Original Research Article

Effect of intrathecal midazolam-bupivacaine combination on post-operative analgesia

Urmi Mittal Dave[1*], Shweta S Mehta[2], Jaykishan Gol[3]

[1]Assitant Professor, Department of Anaesthesiology, PDU Government Medical College, Rajkot, Gujarat, INDIA.
[2]Associate professor, Department of Anaesthesiology, SVPIMSR, Ahmedabad, Gujarat, INDIA.
[3]Junior Resident, Department of Anaesthesiology, PDU Government Medical College, Rajkot, Gujarat, INDIA.
Email: urmidave@icloud.com

Abstract

Background and Aim: Post-operative analgesia is an important aspect of perioperative patient care in elective, emergency as well as day care surgeries due to various advantages. Use of intrathecal adjuvants is increasing to achieve good perioperative care and outcome. **Methods:** A prospective randomized double-blind study was carried out on 50 patients of ASA grade I/II, aged 16-60 years, scheduled for elective lower abdominal and lower limb surgeries. Patients were randomly allocated in two groups. Group A received 3ml 0.5% bupivacaine heavy (15mg) + 0.2 ml of 0.9% saline intrathecally. Group B received 3 ml 0.5% bupivacaine heavy (15 mg) + 0.2 ml preservative free midazolam (1mg). Patients were closely monitored for hemodynamic, sedation or any perioperative complications. 'Effective analgesia' was taken as time from S2 segment regression to administration of first rescue analgesic in minutes (T3 = T2 –T1). **Results:** Statistically significant difference was found with regards to S2 segment regression time between the two groups ($p < 0.05$) (217 min in group A v/s 240 min in group B). In our study, mean time to first rescue analgesic drug (T2) (diclofenac sodium 1mg/kg intramuscularly at VAS score ≥ 40 mm) was significantly prolonged in group B ($p<0.001$) (418±42.6 min in group B v/s 262.2±26.53 min in group A). Effective analgesia time (T3) was also prolonged. (179 min in group B v/s 45 min group A). Two groups did not defer as regards to type/duration of surgery, Time to onset of sensory block and time to achieve maximum sensory block. **Conclusion:** Intrathecal combination of midazolam and Bupivacaine provides longer duration of post-operative analgesia along with prolonged sensory regression time with hemodynamic stability and no significant adverse effects.

Key Word: Intrathecal Midazolam, Post-operative Analgesia, Bupivacaine

[*]**Address for Correspondence:**
Dr. Urmi Mittal Dave, C-102, Shree Gold Palace Ramakrishna Nagar (West) Main Road, Behind Virani Highschool, Rajkot, Gujarat, INDIA.
Email: urmidave@icloud.com

Received Date: 27/08/2019 Revised Date: 19/09/2019 Accepted Date: 02/10/2019
DOI: https://doi.org/10.26611/10151215A

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 07 October 2019

INTRODUCTION

Concept of post-operative analgesia is gaining importance in elective, emergency and day care surgeries due to number of advantages such as:

- Minimal psychological stress
- Improved hemodynamic stability and respiration
- Relief of sympathetic overactivity and prevention of peripheral or central sensitization.
- Greater flexibility about timing of surgery
- Reduced postoperative complication
- Early return to routine activities

Intrathecal adjuvants drugs like fentanyl, clonidine[7], ketamine[19] etc. have been used by various investigators. Side effects of intrathecal opioids[27] like respiratory depression, nausea, vomiting, pruritus limit their use. Likewise, intrathecal administration of clonidine can lead to hemodynamic changes. As there are reports of presence of Benzodiazepine/GABA receptor complex in spinal cord and only few studies on intrathecal midazolam in humans, we decided to asses intrathecal midazolam-Bupivacaine combination with primary aim to study its postoperative

How to site this article: Urmi Mittal Dave, Shweta S Mehta, Jaykishan Gol. Effect of intrathecal midazolam-bupivacaine combination on post-operative analgesia. *MedPulse International Journal of Anesthesiology.* October 2019; 12(1): 21-25.
http://medpulse.in/Anesthsiology/index.php

analgesic effect and co-relate it with sensory dermatomal regression time.

