ORIGINAL RESEARCH PAPER

Anaesthesiology

COMPARISON OF INTRATHECAL BUPIVACAINE AND BUPIVACAINE PLUS MIDAZOLAM IN SPINAL ANALGESIA

KEY WORDS: Intrathecal Midazolam, Intrathecal Bupivacaine, Post operative analgesia

Kanhaiya Lal Kishnani* Associate Professor Department of Anaesthesiology, Peoples College of Medical Sciences and Research Centre Bhanpur Bhopal *Corresponding Author

Ankita Gupta Junior Resident Department of Anaesthesiology, Peoples College of Medical Sciences and Research Centre Bhanpur Bhopal

Akansha Bansal Junior Resident Department of Anaesthesiology, Peoples College of Medical Sciences and Research Centre Bhanpur Bhopal

ABSTRACT

Introduction: The concept of postoperative pain relief has improved dramatically over recent years. Intrathecal local analgesics with different adjuvants are being tried in Spinal analgesia for pain relief and prolongation of time of analgesia. Intrathecal Midazolam is known to produce antinociception and potentiating the effect of local anaesthetics. The aim of this study was to compare intrathecal Bupivacaine and intrathecal Bupivacaine with Midazolam on the onset and duration of sensory block, motor block and effect on pain relief.

Material and Methods: Total 100 patients of ASA Grade I and II between the age group of 25 to 50 years of age undergoing surgery below umbilicus under spinal analgesia were studied. They were divided into 2 groups of 50 patients each. Bupivacaine Group received intrathecal 3.0 ml of Bupivacaine heavy 0.5% and 0.4 ml of Normal saline, Bupivacaine- Midazolam Group received intrathecal 3.0 ml of Bupivacaine heavy 0.5% and 0.4 ml of (5.0 mg/ml) preservative free Midazolam in spinal block. Lumbar puncture was performed at L 3-4 level, with a 25 gauge Quincke spinal needle via midline approach in sitting position. The drugs were injected through a spinal needle over a period of 15 seconds. Time of regression of sensory block and recovery from motor blockade was noted. Time of first rescue analgesia was noted. The patients were also observed for any side effect.

Results: We observed that onset of sensory block was faster in Bupivacaine - Midazolam group than in Bupivacaine Normal saline group. The duration of post operative analgesia was more in Bupivacaine-Midazolam group as request for first rescue analgesia and further requirement of analgesia was also less in this group. The variation in the vital parameters was comparable in both the groups. Symptoms of nausea vomiting were minimal and there was no respiratory depression in both groups.

Conclusion: We arrived at conclusion that addition of preservative free Midazolam to Intrathecal Bupivacaine produced optimal operating conditions and produced prolonged post operative analgesia without significant side effects.

INTRODUCTION

Spinal analgesia is most extensively used regional anaesthesia technique for surgeries below umbilical region. It provides effective postoperative analgesia with less adverse effects like post operative nausea vomiting, respiratory depression and sedation.

Varieties of drugs have been tried as adjuvants for prolongation of effect of local anaesthetics in spinal analgesia like Morphine, Clonidine and Fentanyl. [1][2][3]. The use of intrathecal Midazolam began with the discovery of benzodiazepine receptors in spinal cord. Its use has shown enhancement of intra-operative analgesia and prolongation of the duration of postoperative analgesia, this has also shown reduction in postoperative analgesic requirement [4] [5] [6].

Midazolam is a water soluble benzodiazepine with sedative, amnesic, anxiolytic, muscle relaxant and anticonvulsant properties [7] [8] [9] [10] [11] [12]

The antinociceptive effect of intrathecal Midazolam is produced through GABA- A receptors in spinal cord. These receptors are in highest concentration in lamina – II or the dorsal horn ganglia. Besides analgesia, Midazolam is known to suppress the reflex response to visceral pain. [13] [14][15]. Recent studies suggest that intrathecal Midazolam releases endogenous opioid by acting at spinal delta receptors. [16]

Aim of our study was to compare the efficacy of intrathecal Bupivacaine with Midazolam and intrathecal Bupivacaine alone in patients undergoing surgeries below umbilicus level. The parameters studied included onset and duration of sensory and motor block, changes in vital parameters, duration of post operative analgesia and any adverse effects.

