ORIGINAL RESEARCH PAPER

Medical Science

A COMPARATIVE STUDY OF POST-OPERATIVE ANALGESIC EFFICACY OF BUPIVACAINE ALONE WITH BUPIVACAINE AND MIDAZOLAM COMBINATION INTRATHECALLY IN PATIENTS UNDERGOING SURGERIES BELOW UMBILICUS.

KEY WORDS: Intrathecal anesthesia, post-operative analgesia, infraumbilical surgeries, spinal anesthesia.

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ABSTRACT

Introduction: Recent practice of anesthesia has taken excellent care of pain relief during any surgery but the post-operative pain still remains the most horrible and unpleasant experience for patients.It creates a host of negative side effects on the patient as a whole, mainly respiratory and circulatory complications and effects the metabolic, hormonal and autonomic systems of the body.

Aim : To compare the post-operative analgesic efficacy of intrathecal Bupivacaine and midazolam combination with Bupivacaine alone in infraumbilical surgeries.

Materials & methods : We have undertaken randomized, double blind study of 60 patients undergoing lower abdominal and lower limb surgery under spinal anaesthesia . The study is randomized by closed envelope method. In this 60 envelopes were prepared and were sealed , each containing information about patients either administered 0.5% Bupivacaine (3ml)+0.4 ml Normal saline (group B) or 0.5% Bupivacaine (3ml)+0.4 ml Midazolam (2mg) preservative free (group M). After institutional ethical committee approval, patients undergoing lower abdominal and lower limb surgery under spinal anesthesia of either sex with American Society of Anesthesiologists (ASA) grade I and grade II status posted for elective surgery under regional anesthesia (subarachnoid block) were included in the study .The patients were randomly allocated into 2 groups of 30 each ,namely group B and group M. Informed written consent were taken. Data collected in pretested proforma meeting the objectives of the study.

Results : In the present study the duration of post operative analgesic action was prolonged from 120.6 + 5.4 minutes in group B to 220.6 + 12.2 minutes in group M. This was statistically highly significant as p value is <0.0001. In our study, all the patients in group B required supplemental analgesic within first 200 minutes, where as group M patients required it between 230 to 300 minutes postoperatively.

Conclusion : In conclusion it can be inferred that midazolam 2mg in combination with bupivacaine 0.5% heavy can be safely administered intrathecally for better postoperative analgesia than bupivacaine alone in lower abdominal, gynecological, urological and lower limb surgeries, without any significant side effects.

INTRODUCTION

Recent practice of anesthesia has taken excellent care of pain relief during any surgery but the post-operative pain still remains the most horrible and unpleasant experience for patients.It creates a host of negative side effects on the patient as a whole, mainly respiratory and circulatory complications and effects the metabolic, hormonal and autonomic systems of the body. Effective control of post-operative analgesia stays one of the most important issues in the field of anesthesia with significant impact on health care system. By administrating intrathecal combinations of drugs, targeting different spinal cord receptors; prolonged and superior quality analgesia can be achieved by relatively small concentrations of individual drugs. The dose reductions may avoid drug-related side effects. In addition, the simultaneous targeting of several different receptor sites in the spinal cord may lead to improved pain relief.

Among the local anesthetics, 0.5% hyperbaric bupivacaine is the most commonly used drug for spinal anesthesia [1]. The most important disadvantage of single injection subarachnoid block is the limited duration. Adjuvants have long been used along with local anesthetics to prolong the duration of anaesthesia and analgesia. Prolongation of pain relief by various adjuvants like opioids (like morphine [2], fentanyl [3]) , Ketamine [4] , clonidine [5], and neostigmine [6] were investigated by various investigators. However, each drug has its limitations and side effects, and the need for an alternative methods and drugs always exist.