METHODS

A prospective randomized double-blind study was carried out on 50 patients of ASA grade I/II, aged 16-60 years, scheduled for elective lower abdominal and lower limb surgeries. All the patients were evaluated preoperatively and those having history of allergy to any drug or having any contraindications to spinal anaesthesia were excluded from the study. Patients using any drug that modifies pain perception were excluded from the study. Fasting for minimum 6 hours was advised prior to scheduled time of surgery. Procedure was explained to all patients and informed consent was taken.

Inside the operation theatre, ECG, NIBP monitor and pulse oximeter were applied to all patients and baseline pulse, blood pressure, oxygen saturation and respiratory rate were recorded. Patients were preloaded with 10-15 ml/kg of intravenous Ringer's lactate solution after securing 18 Gauge intravenous line. Patients were randomly allocated in two groups. Group A received 3ml 0.5% bupivacaine heavy (15mg) + 0.2 ml of 0.9% saline intrathecally. Group B received 3 ml 0.5% bupivacaine heavy (15 mg) + 0.2 ml preservative free midazolam (1mg-from 5mg/ml ampoule). Subarachnoid block was performed under all aseptic precautions in sitting/lateral decubitus position(figure-4) with 23 Gauge Quincke's spinal needle in L_2-L_3 or L_3-L_4 space via midline/paramedian approach. Patients were immediately made supine and time to subarachnoid injection was noted. Sensory block was assessed by the loss of sensation to pinprick. Time to onset of sensory block, maximum level of sensory block achieved and time to achieve maximum sensory block were noted in minutes. A dermatomal sensory loss from T_{10}-S_4 level was considered satisfactory according to type of surgery. Pulse rate, arterial blood pressure, SpO_2 and respiratory rate were recorded every five minutes till first half an hour and then every fifteen minutes intraoperatively. Intravenous fluids were continued throughout the surgery. Any intraoperative complications like nausea/vomiting (NV), pruritus(P), shivering(S) and respiratory depression(Rd) were looked for. Sedation levels were assessed using the Observer's Assessment of Alertness/Sedation scale (OAA/S) as used by Chernik *et al*[3]

Responds readily to name spoken in normal tone 5(Alert)

Lethargic response to name spoken in normal tone 4

Responds only after name is called loudly and / or repeatedly 3

Responds only after mild prodding or shaking 2

Does not respond to mild prodding or shaking 1(Asleep)

intraoperatively every 30 mins and every hourly for six hours following arrival in PACU. Hypotension (defined as 30% fall in systolic BP from the baseline BP) was treated with intravenous fluids and inj. mephenteramine 6mg i.v. Bradycardia (defined as pulse rate <60 beats per min) was treated with inj. atropine sulphate 0.6 mg i. v. Shivering was treated with 100% O_2, warm fluids and adequate patient covering. No other sedative or analgesic drug was given to the patients intra operatively. Respiratory depression (defined as RR<12/min or SpO_2<90%) was treated with 100% O_2. Duration of surgery for each case was noted. Postoperatively, time to regression of sensory block to second sacral dermatome (S_2) was assessed by pinprick and recorded in minutes (T_1). Pain was assessed postoperatively using Visual Analogue Scale (VAS). The scale consisting of a 100 mm line with 0 = no pain and 100 = worst possible pain was explained to all patients. All patients were followed up postoperatively till patients complained of pain as per VAS and vitals were monitored at 30 min intervals postoperatively up to 6 hours following arrival in PACU. When VAS score was ≥ 40 mm, the patients were given inj. diclofenac sodium 1mg/kg i.m. and this time was noted. Time from subarachnoid injection to administration of first rescue analgesic was taken as 'Time to first rescue analgesic' and recorded in minutes (T_2). 'Effective analgesia' was taken as time from S_2 segment regression to administration of first rescue analgesic in minutes ($T_3 = T_2 - T_1$). Patients were also observed for any post-operative complications like nausea, vomiting, shivering, respiratory depression, amnesia, pruritus or urinary retention.

