analgesia without prolonging recovery.” International Journal of Clinical Pharmacology and Therapeutics 1999; 37 (10) : 519-523.
9. M. H.Kim and Y. M. Lee, “ Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in

patients undergoing haemorrhoidectomy," The British Journal of Anaesthesia, vol. 86, no. 1 pp. 77-79, 2001.
10. Jahangiri B. and Jahangiri R. Intrathecal midazolam prolongs the analgesic effect of spinal blockade with lignocaine in perineal surgeries. Acta Medica Iranica, 44:5(2006)
11. Sen A, Rudra A,Sarkar SK, Biswas B. Intrathecal midazolam for postoperative pain relief in caesarean section delivery. J Indian Med Assoc, 2001:99(12);683-684, 686.
12. N. Bharti, R.Madan,P.R.Mohanty, and H.L.Kaul, "Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia,"Acta Anaesthesiologica Scandinvica, vol.47, no.9, pp 1101-1105, 2003
13. Prakash S , Joshi N,Gogia A R et al. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing caesarean delivery. Reg Anesth Pain Med 2006; 31(3) 221-6.
14. A. P. Tucker, C.Lai, R.Nadeson, and C.S.Goodchild, "Intrathecal midazolam I : a cohort study investigation safety," Anaesthesia Analgesia, vol. 98, no. 6 pp. 1512-1520, 2004.
15. Bhattcharya D Biswas B,Banerjee A, " Intrathecal midazolam with bupivacaine increase the analgesic effects of spinal blockade after major gynaecological surgery". Journal of Anaesthesiology Clinical Pharmacology; 18(2);183-186,2001
16. Agarwal N Usmani A et al. Effect of intrathecal midazolam bupivacaine combination on postoperative analgesia. Indian Journal of Anaesthesia;49(1) 37-39,2005.

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