Original Research Article

A comparative study of analgesic efficacy of intrathecal bupivacain(0.5) heavy with different doses of midazolam(1mg and 2mg) as adjuvant in patients undergoing elective lower limb surgeries

Swetha H R

Assistant Professor, Department of Anaesthesiology, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, INDIA.
Email: drswetha.md@gmail.com

Abstract

Background: Discovery of spinal receptors like alpha 2 adrenergic, cholinergic, opioid, NMDA and gamma aminobutyricacid(GABA)and benzodiazepine receptors trigger the use of drugs like neostigmine, clonidine, opioids ketamine,midazolam for their synergistic effect with intrathecal local anesthetics. **Methodology:** It was a double blind, prospective, randomised case control study patients with ASA 1 and 2 was taken. Exclusion criteria were patients with cardiac problem, respiratory problem, coagulation disorders, mental disorders and contraindication to regional block. Day before surgery preanesthetic evaluation was carried and procedure was explain to each patient. 0.5 mg alprazolam and ranitidine 150 mg given bedtime the night before surgery patient is kept NPO overnight. **Results:** Duration of motor block in group 1 and group 2 was 3.20(hr)±0.73 & 3.50±0.77 P value 0.226.Duration of sensory block in group 1 and group 2 was 4.08(hr)±0.88 & 6.67 (hr)± 1.29 p-value <0.001 significant.There is higher duration of pain free period with group 2. So we can say that intrathecal 2mg Midazo lam added to bupivacaine,duration of postoperative analgesia was significantly prolonged than 1 mg midazolam. **Conclusion:** Effect of intrathecal midazolam is dose dependent 2mg midazolam prolongs the action of bupivacaine with good sedation and no unwanted side effects.
Keywords: Intra ThecalBupivacain, Midazolam,Elective Lower Limb Surgeries

Address for Correspondence:
Dr. Swetha H R, Assistant Professor, Department of Anaesthesiology, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka.
Email: drswetha.md@gmail.com
Received Date: 14/01/2018 Revised Date: 17/02/2018 Accepted Date: 05/03/2018
DOI: https://doi.org/10.26611/1015533

Access this article online

Quick Response Code:

Website: www.medpulse.in

Accessed Date: 10 March 2018

INTRODUCTION

Central neuraxialblocks(CNB) reduces the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding, respiratory depression and postoperative pain relief.[1] But CNB with local anaesthetic has limited duration of analgesiab.[2] Discovery of spinal receptors like alpha 2 adrenergic, cholinergic, opioid, NMDA and gamma aminobutyric acid(GABA)and benzodiazepine receptors trigger the use of drugs like neostigmine, clonidine, opioids ketamine,midazolam for their synergistic effect with intrathecal local anesthetics.[2,3] Local anesthetics with opioid has effective action but produces respiratory depression, urinary retention, nausea and pruritis.[4] Benzodiazepine receptor(benzodiazepine GABA -A receptor Complex) within the spinal cord which lead to enhance activity of GABA or inhibitory neurotransmitter.[5] There are studies for analgesics benefits of midazolam in early postoperative period following cesarean section and hemorrhoidssurgery.[6,7] In these studies to 2mg

How to site this article: Swetha H R A comparative study of analgesic efficacy of intrathecal bupivacain(0.5) heavy with different doses of midazolam(1mg and 2mg) as adjuvant in patients undergoing elective lower limb surgeries. *MedPulse International Journal of Anesthesiology.* March 2018; 5(3): 50-54. http://medpulse.in/Anesthsiology/index.php

Midazolam is used there is no study which compares analgesic efficiency of midazolam with 1 mg and 2 mg doses.[8,9] So your study is aimed to do comparative study of analgesic efficacy of intrathecal bupivacaine with midazolam of 1 mg and 2 MG in patient undergoing lower Limb surgeries. The study is designed to compare the analgesic efficacy of intrathecal bupivacaine with the midazolam 1 mg and 2 MG in patients undergoing lower Limb surgeries. Here we are assessing the onset of action, duration of sensory and motor block,quality of block and undesirable Side Effects like bradycardia, hypotension,nausea, vomiting and sedation