Statistical Analysis: Data were presented as mean value, mean ± SD and percentage as appropriate. Two groups were compared by unpaired t-test and p value < 0.05 was considered statistically significant while p value < 0.001 was considered highly significant.

RESULTS

Demographic and surgical variables were comparable in both groups (P>0.05). (Table: 1)

Table 1: Types and Duration of surgery

	Group A		Group B	
Age (Years)	35.92 ±11.66		34.4 ± 11.67	
Sex (M/F)	20/5		21/4	
Types of surgeries	**No.**	**%**	**No.**	**%**
Orthopaedics	7	28%	9	36%
Plastic	4	16%	5	20%
General Surgery	9	36%	7	28%
Urosurgery	5	20%	4	16%
Duration of surgery(min)(mean ± SD)	90 ± 23.8		98.2 ± 30.5	

No statistically significant difference was found with regards to – time to onset of sensory block, maximum sensory level achieved and time to achieve maximum block height as judged by pinprick method. (Table 2).

Table 2: Characteristic of sensory blockade

	Group A (mean ± SD)	Group B (mean ± SD)
Time to onset of block (min)	6 ± 1.68	5.2 ± 1.38
Time to achieve highest level of block(min)	10.48 ± 2.12	10.04 ± 1.51

Level of sedation was assessed using Observer's Assessment of Alertness/Sedation (OAA/S) scale and the scale was comparable in both the groups. (Table 3)

Table 3: Intraoperative sedation by OAA/S scale

OAA/S Scale at 30 min after spinal anaesthesia	Group A		Group B	
	No.	**%**	**No.**	**%**
5 (Alert)	22	88%	20	80%
4	2	8%	4	16%
3	1	4%	1	4%
2	-	-	-	-
1(Asleep)	-	-	-	-

Time for regression of sensory block to S2 segment was 217 min in group A v/s 240 min in group B ($p < 0.05$). Time to first rescue analgesic was prolonged significantly in group B as compared to group A ($p < 0.001$) (262 min in group A v/s 418 min in group B) (Table 4) and patients' subjective response to analgesia was definitely better in group B.(Table 5)

Table 4: Duration of analgesia

	Group A (mean ± SD)	Group B (mean ± SD)	p value
S_2 regression time (T_1) (min)	217.4 ± 22.68	240 ± 26.61	0.002 ($p < 0.05$)
Time to first rescue analgesic (T_2)(min)	262.2 ± 26.54	418.4 ± 42.64	$p < 0.001$
Effective analgesia ($T_3=T_2-T_1$)(min)	44.8 ± 7.56	178.6 ± 23.83	$p < 0.001$

Table 5: Subjective response to analgesia

Patients' response	Group A		Group B	
	No.	**%**	**No.**	**%**
Good (G)	7	28%	20	80%
Fair (F)	16	64%	5	20%
Poor (P)	2	8%	0	0%

No significant difference was observed in vital parameters during intraoperative monitoring between the two groups. Use of intrathecal midazolam did not increase rate of any perioperative complications.