MATERIAL AND METHODS

After approval of Institutional Ethics committee and written informed consent from patients; we studied 100 patients of ASA status I and II, between the age group of 25 to 50 years of age planned to undergo elective surgery below umblicus under spinal analgesia. All patients were detailed about the procedure of spinal block and assessment of level of block. Patients were divided into 2 groups of 50 patients each. The drugs were prepared by separate Anaesthesiologist not involved in study and were injected by separate Anaesthesiologist. Patients were given Tab Alprazolam 0.25mg, on the previous night of surgery.

Bupivacaine-Normal saline group received 3.0 ml of Bupivacaine heavy 0.5% and 0.4 ml of normal saline, Bupivacaine-Midazolam group received 3.0 ml of Bupivacaine heavy 0.5% and 0.4 ml (5.0 mg/ml) of preservative free Midazolam. Patients with H/O long-term uncontrolled hypertension, uncontrolled DM cases, known neurologic or psychological disorders, spinal column surgery, low back pain, chronic alcoholism, opium addiction or on any drug which modifies pain were not included in this study. Patient with coagulation abnormality, patient with infection at the site of injection were also excluded.

Patient's weight and height were recorded. After inserting 20 gauge intravenous cannula, patients were pre-loaded with I/V lactated Ringer's solution (15 ml/ kg body weight) before spinal analgesia. Base line blood pressure and the heart rate were recorded. Standard monitoring (ECG, NIBP, and pulse oximetery) was done during surgery. Under strict aseptic precautions, lumbar puncture was performed in sitting position through midline approach using 25 gauge spinal needle at L3-L4 intervertebral space. After successful lumber puncture the drugs were injected over a period of 15 seconds according to allocated group.

After injection, the patient was retained in supine position for at least 20 minutes before positioning for surgery. The dermatomal levels of sensory analgesia were evaluated by pinprick every minute for the first 20 minutes and then at 10 minutes interval until pinprick sensation returned to L 1 segment. The highest level of sensory loss 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 regression of the sensory blockade to the L1 segment.
d) Time of complete motor blockade. This was assessed and graded at the same time intervals as sensory blockade using the bromage scale.
e) Time for recovery of motor blockade to L 2 (hip flexion)
f) Central effects – sedation was graded as described by Filos et al. using four point sedation score.
g) Intra operatively the blood pressure and heart rate were monitored at 1 minute interval for the first 10 minutes and later every 10 minutes.
h) Postoperative analgesia was evaluated using standard 10 point linear visual analogue scale (VAS) for pain.
i) Patients were observed and monitored for 12 hours postoperative.

Base line pulse rate, blood pressure and respiratory rate were recorded on arrival in O.T. Inj. Atropine intravenously for bradycardia if needed. Hypotension (defined as 30% of fall from basal systolic blood pressure) was treated with Inj. Mephentaramine 6mg intravenously and infusions of Ringer lactate. Respiratory depression was taken as respiratory rate less than 10/minute. No analgesics were given in the intra-operative period.

Patients were monitored every 15 minutes for 2 hours in the recovery room and on hourly basis in postoperative ward. Patients were requested to inform immediately the early feeling of pain and this time was noted. Symptoms if any were looked for. All patients were followed up till discharge for any signs of neurological symptoms like numbness, weakness and paraesthesia, urinary retention. No analgesics were given in the postoperative period except when the patient complained of discomfort with pain.

The assessment of pain was done by VAS scoring system from 0 to 10 scale, "No pain' at 0 scale and "Worst pain" at 10 score of scale. All the patients were detailed about this assessment at the beginning of procedure. The patients were requested to indicate the exact point of pain feeling along with intensity.

When the patient complained of pain the time was noted and analgesic injection was prescribed. The duration of analgesia was calculated as the time interval between the time of intrathecal administration of drug and the time of first rescue analgesic. The numbers of rescue analgesia were noted in both groups. The incidences of side effects were closely watched into postoperative period. Patients having nausea and vomiting were treated with Injection Odensteron 4 mg intravenously. Patients who were drowsy were checked whether they were arousable by verbal command. The sedation was assessed by "**"Filos Sedation Score"** as follows:

1. Awake and alert
2. Drowsy, responsive to verbal stimuli.
3. Drowsy, arousable to physical stimuli.
4. Un-arousable

RESULTS

Table 1 Demographic characteristics of patients in two groups.

