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COMPARATIVE STUDY OF INTRATHECAL MIDAZOLAM VERSUS MAGNESIUM SULPHATE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE

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ABSTRACT

Background: Intrathecal drugs when used as adjuvant to spinal anaesthesia produce substantial anti-nociception and potentiate analgesia of bupivacaine. This study was planned to evaluate the effects of intrathecal non opioid drug midazolam and magnesium sulphate on duration of analgesia, characteristics of SAB and hemodynamic stability when added to 0.5% hyperbaric bupivacaine for spinal anaesthesia.

Methods: Sixty ASA physical status I-II patients of age group between 20 to 60 years with elective forearm and hand surgery under brachial plexus blocks were randomly allocated into two equal groups in a randomised double blind fashion. Group MZ received midazolam 2mg and Group MG received Mgso4 50mg with 15mg hyperbaric bupivacaine. The onset time and duration of sensory and motor blocks, quality of intraoperative analgesia and duration of analgesia were assessed.

Results: The duration of postoperative analgesia was significantly prolonged in MZ group 391.64 (132.98) minutes as compared to MG group 252.2 (86.76) minutes ($P < 0.05$). The numbers of analgesic doses in 24 hours were significantly less in BM group.Time of onset of sensory and motor block was significantly less in group MZ as compared to group MG ($P < 0.05$). The duration of the sensory and motor block as well as duration of post-operative analgesia was significantly more in group BM as compared with group BMG ($P<0.05$), but there was no statistically significant difference between both the groups with respect to the heart rate, mean arterial pressure and spo2.

Conclusions: Intrathecal midazolam 2mg provides superior analgesia without clinically relevant side effects. The onset of analgesia was rapid and duration of sensory and motor block was prolonged with intrathecal midazolam and it also prolongs the duration of post-operative analgesia.

KEYWORDS : Subarachnoid block, Hyperbaric Bupivacaine, Magnesium sulphate, Midazolam, Postoperative analgesia.

INTRODUCTION:

Neuraxial blockade is the preferred mode of anaesthesia for lower abdominal and lower limb surgeries. It has rapid onset, superior analgesia, less failure rate and it is cost effective. It provides excellent pain relief as compared to intravenous or epidural route.[1] But the duration of block is short and it lacks postoperative analgesia. Use of intrathecal adjuvants has gained popularity with the aim to prolong postoperative analgesia, patient satisfaction and fast recovery. Neuraxial opioids though effective are associated with a number of undesirable side effects like delayed respiratory depression, nausea, vomiting, urinary retention and pruritus that limit their use in ward.[2,3]

Currently researchers have focused on non-opioid spinal receptors that inhibit transmission of pain signals. Increased understanding of spinal processing of pain has led to development of specific drugs that inhibit pain transmission. Intrathecal magnesium sulphate produce substantial anti-nociception without neurotoxicity, potentiate analgesia of bupivacaine and opioids as evident from animal and human studies[3-5] Also intrathecal midazolam produce a dose dependent anti-nociception when used alone or in combination with local anaesthetics.[6,7] They improve intraoperative analgesia, prolong duration of sensory and motor blockade along with sparing effect on post-operative analgesic consumption.[3,8,9]

We compared the non-opioid adjunct analgesic drugs to establish the superior additive for postoperative analgesia after neuraxial administration. Adjuvant analgesic strategy to prolong the analgesic duration, to reduce the potential risk of side effects of local anaesthetics by decreasing the dose of local anaesthetics has been tried by many investigators. Drugs like clonidine & neostigmine potentiate spinal antinociception and also exhibit adverse effects like respiratory depression, priritis, and excessive nausea and vomiting. Drugs like dexmedetomidine, dexamethasone have also been used successfully as an adjunct in spinal anesthesia along with local anesthetic.