METHODOLOGY

Comparative study of analgesic efficacy of intrathecal bupivacaine with midazolam of 1 mg and 2 MG in patients undergoing lower Limb surgery was carried in KIMS Hospital Bengaluru after local ethical committee and written informed consent from 40 patients scheduled for elective lower limb orthopaedic surgeries . It was a double blind, prospective, randomised case control study patients with ASA 1 and 2 was taken. Exclusion criteria were patients with cardiac problem, respiratory problem, coagulation disorders, mental disorders and contraindication to regional block. Day before surgery preanesthetic evaluation was carried and procedure was explain to each patient. 0.5 mg alprazolam and ranitidine 150 mg given bedtime the night before surgery patient is kept NPO overnight

In the operating room, 18 G cannula secured in left upper limb. All patients were premedicated with 150mg ranitindine and 4mg ondansetron. Preloading done with 10ml/kg of ringer lactate prior to subarachnoid block. Baseline monitors were connected to record heart rate(HR), non invasive blood pressure(NIBP), ECG, oxygen saturation(sp02). After recording the baseline parameters, patient is put in sitting position and under sterile aseptic precautions, lumbar puncture done at L4-L5 level with 26G Quincke'sneedle.After free flow of CSF ,drug is injected slowly into the subarachnoid space. Patient is immediately place supine and onset of action assessed by pinprick, senasation at T6 level

Patients were randomly allocated into two equal groups 20 patients in each group. Group 1 received 2.8 ml of 0.5% hyperbaric bupivacaine with 0.1 ml of preservative free midazolam and 0.1 ml of distilled water Group 2 received 2.8 ml of 0.5% bupivacaine with 0.2 ml of preservative free midazolam

The onset of sensory block(time taken for complete loss of pin prick sensation at T10 level)

Duration of sensory block(time taken for sensory block to regress below T12)

Onset of motor block(time taken to achieve bromage Motor Scale 3)

Duration of motor block(bromage score 0)

Duration of effective analgesia (time for rescue analgesia intraoperatively IV fentanyl and postoperatively IM diclofenac, IV paracetamol, IV tramadol)

Surgery started following confirmation of subarachnoid block

Intraoperatively hypotension, fall in BP >20% in SBP from the baseline) treated with IV fluids and Mephentermine 6mg. Bradycardia treated with 0.6mg atropine when PR<60/min. Sedation score recorded.

Sedation score

0= awake

1= sleeping comfortably easily arousable

2= deep sleep but arousable

3= deep sleep not arousable

The obtained results were subjected to statistical analysis. Independent 't' test was used. P value determined

P value >0.05 taken in significant

< 0.05 significant

< 0.01 highly significant

< 0.001 very highly significant

Postoperatively ,patient observed for 24hours. Rescue analgesia was given with IV tramadol, IM diclofenac. Duration of sensory block was taken from starting of surgery till patient complains of pain and ask for rescue analgesia

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions: 1.**Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

RESULTS

No difference in demographic distribution of patients. No difference in onset of action duration of motor block and

side effects. Onset of sensory block in group 1 onset of sensory block in group 1 and and Group 2 was 2.33(min) ± 0.65 & 2.28±0.57 respectively P value of 0.845,which is not significant. Duration of motor block in group 1 and group 2 was 3.20(hr)±0.73 & 3.50±0.77 P value 0.226. Duration of sensory block in group 1 and group 2 was 4.08(hr)±0.88 & 6.67 (hr)± 1.29 p-value <0.001 significant. There is higher duration of pain free period with group 2. So we can say that intrathecal 2mg Midazo lam added to bupivacaine, duration of postoperative analgesia was significantly prolonged than 1 mg midazolam. So effect of intrathecal midazolam is dose dependent 2mg midazolam prolongs the action of bupivacaine with good sedation and no unwanted side effects.

Table 1: Age distribution of patients studied

Age in years	Group I	Group II	Total
31-40	1(5%)	7(35%)	8(20%)
41-50	1(5%)	6(30%)	7(17.5%)
51-60	3(15%)	6(30%)	9(22.5%)
61-70	7(35%)	1(5%)	8(20%)
71-80	7(35%)	1(5%)	8(20%)
>80	1(5%)	0(0%)	1(2.5%)
Total	20(100%)	20(100%)	40(100%)
Mean ± SD	67.30±11.44	48.80±11.16	58.05±14.21

P<0.001**, Significant, Student t test

Table 2: Gender distribution of patients studied

Gender	Group I	Group II	Total
Female	11(55%)	3(15%)	14(35%)
Male	9(45%)	17(85%)	26(65%)
Total	20(100%)	20(100%)	40(100%)