Parameter	Bupivacaine-Midazolam group (Study Group)	Bupivacaine-Normal Saline (Control Group)
Average height in cms	**161.43**	**162. 30**
Average weight in kgs	**60.2**	**61.17**

Table2. Age distribution

Age in years	**Bupivacaine-Midazolam group (n=50)**	**Bupivacaine-Normal Saline (n=50)**
25-30	12 (24.0 %)	10 (20.0 %)
31-35	10 (20.0 %)	12 (24.0 %)
36-40	10 (20.0 %)	10 (20.0 %)
41-45	10 (20.0 %)	10 (20.0 %)
46-50	08 (16.0%)	08 (16.0%)

Table 3 Number (%) of male and female patients in each group

Group	Male	Female
Bupivacaine- Midazolam	35 (70 %)	15 (30 %)
Bupivacaine- Normal Saline	40 (80 %)	10 (20 %)

Table 4 Time taken for attainment of Sensory Block

Group	Onset of Sensory Block	Mean duration of attainment of highest Sensory Block(Min)	Mean Duration of two segment regression of Sensory Block (Min)
Bupivacaine-Midazolam	4.33 minutes	14.0 min	122.9 min
Bupivacaine-Normal Saline	6.7 minutes	14.5 min	90.0 min

Table 5 Time of Motor Block

Group	Mean duration of achieving complete Motor Block (min)	Mean duration of recovery of Motor Block (min)
Bupivacaine-Midazolam	6.26	122.2
Bupivacaine-Normal Saline	6.30	100.3

Table 6 Sedation Score

Group	Mean
Bupivacaine-Midazolam	2.70
Bupivacaine- Normal Saline	1.06

Table 7 Maximum change (Mean) in the heart rate from base line

Group	Mean (min)
Bupivacaine-Midazolam	18.9
Bupivacaine- Normal Saline	20.5

Table 8 Change in Systolic and Diastolic blood pressure from base line

Group	Max change (Mean) in Systolic Pressure (mm of Hg)	Max change (Mean) in Diastolic Pressure (mm of Hg)
Bupivacaine-Midazolam	25.2	18.00
Bupivacaine-Normal Saline	25.4	15.90

Table 9 Incidence of side effects

	Bupivacaine+ Midazolam Group		Bupivacaine + Normal Saline Group	
Symptoms/ Untoward incidence	No. of Patients	Percentage	No. of Patients	Percentage
Nausea & Vomiting	1	2 %	2	4 %

Respiratory depression	0	0	0	0
Desaturation	0	0	0	0
Sedation	0	0	0	0
Neurological symptoms	0	0	0	0

DISCUSSION

The purpose of this study was to evaluate property of Midazolam for enhancement of analgesia when given with intrathecal Bupivacaine. Demographically the patients of both groups had similarity in distribution of height, weight, age and gender. [Table 1, 2, 3].

Onset of sensory block was duration between from administration of drug to the loss of pinprick sensation at T10 (Umblical level) dermatome bilaterally. Midazolam group showed faster onset of sensory block, 4.33 minutes as against 6.7 minutes in the control (Bupivacaine alone) group.

In our study, the mean duration of motor block regression in Bupivacaine -Midazolam group was 122.9 min. while the mean duration in Bupivacaine-Normal Saline group was 90.0 min.

Midazolam is water soluble benzodiazepine as reported in 1978 [17] and is being extensively used in critical care medicine and operating theatres. It is used as sedative, anxiolytic, and amnesic agent [18]. Its intrathecal use as an adjuvant is a relatively newer in anaesthesia practice.

Faull and Villiger undertook detailed anatomical and pharmacological study of benzodiazepine receptors in human spinal cord under the electron microscope in 1986. This has led to appreciation of site and mode of action of Midazolam. They demonstrated the consistent similar distribution of benzodiazepine receptors in grey matter in Cervical, Thoracic, Lumber and Sacral area of spinal cord. Highest densities of benzodiazepine receptors were found to be localized in lamina II of the dorsal horn. [19]. Midazolam has a relatively high affinity for the benzodiazepine receptor roughly two times that of the diazepam.

In 1989 Serrao et al. reported that segmental analgesia was produced by Midazolam in rats and this was reversed by Naloxone. [20]. Effect of intrathecal Midazolam with hyperbaric Bupivacaine for caesarean delivery under spinal anaesthesia was studied by Valentine et al. in1996.They did not find any side effect identifiable to Midazolam. They concluded that use of intrathecal Midazolam is safe and has clinical detectable analgesic properties. [21]

In our study nausea was experienced in one case in Bupivacaine- Midazolam group and in 2 cases in Bupivacaine-Normal saline group. No other symptom was noted in both groups. Kim and Lee [22] found the potentiation of analgesic effect of intrathecal Bupivacaine by addition of 1 to 2 mg of intrathecal Midazolam in patients for haemorrhoidectomy. The postoperative analgesia was prolonged approximately 2 to 4.5 hrs when compared to control group. They also found that the use of analgesics was also reduced in immediate 24 hours of post operative period.