Magnesium sulphate exerts its analgesic action as a noncompetitive N-Methyle-D-aspartate (NMDA) receptor antagonist, blocking ion channels in a voltage dependent manner when used intrathecally. The addition of magnesium reduces the activation of C-fibers by inhibiting the slow excitatory postsynaptic currents produced by NMDA receptor activation. NMDA receptor antagonists abolish calcium & sodium influx into cells leading to central sensitization and windup attributed to peripheral nociceptive stimulation. They abolish hypersensitization by blocking NMDA receptor activation in the dorsal horn by excitatory amino acid transmitters, notably glutamate, and aspartate. Magnesium is also known as nature's physiological calcium blocker. On the other hand intrathecal midazolam has been shown to have analgesic properties & potentiate the effects of intrathecal local anesthetic. The mechanism by which midazolam provides analgesia has been explored in several recent studies, it acts through gamma- aminobutyric acid (GABA) receptors present in the dorsal horn of spinal cord with the highest density of these receptors found within the lamina 2 of the dorsal horn ganglia, a region that plays a prominent role in processing nociceptive & thermoceptive stimulation. It may also have central antinociceptive effect via the activation of spinal δ opioid receptors.

MATERIALS AND METHODS:

After obtaining institutional ethical committee approval and informed consent the study was conducted on 60 normotensive patients of ASA physical grade 1 and 2of either sex between 18-60 years of age. All the patients were randomly divided into 2 groups:

Group MZ (n = 30), received 3 ml of 0.5% hyperbaric bupivacaine and 0.5 ml of midazolam 2mg preservative free, making a total of 3.5 ml. While

Group MG (n = 30), received 3 ml of 0.5% hyperbaric bupivacaine and 0.5 ml of magnesium sulphate 50 mg preservative free, making a total of 3.5 ml.

Exclusion criteria:

Patients with psychiatric disorder, chronic pain or any condition that precludes spinal anaesthesia or those taking antihypertensive medication and failure of spinal block with need for general anaesthesia, with known hypersensitivity to local anaesthetic, and pre-existing peripheral neuropathy, were excluded from the study.

METHOD:

In the pre-operative room, intravenous access was secured with 18-G cannula on the contralateral hand and baseline parameters such as heart rate mean arterial pressure, oxygen saturation was observed and recorded.

In the operation theatre, a slow IV infusion of Ringer lactate was started and monitors were connected (pulse oximetry, electrocardiography and non-invasive arterial blood pressure monitoring). Premedication with intravenous (IV) ranitidine 50mg and ondansetron 4mg given just before induction of anaesthesia. Oxygen was administered via a Hudson mask at a rate of 5 L/min. Spinal anaesthesia was carried out in lateral position at lumbar 3-4 inter space using 23 gauge disposable spinal needle. A skin wheal with local anaesthetic was raised at site of spinal needle insertion. After clear and free flow of cerebrospinal fluid (CSF), one of the study solutions was administered intrathecally depending upon the group at the rate 0.2 ml per second. The head end of the operating table was elevated by 10-20 degree. Sensory block was assessed by loss of sensation to pin prick. Motor block assessed as inability to move lower limb.

Supplemental oxygen via ventimask was given at 5 liter/minute during procedure. Pulse rate, blood pressure and oxygen saturation (SPO2) was recorded at baseline 5, 10, 15, 30, 60, 120, 180 min after the block intra-operatively. IV fluids (crystalloids, colloids or blood) were administered for maintenance and according to surgical blood loss. Hypotension was defined as systolic BP <90mmHg or 20% fall in systolic BP from baseline value and treated with 250ml bolus IV fluids and IV mephenteramine 6 mg. Bradycardia was defined as pulse rate <60/min and treated with IV atropine sulphate 0.6mg. The pain score was recorded on 10cm visual analogue scale, 0= no pain, 10= Intolerable pain). Each patient received intramuscular diclofenac sodium 75mg immediately after shifting in ward. Further analgesic dose was administered on patient's demand. If pain persists (VAS>5), IV tramadol 1mg/kg was given.

All durations were calculated considering the time of spinal injection as time zero.