. Midazolam, synthesized by Walsar and colleagues in 1976, was the first clinically used water soluble benzodiazepine [7] . It is also the first benzodiazepine that was produced primarily for use in anesthesia [8] . In 1986, Faull and Villiger demonstrated that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of the dorsal horn in the human spinal cord , suggesting a possible role in pain modulation [9] . One year later, Goodchild and Serrao reported that benzodiazepines might have analgesic effects at the spinal cord level in animals [10] . In 1990s, analgesic efficacy of intrathecal midazolam in humans has been demonstrated [11-13] .
Materials & methods

This clinical study was conducted during February 2016 to March 2018 at Hi-Tech Medical College & Hospital, Bhubaneswar. We have undertaken randomized, double blind study of 60 patients undergoing lower abdominal and lower limb surgery under spinal anaesthesia . The study is randomized by closed envelope method. In this 60 envelopes were prepared and were sealed , each containing information about patients either administered 0.5% Bupivacaine (3ml)+0.4 ml Normal saline (group B) or 0.5% Bupivacaine (3ml)+0.4 ml Midazolam (2mg) preservative free (group M). After institutional ethical committee approval, patients undergoing lower abdominal and lower limb surgery under spinal anesthesia of either sex, age between 20 to 60 with American Society of Anesthesiologists (ASA) grade I and grade II status posted for elective surgery under regional anesthesia (subarachnoid block) were included in the study .The patients were randomly allocated into 2 groups of 30 each ,namely group B and group M. Informed written consent were taken. Data collected in pretested proforma meeting the objectives of the study.

Upon arrival to the operating theatre, venous access was secured using an 18G venous cannula with no premedication given. An infusion of Ringer's lactate solution was started as a bolus of 500ml. All patients were administered spinal anaesthesia in sitting position. Under strict aseptic precautions, the back was sterilized using povidone iodine. At the site of insertion, tips of lumbar spine was palpated and L2-L3/ L3-4 space was selected. The skin was infiltrated with about 2ml of 2% lignocaine. Lumbar puncture was performed at the L2-L3/L3-L4 level through a midline approach using a 25G Quincke's spinal needle. Monitors were attached and base line vitals were recorded when patient taken into operation theatre. Surgery was started after achievement of the adequate level of sensory and motor block. After intrathecal injection, patients were positioned immediately in supine position and oxygen 4L/min was given through a face mask. All patients received Inj. Rantidine 50mg IV and Inj. Ondansetron 4mg IV for aspiration prophylaxis before surgery. Monitoring was done using standard monitor having non-invasive blood pressure (NIBP), electrocardiogram(ECG) , respiratory rate, arterial pulse oxygen saturation(SPO2).

All the patients were observed for time for onset (T10) of action measured by complete loss of sensation to pin prick, highest dermatomal level of sensory blockade, duration of sensory blockade, time of 2 segment regression of sensory block, duration of maximum motor blockade according to Bromage scale, effectiveness of pain relief in the post operative period assessed by Visual Analogue Score, systolic and diastolic blood pressure, pulse rate and respiratory rates were recorded at every 5 minutes till 20 minutes and then every 10 minutes till regression of the block. Onset of sensory blockade is defined as time taken from the completion of the injection of local anaesthetic solution with or without midazolam till the subject does not feel the pin prick at T10 level. Level of sensory block is defined as the highest dermatomal level of sensory blockade. Duration of sensory blockade is defined as the time interval from injection of local anaesthetic solution with or without midazolam to regression of 2 dermatomal segments of maximal level of analgesia. Onset of motor blockade is defined as the time taken from the completion of injection of the study drug till patient is unable to lift his leg against gravity but is able to flex his knee and ankle. Duration of maximum motor blockade is the time taken from the time of injection till the subject attains complete motor recovery. Duration of analgesia is defined as the time interval between administration of local anaesthetic solution with or without midazolam to the first request /need for supplementary analgesics. Effectiveness of pain relief in the post operative period was assessed by Visual Analogue Score.The patient makes a mark on a 10 cm scale horizontal or vertical,one end of which is marked as no pain and the other as the worst pain one can imagine. The position of the mark on the line measures how much pain the patient experiences.

Hypotension was assessed as reduction of Systolic blood pressure (SBP) more than 20% below baseline or fall in SBP less than 90 mm of Hg, and it was to be treated with increased rate of intravenous (IV) fluids and if needed injection Ephedrine 6mg IV bolus dose. Bradycardia was assessed as heart rate less than 60 beats/minute and was to be treated with injection Atropine 0.3mg IV.