DISCUSSION

Edward M, Serrao *et al*[9] (1990) observed that administration of benzodiazepine antagonist flumazenil and $GABA_A$ antagonist bicuculline reversed the analgesic effect of intrathecal midazolam, suggesting that antinociceptive actions are mediated via $BZD/GABA_A$ receptor complex which are abundantly present in lamina II of dorsal horn of spinal cord. Goodchild CS *et al*[14] (1996) reported that intrathecal midazolam probably causes release of an endogenous opioid at spinal delta receptors as naltrindole, a delta selective opioid antagonist suppressed analgesic action of intrathecal midazolam. Tucker P *et al*[28] (2004) did a cohort study with >1000 subjects investigating safety of intrathecal Midazolam in humans. In contrast with the studies that reported histopathological changes in animals[17], they found no adverse effects with intrathecal Midazolam when assessed by symptoms and long term follow up in humans. This is consistent with administration of a dose of intrathecal midazolam, approximately 0.03 mg/kg, which is less than that associated with both histopathology and behavioural changes in previous animal studies. Kim MH and Lee YM[20] (2001) studied the effect of two different doses of intrathecal midazolam (1mg and 2mg) on post op analgesia, while we used 1 mg preservative free intrathecal midazolam. In our study, Sedation scores were comparable in both groups. However, Nishiyama T *et al*[23] (1992) reported sedation with higher doses of epidural midazolam. In our study, Time taken for regression of sensory block to second sacral dermatome (S_2) was significantly longer in Group B than in Group A (240 ± 26.61 min in Group B v/s 217.4 ± 22.68 min Group A) ($p<0.05$). Batra *et al*[2]and N Bharti, R Madan *et al*[22] , Shadangi et al[27] (2011) also found similar results. However, Agrawal N *et al*[1] (2005) found no statistically significant difference with respect to time for sensory block regression to first sacral dermatome ($p>0.05$). Mean time to first rescue analgesic drug (T_2) (diclofenac sodium 1mg/kg im at VAS score ≥ 40 mm) was significantly prolonged in group B ($p<0.001$) (418±42.6 min in group B v/s 262.2±26.53 min in group A). So, total duration of pain relief was increased by about 2 hours in the midazolam group. However, Agrawal N *et al*[1] (2005) reported that time to first rescue analgesic in bupivacaine – Midazolam group (1 mg) was significantly longer than in bupivacaine group [17.56 ± 8.87 hours v/s 4 ± 3.5 hours]. Effective analgesia time (T_3) was also prolonged by approximately 2 hours (179 min in group B v/s 45 min group A). Thus raising the possibility of another mechanism of action of intrathecal midazolam besides segmental cord level analgesia. Patient's response to overall analgesia was good in most of the cases of group B as compared to group A. (28% in group A v/s 80% in group B). Characteristics of motor blockade were not studied in detail, as our primary aim was to assess postoperative pain relief. However, onset and duration of motor block as well as surgical relaxation was satisfactory in all the patients perioperatively. In our study, no significant difference was observed in vital parameters during intraoperative monitoring between the two groups. Three patients in midazolam group (group B) developed transient bradycardia(12%) as compared to two patients in control group (group A – 8%) that was treated with inj. atropine 0.6 mg iv. In our study, no statistically significant difference was observed between two groups with regards to rates of hypotension, shivering, nausea vomiting, pruritus or respiratory depression More studies on larger sample of human populations are needed to evaluate the possible mechanism of analgesia of intrathecal midazolam.

So, to conclude, Addition of 1 mg (0.2 ml) preservative free midazolam to intrathecal 15 mg (3 ml) hyperbaric 0.5% bupivacaine produces satisfactory anaesthesia along with prolonged sensory regression times, prolonged post-operative analgesia with better subjective response to analgesia, perioperative hemodynamic stability without any significant adverse effects.