P=0.008**, Significant, Chi-Square Test

Table 3: ASA Grade distribution in two groups of patients studied

ASA Grade	Group I	Group II	Total
1	8(40%)	9(45%)	11(27.5%)
2	11(55%)	10(50%)	21(52.5%)
3	1(5%)	1(5%)	2(5%)
Total	20(100%)	20(100%)	40(100%)

P=1.000, Not Significant, Fisher Exact Test

Table 4: Weight (kg) distribution in two groups of patients studied

Weight (kg)	Group I	Group II	Total
<40	2(10%)	0(0%)	2(5%)
40-50	7(35%)	2(10%)	9(22.5%)
51-60	3(15%)	1(5%)	4(10%)
61-70	7(35%)	7(35%)	14(35%)
71-80	1(5%)	10(50%)	11(27.5%)
Total	20(100%)	20(100%)	40(100%)
Mean ± SD	54.75±12.63	68.95±8.92	61.85±12.97

P<0.001**, Significant, Student t test

Table 5: Onset of Actions (mins) distribution in two groups of patients studied

Onset of Actions (mins)	Group I	Group II	Total
1	2(10%)	1(5%)	3(7.5%)
2	9(45%)	11(55%)	20(50%)
2.5	1(5%)	0(0%)	1(2.5%)
3	8(40%)	6(30%)	14(35%)
Total	20(100%)	20(100%)	40(100%)

P=0.741, Not Significant, Fisher Exact Test

Table 6: Comparison of clinical and outcome variables in two groups of patients studied

variables	Group I	Group II	Total	P value
Age in years	67.30±11.44	48.80±10.16	58.05±14.21	<0.001**
Weight (kg)	54.75±12.63	68.95±8.92	61.85±12.97	<0.001**
Onset of actions (mins)	2.33±0.65	2.28±0.57	2.30±0.61	0.815
Duration of surgery (hrs)	2.60±1.10	2.08±0.65	2.36±0.94	0.090+
Duration of Motor Blockade (hrs)	3.20±0.73	3.50±0.77	3.34±0.75	0.226
Duration of Sensory Blockade(hrs)	4.08±0.88	6.67±1.29	5.30±1.70	<0.001**

Table 7: Sedation distribution in two groups of patients studied

Sedation	Group I	Group II	Total
Negative	0(0%)	2(10%)	2(5%)
Positive	20(100%)	18(90%)	38(95%)
Total	20(100%)	20(100%)	40(100%)

P=0.487, Not Significant, Fisher Exact Test

Table 8: Side Effects distribution in two groups of patients studied

Side Effects	Group I	Group II	Total
Negative	20(100%)	20(100%)	40(100%)
Positive	0(0%)	0(0%)	0(0%)
Total	20(100%)	20(100%)	40(100%)

P<0.001**, Significant, Fisher Exact Test

Table 9: Frequency distribution of Duration of motor blockade and Sensory blockade of patients studied

variables	Group I (n=20)	Group II (n=20)	Total (n=40)	P value
Duration of Motor Blockade (hrs)				
• <3	3(15%)	2(10%)	5(12.5%)	
• 3-4.5	16(80%)	14(70%)	30(75%)	0.755
• >4.5	1(5%)	2(10%)	3(7.5%)	
Duration of Sensory Blockade(hrs)				
• <5	13(65%)	1(5%)	14(35%)	
• 5-8	7(35%)	14(70%)	21(52.5%)	<0.001**
• >8	0(0%)	3(15%)	3(7.5%)	

Chi-Square/Fisher Exact Test

Table 10: Comparison of study variables in two groups studied

Variables	Group I	Group II	Total	P value
Duration of surgery (hrs)	2.60±1.10	2.08±0.65	2.36±0.94	0.090+
Duration of Motor Blockade (hrs)	3.20±0.73	3.50±0.77	3.34±0.75	0.226
Duration of Sensory Blockade(hrs)	4.08±0.88	6.67±1.29	5.30±1.70	<0.001**