Prochazka reported in 2006 their 10 years experience of using intrathecal Midazolam. According to them intrathecal Midazolam was able to give good analgesia in majority of the patients, It was very much useful as suitable supplement for postoperative and long-term analgesia. [23]

In 2008, Ho and Ismail [10] reported that intrathecal Midazolam appears to improve peri-operative analgesia and reduces nausea and vomiting during caesarean delivery in the meta-analysis done by them to evaluate effectiveness and side effects of intrathecal Midazolam in postoperative and peripartum settings. Addition of Midazolam to Bupivacaine given intrathecally resulted in prolonged postoperative analgesia without increasing motor block as concluded by Shadangi et al. [23] in 2011.

Midazolam has been investigated as an adjuvant with Lignocaine also. Talebi et al. [24] found, intrathecal administration of Midazolam with Lidocaine reduced post operative pain in patients for herniorraphy with no side effects. Joshi et al. [25] found that Midazolam gives better analgesia than Clonidine in spinal analgesia with fewer side effects. Shadangi B K, Garg R, Pandey R, Das T found that addition of preservative-free midazolam to bupivacaine intrathecally resulted in prolonged postoperative analgesia without increasing motor block. [26]. No significant difference in sedation levels has been reported in the intrathecal Midazolam- Alprazolam 0.25mg group as compared to the control group without intrathecal Midazolam as found by Bharti N, Madan R, Mohanty PR, Kaul HL. (27). We also did not find any sedation in both the groups.

Yegin et al used 2 mg Midazolam with Bupivacaine for perianal surgery, however, they found that there was no significant difference in the onset time of action between the two groups. [28]

SUMMARY

When 3.0 ml of 0.5% intrathecal Bupivacaine with 0.4ml preservative free Midazolam (2mg) was compared with 3.0 ml of 0.5% intrathecal Bupivacaine with 0.4ml of 0.9% Normal saline we observed that the onset of sensory block was faster in Midazolam group. The duration of post-operative analgesia was prolonged as evidenced by the time at which patient requested rescue analgesic. The requirement of rescue analgesic was also less in Bupivacaine-Midazolam group compared to Bupivacaine-Normal Saline group. Variations in vital parameters (Blood pressure, heart rate) were comparable in both groups. There was no incidence of respiratory depression, desaturation. There was no incidence of neurological symptoms.

CONCLUSION

We conclude from results of our study that preservative free Midazolam can be added to Bupivacaine (0.5% heavy) for spinal anaesthesia this combination provides optimal operating conditions and longer duration of post operative analgesia without significant side effects.

REFERENCES

[1] Serrao JM, Goodchild CS, Gent JP. Reversab by nalaxone of spinal antinociceptive effects of fentanyl,, Midazolam and ketocyclozocine. Eur. J. Anaesthsiol 1991:8 401-406.

[2] Kim MH, Lee YM, Intrathecal – midazolam increases the analgesic effect of spinal blockade with Bupivacaine in patients undergoing haemorrboidectony Br J Anaesth 2001;86:77-9.

[3] Bharti N, Madan R, Mohanty PR, Kaul HL, Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal Anaesthesia. Acta Anaesthesiolscad 2003:47:1101-5.

[4] Bahar M, Cohen ML, Grinshpon Y, Chanimov M. Spinal anaesthesia with midazolam in rat can J. Anaesthe 1997.44:208-15.

[5] Goodchild CS. Noble J. The effects of intrathecal Midazolam on sympathetic Nervous system reflexes in man- A Pilolstudy BR J

[6] Smita P, Nandita J, Anoop G, Sunil P, Rajvir S Analgesic efficacy of two doses of intrathecal midazolam with Bupivacaine in patients undergoing cesarean section . regionalAnaesth or pain med 2006 : 31:221-226.

[7] Crawford ME, Jensen FM, Toftdahl DB, Madsen JB Direct spinal offect of intrathecal and Extradural midazolam on visceral noxious stimulaton in rabbits Br J Anaesth 1993;70:642-6

[8] Yaksh TL, Allen JW. The use of intrathecal midazolam in humans. A case study of process. Anaesth Analog. 2004;98:1536-45

[9] Edwards M, Serrao JM, Gent JP, Goodchild CS, ON Mechanism by which midazolam causes spinally mediated analgesia. Anaesthesiologg 1990; 73-273-7.