Statistical analysis

Student's t test was used for comparison between the groups and one-way analysis of variance was used for hemodynamic parameters. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the patient characteristics of the group B and M. There was no significant difference in patient's age, sex, type of surgery among the groups.

Table 1: Patient characteristics

Patient characteristics	Group B	Group M
Age (yrs)	35.6 ± 8.6	36.7 ± 7.8
Sex (male/female)	17/13	18/12
Nature of surgery		
Surgical	12	10
Gynaecological	05	7
Orthopedics	13	13

Table 2 shows duration of sensory blockade and analgesia is significantly higher in group M compared to group B. It has been observed that addition of preservative free midazolam added to bupivacaine offers a significant increase in the duration of analgesia with $P < 0.05$.

Table 2 : Study parameters

Study parameters	Group B	Group M	P value
Onset of sensory block	4.6 ± 0.07	4.5 ± 0.08	0.1
Two segment regression	80.34 ± 5.2	113.25 ± 6.3	0.0001
Duration of analgesia	120.6 ± 5.4	220.6 ± 12.2	0.0001

In our study, all the patients in group B required supplemental analgesic within first 200 minutes, where as group M patients required it between 230 to 300 minutes post-operatively. Group M patients had better analgesic effects in the postoperative period.

The hemodynamic parameters like pulse rate and blood pressure in both the groups were comparable and there was no statistical difference observed. In group B, 5 patients had bradycardia which was treated with atropine successfully, 8 had hypotension and 5 patients had nausea and vomiting. In group M, 5 patients had bradycardia, 8 had hypotension and 4 patients had nausea and vomiting. No patient in any group had any serious incidence of side effects like respiratory depression, severe hypotension, neurological problems or any other devastating condition. There was no incidence of respiratory depression, signs of neurotoxicity, headache, backache, lower limb weakness, sphincter incontinence during micturition during the study.

DISCUSSION

Pain is " an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1] as defined according to the International Association for the Study of Pain (IASP). Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly.

The role of anaesthesiologist is very well played to keep the patient pain free during surgery but post-operative pain still exists as a concern as its a much neglected issue all over the globe.Apart from obvious humanitarian ground, effective post-operative analgesia results in decreased incidence of systemic complications, early return of gastrointestinal motility, early ambulation and discharge from hospital.

In 1983,D.Niv et al [14]established the antinociceptive effects of midazolam , a water soluble benzodiazepine , after the presence of benzodiazepine receptors in central nervous system and their interaction with GABA system had been established.

Goodchild C.S.,Noble J.in [15]1987 studied the effects of intrathecal midazolam on sympathetic nervous system reflexes in man. This pilot study was done in 9 patients, showed no change in resting heart rate and blood pressure.The study concluded that intrathecal midazolam in the dosage used (0.3-2mg dissolved in 3ml of 5%D) interrupted somatic nociceptive afferent pathways but not abdominal visceral nociceptive afferent pathways.

In 1990 J.M.Serrao, M.Edwards and C.S.Goodchild [16]performed a study on the mechanism by which midazolam causes spinally mediated analgesia.The electrical current thresholds for pain in the skin of neck and tail were measured in rats with chemically implanted lumbar subarachnoid catheters. The aurhors concluded that segmental analgesia produced by intrathecal midazolam is mediated by benzodiazepine-GABA receptor complex that is involved in other benzodiazepine actions.

Among recent studies in 2011, Shadangi BK et al. [17], In 2012 K.Malavika et.al.[18], in 2012,Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. [19], Sanwal MK, Baduni N, Jain A. in 2013 [20], In 2015, G.Anshu, K.Hemlata, K.Utpala [21] and in 2017, Ganesh, et.al. [22] has shown the significant postoperative analgesic prolongation with different intrathecal doses of midazolam along with local anesthetics.

Our study shows addition of 2mg of preservative free Midazolam to 0.5% heavy Bupivacaine significantly prolongs the duration of sensory blockade as well as duration of effective analgesia without producing any significant adverse effects.