REFERENCES

1. Agrawal N *et al* Effect of intrathecal midazolam bupivacaine combination on post operativeanalgesia.Indian J. Anaesth. 2005; 49 (1) :37-39
2. Batra YK, Jain K, Chari P, Dhillon MS, Shaheen B, Redd y GM. Addition of intrathecal midazolam to bupivacaine produces better postoperative analgesia without prolonging recovery. Int J Clin PharmacolTher 1999; 37: 519–23.
3. Chernik DA, Gillings D, Laine H, *et al.* Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. J Clin Psychopharmacol 1990, 10: 244-51.
4. Collins VJ : Principles of anaesthesiology ,3rd edition , volume : 2 , 199
5. Cox RF, Collin MA : Anaesthesia and Analgesia Aug 2001, 93:2, 354-358
6. Crawford ME *et al*, Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits. Br J Anaesth 1993; 70: 642-6
7. Dobrydnjov I, Axelsson K, Samarutel J, Holmstrom B. Post operative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. Acta Anaesthesiol Scand 2002; 46(7): 806-14.
8. Edward Morgan, Maged S Mikhail, Michael J Murray : Clinical anaesthesiology , 4th ed. 2006.
9. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia.Anesthesiology 1990; 73: 273–7.
10. Faull RLM, Villiger JW. Benzodiazepine receptors in the human spinal cord : a detailed anatomical and pharmacological study. Neuroscience 1986; 17: 791-80

11. GanongWF : Review of medical physiology , 22nd edition , 2005
12. Goodchild CS , Noble J. The effect of intrathecal midazolam on sympathetic nervous system reflexes in man- a pilot study. Br J Clin Pharmacol 1987; 23: 279-85
13. Goodchild CS , Serrao JM. Intrathecal midazolam in the rat: evidence for spinally-mediated analgesia. Br J Anaesth 1987; 59: 1563-70
14. Goodchild CS *et al*. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. Br J Anaesth 1996; 77: 758-63
15. Goresky GV. The clinical utility of epidural midazolam for inguinal hernia repair in children. Can J Anaesth1995; 42: 755–7.
16. Gupta A *et al* The Effect of Intrathecal Midazolam 2.5mg with Bupivacaine on Postoperative Pain Relief in Patients Undergoing Orthopaedic Surgery. J Anaesth Clin Pharmacol 2008; 24(2): 189-192
17. Gupta A, Kamat H, Kharod U. Efficacy of intrathecal midazolam in potentiating the analgesic effect of intrathecal fentanyl in patients undergoing lower limb surgery. *Anesth Essays Res*. 2015;9(3):379–383.
18. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). AnesthAnalg1999; 88: 797–809.
19. International association for the study of pain. Pain 1979; 6:249-52
20. Karthivel S, Sadhasivam S, Saxena A, Kannan TR, Ganjoo P. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. Anaesthesia 2001; 55(9): 899-904
21. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br J Anaesth 2001; 86: 77–9
22. Lee's Synopsis of Anaesthesia , 11th edition , 1993.
23. N. Bharti , R. Madan *et al* Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia Acta Anaeasthesiologica Scandinavica,2003, Vol 47, issue 9:1101-1105
24. Nishiyama T, Hirasaki A, Odaka Y, Kanishi H, Seto K, G oto I. Epidural midazolam with saline – optimal dose for postoperative pain. *Masui* 1992; **41**: 49–54
25. Ronald D Miller : Miller's anaesthesia , 7th edition , 2009.
26. Serrao JM *et al*. Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. Pain 1992; 48: 5-12
27. Shadangi, Bijayaand Garg, Rakesh and Pandey, Ravindra and Das, T. (2011). Effects of intrathecal midazolam in spinal anaesthesia: A prospective randomised case control study. Singapore medical journal. 52. 432-5.
28. StoeltingRK : Pharmacology and physiology in anaesthetic practice , 4th edition
29. *Tan PH, Chia YY, Lo Y.* Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement. Can J Anaesth 2001; 48(6): 551-56.
30. Tucker *et al* Intrathecal Midazolam I: A Cohort Study Investigating Safety. AnesthAnalg2004;98:1512–20
31. Valentine JM *et al*. The effect of intrathecal midazolam on postoperative pain. Eur J Anaesthes 1996; 13: 589-93
32. Wylie and churchgilldavidson : A practice of anaesthesia, 7th edition, 2003.

Source of Support: None Declared
Conflict of Interest: None Declared