The primary outcome measure was duration of postoperative analgesia i.e. time from IT injection till demand for rescue analgesic or VAS>5. Pain score was recorded every two hours until first rescue analgesic dose. The total number of analgesic doses in 24 hours was recorded.

Data was collected regarding the onset of sensory block (Time taken from IT injection to loss of pinprick sensation bilaterally at L1, duration of sensory block (Time from IT injection to 2 segment regression), onset of motor block (Time from IT injection to disappearance of leg movements) duration of motor block (Time from IT injection till reappearance of leg movements), Side effects like hypotension, bradycardia, sedation, nausea, vomiting, respiratory depression (SPO2<90%) shivering, itching, drowsiness, headache bowel/bladder dysfunction, neurological deficit were recorded as and when they occur. IV metoclopramide 10mg was given as rescue antiemetic. Each subject was observed for 24 hours, 48 hours after surgery. The recruitment stopped after enrolling 30 participants in each group.

STATISTICAL ANALYSIS:

The sample size of 30 subjects per group was necessary for detecting clinically significant difference of 67 minutes in duration of analgesia assuming a power of 80% and a significance level of 5% using GraphPad StatMate 2.00 software. The data was analysed using one way ANOVA with Tukey HSD post-hoc test [MedCalc Version 17.6- MedCalc software bvba (BE), Belgium]. Catagorical data was analysed by Chi square test with Yates correction using OpenEpi version 3.01 (www.openepi.com).

RESULTS:

Table 1: Demographic data of the study subjects

Patient Characteristics	Group MZ	Group MG	P value
Age in years(mean ±SD)	34.19 ±11.11	34.68±10.12	0.859
Weight in kg(mean ±SD)	62.35±4.26	64.23±7.22	0.224
Height in cm(mean ±SD)	167.18±1.66	166.83±2.10	0.350
Gender(M/F)	14/16	13/17	0.38
Duration of surgery	58.94±10.66	60.12±11.44	1.180

Table 1 shows the demographic data of the patients. There was no statistically significant difference between the two groups with respect to age, weight, height, sex and duration of surgery.

Table 2: Characteristics of sensory and motor block in both groups

Group DM	Group MZ	Group MG	P value
Onset time of sensory block (min)	1.87± 0.71	1.31± 0.61	0.0018
Onset time of motor block (min)	2.21± 0.89	1.94± 1.12	0.0039
Duration of sensory block (min)	198.5± 41.7	108 ± 26.4	0.0001
Duration of motor block (min)	283.97± 57.2	232.2 ± 38.08	0.0001
Duration of analgesia (min)	378.5± 94.2	306.35 ± 69.74	0.0013
No. of analgesic doses	2.08 ± 1.02	3.68 ± 0.81	0.0001

The onset of sensory and motor block was earlier in group MG as compared to group MZ (table 2; p<0.05). The duration of sensory and motor block were longer in MZ group than group MG (table 2; p<0.001). Duration of analgesia was significantly longer in MZ group than MG group (table 2; p<0.001). However, intraoperative analgesia was excellent and similar in both groups and statistically insignificant.

Figure 1: Comparison of pulse rate in both the groups

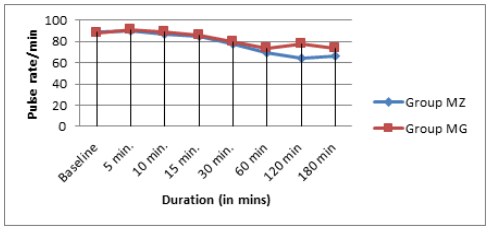

Figure 1 shows the comparison of pulse rates in both the groups and were found comparable without any statistical significance.