Conflicts of interest : None.

REFERENCES

1. Morgan GE, Jr., Mikhail MS, Murray MJ, Larson CP., Jr. Clinical Anaesthesiology. 4th edition. New York, NY, USA: Lange; 2002.
2. Tan PH, Chia YY, Lo Y, Liu K, Yang LC, Lee TH. Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. Canadian Journal of Anesthesia.2001;48(6):551–556. [PubMed]
3. Hunt CO, Naulty JS, Badder AM, et al. Peri operative analgesia with subarachnoid fentanyl-bupivacaine for caesarian section. Anaesthesiology. 1989;71(4):535–540. [PubMed]
4. Karthival S, SdhasivamS, Saxena A, Kannah TR, Ganjoop P. Effects of intrathecal ketamine added to bupivacaine for spinal anesthesia. Anarsthesia. 2001;55(9):899–904. [PubMed]

5. Dobrydjnovl, Axelsson K, Samarutel J, Holmstrom B. Post operative pain relief following intrathecalbupivcaine with intrathecal or oral clonidine. ActaAnaesthesiologicaScandinavica. 2002;46(7):806–814.[PubMed]
6. Liu S. Dose-response effects of spinal neostigmine added to bupivacaine spinal anesthesia in volunteers.Anesthesiology. 1999;90(3):710–717. [PubMed]
7. Webb PJ,JAMES FM III,WheelerAS,Shivering during epidural analgesia in women in labour.ANAESTHESIOLOGY 1981;55:706-7
8. Crossley AW .Peri-operative shivering .Anaesthesiology 1992;47:193-5
9. Sessler DI ,Ponte J.shivering during epidural anesthesia .Anaesthesiology 1990;72:816-21
10. OzakiM, KurzA, SesslerDI, LenhardtR, Schroederm, moayeriA, NoyesKM,. Thermoregulatorythreholds during epidural and neuraxial blockade. Anaesthesiolgy 1994;81:282-8
11. HynsonJM,SesslerDI,MoayeriA,Mcguire J:Absence of non shivering thermogenesis in anesthetized humans.anaesthesiology 1993;79:695-703
12. Ciofolo MJ ,ClergueF,DevilliersC,BenAmmarM,ViarsP,changes in ventilation, oxygen uptake and carbon dioxide output during recovery from isofluraneanesthesia. ANAESTHESIOLOGY 1989;70:737-41
13. Jones HD,McLarenCAB.postoperative shivering and hypoxemia after halothane ,nitrous oxide and oxygen anesthesia.Br J ANAESTHESIOLOGY 1965;37:35-41.
14. Niv, David & Davidovich, Shaul & Geller, Eran & Urca, Gideon. (1989). Analgesic and Hyperalgesic Effects of Midazolam: Dependence on Route of Administration.. Anesthesia and analgesia. 67. 1169-73. 10.1213/00000539-198812000-00010.
15. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man--a pilot study. Br J Clin Pharmacol. 1987 Mar;23(3):279-85.
16. Edwards M1, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. Anesthesiology. 1990 Aug;73(2):273-7.
17. Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: A prospective randomised case control study. Singapore Med J 2011;52:432-5.
18. Kulkarni, Malavika and Kurdi, Madhuri and Sujatha, DA and Kulkarni, Muralidhar M (2012) The role of intrathecal midazolam as an adjunct to bupivacaine in providing post-operative pain relief. International Journal of Health & Allied Sciences, 1 (4). pp. 231-234. ISSN 2278-4292.
19. Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. Indian J Pharmacol. 2012;44(3):357-61.
20. Sanwal MK, Baduni N, Jain A. Bupivacaine sparing effect of intrathecal midazolam in sub- arachnoid block for cesarean section. J Obstet Anaesth Crit Care 2013;3:27-31.
21. 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):379-83.
22. M. Venkata Ganesh, P.V.S. Lavanya. Comparative clinical study of 0.5% hyperbaric bupivacaine alone and 0.5% hyperbaric bupivacaine with midazolam intrathecally for lower limb orthopaedic surgeries. International Journal of Contemporary Medical Research 2017;4(8):1644-1647.