DISCUSSION

Bupivacaine, a potent drug acting, amide local anaesthetic, blocks the generation, propagation and oscillation of electrical impulses in peripheral and central nervous system. The sodium channel is a key target to local anaesthetic actively. Bupivacaine blocks sodium currents and rapidly inactivates potassium currents in the neurons of spinal dorsal horn.[9,10,11] Benzodiazepines produce sedative hypnotic, anxiolytic, anticonvulsant and antinocioceptive effect by interaction with $GABA_A$ receptors. These receptors are known to be involved in nociceptive mechanism. The receptors are present in higher concentration in lamina II at dorsal horn ganglia. Yegin *et al* who studied 44 patients with bupivacaine and midazolam combination. No difference in onset of sensory block.[12] But there are no study done which compares the action of 1mg & 2mg midazolam intrathecally. Vlentine *et al* compared intrathecally bupivacaine, bupivacaine-midazolam, bupivacaine-dimorphine& found no side effects due to midazolam.[13] Tucker *et al* did a cohort study and concluded administration of 2mg midazolam intrathecal did not course any neurotoxicity.[14] Kim & Lee Prakash *et al* administered intrathecal bupivacaine, together with midazolam, in either 1mg or 2mg dose showed prolonged duration of action with addition of midazolam[15,16]

CONCLUSION

In our study, the duration of sensory block is prolonged in group II with mild sedation and no side effects. So we conclude that duration of action of intrathecal midazolam is dose dependent.

REFERENCES

1. Ganong WF Cutanious Deep and visceral sensation review of medical physiology. 13th edditon los altos CA : Lange Medical Publication 1987 Page No. 106-916
2. Khazri MB, Yoghobi S , Haji, Khani M asefzadeg S Comparition of post op analgesic effect of intrathecal magnesium and fentany added to bupivocail in patients undergoing lower limb orthopedic surgery ActaAnasthesio taiwan2012, 50(1) 19-24
3. Safari F Dabbagh A, Shariefnia M, The effect of Adjuvantmidazolom compared with fentanyl on duration of spinal anasthesia with 0.5 Percent bupivocaine in opium obusers korean J Anasthesio 2012, 63,521 (Pmc Free Article) (Pub Med) Cross reference.
4. Morgan M the rational use of intrathecal and extra duralopoid. Br.JAnastesio 1989, 63,165-88.
5. Chrubasck S Chrubasic J selection of the optimum opoid for extradural administration in treatment of post operativepain.Br.JAnastesio 1995, 74,121.
6. Edward M SerraoJm gent JP good child CS. on the mechanism by which midazolam causes spinally mediated anlgesicAnasthesio 1990, 73:273-277.
7. Manoj S Sanwal, Neha, Aruna Jain, bupivocain Sparing effect of intrathical midazolam in sub : arachnoid block for C Section. Journal of obstricAnasthesio and critical care 2013 Volume 3 issue 1 page 27 - 31.
8. MH Kim, YM Lee. intrathical midazolam increase the enalgesic effect of spinal blockage withbupivocain in patients undergoing haemorrhoidectomy BJA 2001 86(1) 77-79.
9. Rashiq S Fincan BT Nerve Conduction and local anesthetic action. In healing T Knight P, editorswylie and churchlldavidson of practice of anasthesio 7th edition. London hodder arnold 2003 page No 271.
10. Spencer S Liu, Raynold S, local anasthesia. In Barash PG. Cullen F, Stoelting RK, editors Clinical anesthesia. 5th edition. Philadelphia: Lippincott Williams and Wilins, 2005:page 453 (Goolge Scholar)
11. Olschewski A, Hemapelman G, Vogel W, Safranv BV. Blockade of Na and K Channels by local anaesthesia dorsal horn neurons of the spinal cord. Anaesthesiology.1998; 88 (1) : 171-179.
12. Yegin A, Sali S, Dosemeci L, et as. Analgesic and sedative effects on intrathecal midazolam in perianal surgery Eur J Anaestesiol. 2004; 21(8) 658-662.
13. Valentine JM. Lyons G, Bellany CM. The effect of Intrathecal midazolam on postoperative pain. Eur J Anaestesiol. 1996; 13(6) 589-593.
14. Tucker AP, Lai C, Nadeson R, Goodchild CS Intrathecalmidasolam l; a cohort study investigating safety. AnesthAnalg. 2004; 98(6) 1512-20.
15. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockage with bupivacaine in patients undergoing haemorhoidectomy. Br J Anaesth. 2001. 86(1): 77-79.
16. PrakashSm Joshi N, Gogia DR, Singh R. Analgesic efficacy of two doses of Intrathecal idazolam with bupivacaine in patients undergoing caesarean delivery. RegAnesth Pain Med. 2006; 31(3)221-226

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