Figure 2: Comparison of mean arterial pressure in both the groups

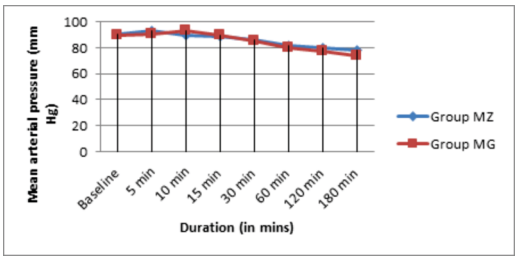

Figure 2 shows the comparison of mean arterial pressure which was comparable in both the groups without any statistical significance.

DISCUSSION:

Addition of both the adjuvant to local anaesthetic caused early onset, prolonged sensory and motor block, delayed onset of postoperative pain, decreased requirement of opioid analgesic in post-op period and lower incidence of post-operative nausea and vomiting. We observed superior quality of analgesia as well as prolonged sensory and motor block with intrathecal midazolam as compared to MgSO4.

Several investigators have shown that intrathecal midazolam produces a dose dependent anti-nociception sufficient to produce anaesthesia for abdominal surgery.[11] Patient do not require opioid analgesic when subjected to painful somatic stimulus like leg surgery.[12] It is also effective in relieving chronic mechanical low back pain as well as pain due to metastatic bone tumours.[11] Sympathetic nervous system function remains intact after intrathecal midazolam.[12-14] This sparing effect on sympathetic nervous system may explain lesser degree of hypotension and bradycardia in midazolam group in our study.

Three possible mechanisms are suggested for the antinociceptive action of midazolam. First the benzodiaze pine/GABA-A receptor complex mediated analgesia as they are abundantly present in lamina II of dorsal horn of spinal cord.[15,16] It also causes release of endogenous opioid acting at spinal delta receptors as naltrinadole, a delta receptor opioid antagonist suppresses its analgesic effect.[17] Thirdly it inhibits adenosine uptake or enhance adenosine release.[14] The use of intrathecal midazolam in humans is reported in at least 18 peer reviewed reports in about 797 patients since 1986. It is shown to be free of neurotoxicity or other side effects up to 2mg dose and in continuous infusion up to 6mg/day for long period in man.[3,13,18,19]

Magnesium sulphate reveals anti-nociceptive effect in animal and human pain models; it has potential to prevent central sensitization from peripheral nociceptive stimuli. Painful stimulus release glutamate and aspartate neurotransmitters which binds to the NMDA receptors. Activation of these receptors leads to calcium entry into the cell that initiate a series of central sensitization such as wind-up and long term potentiation in spinal cord. This NMDA signaling is important in determining the duration and intensity of postoperative pain.[20-22] Magnesium blocks the calcium influx into the cell i.e. natural physiological calcium antagonism and non-competitively antagonises the N-methyl-D-aspartate (NMDA) receptors. Mg++ is a neuro-protectant protecting cerebellar neurons against glutamate toxicity and spinal cord from ischemic injury during aortic cross clamping.[23-25] Selective NMDA receptor antagonists is not available for clinical pain management. However several compounds like magnesium sulphate and ketamine approved for use in humans for other indications have significant NMDA receptor blocking properties. The dose of Mgso4 was based on data from previous human studies and rat models of postoperative pain.[4,10,26,27] Further dose response studies are required to determine whether large doses of intrathecal MgSO4 can produce better potentiation of analgesia and reduction in analgesic requirement.[10,28] It is possible that effects of magnesium sulphate on NMDA receptor complex are weaker or they do not play an important role in maintenance of postoperative pain.[23] But the super additive interaction of magnesium sulphate is also reported.[25] In present study mild sedation was observed in 56% subjects with MgSO4, the patients were sleeping comfortably. The incidence was similar to that reported previously.

CONCLUSION:

Although both midazolam and MgSo4 are good adjuvants for subarachnoid block but our present study suggests that addition of intrathecal midazolam to hyperbaric bupivacaine prolongs sensory and motor block as well as provides prolonged duration of postoperative analgesia as compared to MgSo4 without any adverse side effect.

Ethical Clearance: No deviation from standard care of treatment.

Conflict of Interest: None.

Source of Support: Nil.

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