[10] HO KM, Ismail H. Use of intrathecal Midazolam to improve perioperative analgesia. A meta analysis. Anaseth intensive care. 2008:36:365-73

[11] Yun MJ, Kim YH, Kim JH, Kim Ko, Oh Ay, Park Hp, Intrathecal midazolam added to bupivacaine prolongs the duration of spinal blockade to T10 dermatome in sorthopaedic patients Korean J Anaesthesiol 2007;53:S22-8.

[12] Salimi A, Nejad RA, Safari F, Mohajaerani; SA, Naghade RJ Mottaghi K. Reduction in labour pain by intrathecal Midazolam as an adjunct to sufentanil. Korean J Anaesthes 2014;66:204-9

[13] Goodchild CS, GuoZ, Musgreave A, Gent JP. Antinociception by intrathecal midazolam involves endogenous neurotranismitters acting at spinal cord

delta opiodreceptors. BR J Anaesthe. 1996; 77:758-63 Comparison of Intrathecal Bupivacaine and Bupivacaine plus Midazolam 12

[14] Serrao JM, Marks RL Morley SJ, Goodchild CS. Intrathecal Midazolam for treatment of chronic Mechanical low back pain. A Controlled comparison with Epidural steroid in a pilot study pain 1992; 48:5-12.

[15] Borg PA, Krijinen HJ. Longtermintrathecal administration of Midazolam and clonidine clin J Pain 1996:12 63-8.

[16]. Goodchild CS, Guo Z, Musgreave A, Gent JP. Antinociception by intrathecal Midazolam involves endogenous neurotransmitters acting at spinal cord delta opiod receptors. British Journal of Anaesthesia, 1996; 77: 758-763.

[17]. A. Walser, L.E. Benjamin Sr., T. Flynn, C. Mason, R. Schwartz, and R. I. Fryer, "Quinazolines and 1,4-benzodiazepines. 84. Synthesis and reactions of imidazo[1,5-a] [1,4]benzodiazepines," Journal of Organic Chemistry, vol. 43, no. 5, pp. 936–944, 1978.

[18]. J. G. Reves, R. J. Fragen, H. R. Vinik, and D. J. Greenblatt, "Midazolam: pharmacology and uses," Anesthesiology, vol. 62, no. 3, pp. 310–324, 1985.

[19]. R. L. M. Faull and J. W. Villiger, "Benzodiazepine receptors in the human spinal cord: a detailed anatomical and pharmacological study," Neuroscience, vol. 17, no. 3, pp. 791–802, 1986.

[20]. J. M. Serrao, J. P. Gent, and C. S. Goodchild, "Naloxone antagonizes the spinal analgesic effects of midazolam," The British Journal of Anaesthesia, vol. 62, no. 2, pp. 233–234, 1989.

[21]. J. M. Valentine, G. Lyons, and M. C. Bellamy, "The effect of intrathecal midazolam on post-operative pain," European Journal of Anaesthesiology, vol. 13, no. 6, pp. 589–593, 1996.

[22]. 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.

[23]. J. Prochazka, "775 intrathecal midazolam as an analgesic—10 years experience," European Journal of Pain, vol. 10, no. S1, article S202, 2006.

[24]. H. Talebi, B. Yazdi, S. Alizadeh, E. Moshiry, A. Nourozi, and P. Eghtesadi-Araghi, "Effects of combination of intrathecal lidocaine and two doses of intrathecal midazolam on post-operative pain in patients undergoing herniorrhaphy: a randomized controlled trial," Pakistan Journal of Biological Sciences, vol. 13, no. 23, pp. 1156–1160, 2010.

[25]. S. A. Joshi, V. V. Khadke, R. D. Subhedar, A. W. Patil, and V. M. Motghare, "Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial," Indian Journal of Pharmacology, vol. 44, no. 3, pp. 357–361, 2012.

[26]. B. K. Shadangi, R. Garg, R. Pandey, and T. Das, "Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study," Singapore Medical Journal, vol. 52, no. 6, pp. 432–435, 2011.

[27]. Bharti N, Madan R, Mohanty PR, Kaul HL, Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal Anaesthesia. ActaAnaesthesiolscad 2003: 47:1101-5.

[28] . Yegin A, Sanli S, Dosemeci L, Kayacan N, Akbas M, Karsli B. The analgesic and sedative effects of intrathecal Midazolam in perianal surgery. European Journal of Anaesthesiology, 2004; 21(8): 658-662.