EFFICACY AND SAFETY OF INTRATHECAL MAGNESIUM SULPHATE AS AN ADJUNCT TO BUPIVACAINE FOR LOWER LIMB ORTHOPAEADIC SURGERY

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Summary

This randomized, placebo controlled, double blind prospective study was designed to assess the effect of intrathecal magnesium sulphate on the onset and duration of sensory block by bupivacaine (heavy in spinal anaesthesia).
Sixty patients undergoing elective lower limb orthopaedic surgery were randomly allocated in one of the two following groups. Group M received 50 mg of magnesium sulphate 5% (1 ml) followed by 15 mg of bupivacaine (heavy). Group P patients were given 1 ml 0.9% sodium chloride followed by 15 mg of bupivacaine (heavy). The duration of onset, highest level and time to reach the highest level of sensory block and the time of rescue analgesia given were recorded. Magnesium sulphate caused a delay in the onset of sensory block. Time to achieve peak sensory level was more in group M. Time for rescue analgesia was also prolonged in group M. The addition of intrathecal magnesium sulphate with bupivacaine (heavy) in spinal anaesthesia delays the onset of sensory block but prolongs the period of analgesia without additional side effects.

Key Words: *Magnesium sulphate, Sensory block, Spinal anaesthesia*

Introduction

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation [1, 2]. It is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptor antagonists block the central sensitization induced by peripheral nociceptive stimulation [3]. Magnesium blocks the dorsal horn NMDA receptor activation by excitatory amino acid transmitters like glutamate and aspartate.[4] Koining and Colleagues [5] reported that intravenously administered magnesium led to a significant reduction in fentanyl consumption in the peri operative and post operative period.

Magnesium sulphate has been used intrathecally in animal experiments and it prolongs the action of spinal anaesthesia and analgesia [6, 7]. The route of administration has been shown to be clinically safe in human also [8] and its safety profile has been evaluated in several experimental settings, including histopathologic analysis [9].The present randomized, placebo controlled, double blind, prospective study was designed to assess the efficacy of intrathecally administered magnesium sulphate used as a supplementation with bupivacaine to prolong sub-arachnoid block and also the duration of post operative analgesia.

Patients and Methods

The present study was undertaken by the departments of Orthopedics and Anesthesiology of Calcutta National Medical College and Hospital, Kolkata in collaboration with the department of Pharmacology, Medical College, Kolkata. The study protocol was approved by the Institutional Ethical Committee. Study subjects were enrolled from the patients presenting for elective lower limb surgery in both outpatients' department and inpatients' wards of the Department of Orthopedics, Calcutta National Medical College after they fulfilled the inclusion and exclusion criteria laid down for the study. Written informed consent was duly obtained from all the participants in their own language. The study period was April 2008 to March 2009. Actual data collection period was from May 2008 to February 2009 excluding initial month for preparation of study and last month kept for analysis & report writing. All the patients satisfying the selection criteria were recruited for the study during these ten months and after five patients were excluded due to exclusion criteria, finally sixty patients became the study subjects.

Subject selection criteria

Screening for eligibility of the subjects was performed on the basis of the following criteria:

Inclusion Criteria:

- Patients of either sex.
- Undergoing elective lower limb orthopaedic surgery.
- Fit for major elective surgery as opined by orthopedician & anesthesiologist.
- Willingness to give written informed consent for the study procedures.

Exclusion criteria:

- Patients with high cardiac risk factors (B.P >160/110 mm of Hg; Grade III, IV angina; uncontrolled heart failure etc.)
- Significant renal impairment (creatinine clearance < 30 ml / min).
- Significant hepatic impairment (ALT >200μ g /dl; Prothrombin Time >15 sec).
- BMI ≥ 40, pregnancy.
- diabetic neuropathy and neuromuscular disorders.
- Patients treated with Ca-channel blockers, opioids, magnesium sulphate and drugs known to have interaction with NMDA within six months of inclusion in the study.
- Any other clinically significant physical & mental abnormalities .

Procedure

Sixty ASA Grade I and II patients undergoing lower limb orthopedic surgery were thus randomly assigned to one of the two equal groups (n=30) in a double blind manner -Group M (magnesium group) and Group P (Control group). All patients were examined a day before surgery. They were kept fasting over night and received diazepam 0.2 mg/kg orally as pre medication.

On the operating table, routine monitoring (ECG, pulse oximetry, NIBP) was started and baseline vital parameters like heart rate, blood pressure and arterial oxygen saturation (SPO_2) were recorded. An intravenous line was secured and all patients were preloaded with Ringer lactate 15 ml/kg. The patients were randomly assigned to one of the two groups. Group M (n=30) patients received 50 mg of magnesium sulphate 5% (1ml), followed by 15 mg of bupivacaine (heavy). Group P were given 1ml of 0.9% sodium chloride following 15mg of bupivacaine (heavy).The patients were made to lie in left lateral position and sub-arachnoid block was administered intrathecally in L_{3-4} space with 25 gauze spinal needle. The anesthesiologist administering the drugs was blinded to the solution. Patients were then made supine and following were noted.

- Time of sub-arachnoid block
- Time of onset of sensory block (assessed by pin prick)
- Time to achieve the maximum level of sensory block
- Duration of surgery
- Time of rescue analgesia given

Heart rate, blood pressure and arterial oxygen saturation was monitored at every five minutes interval intra-operatively and at every twenty minutes interval postoperatively till rescue analgesia was given. Hypotension was defined as > 20% decrease in systolic blood pressure from baseline value and was treated with intravenous fluids and intravenous mephenteramine (3 mg) in incremental doses. Bradycardia (pulse < 60 beats / min) was treated with intravenous atropine sulphate. Adverse effects such as nausea, vomiting, drowsiness were also noted. No other sedative or analgesic was given to the patients intra-operatively. Postoperative rescue analgesia in the form of diclofenac sodium (1.5mg/kg) intramuscular was given on patient's demand. Duration of pain relief was taken from onset of sub-arachnoid block to time of administration of rescue analgesia.

Statistical analysis

The results obtained from the study were presented in the following section in a tabulated manner. The results are expressed in mean ± SD. Comparison between the groups were performed with the Kruskal-Wallis one way ANOVA by ranks and Fisher's exact test for small samples with a 5% risk. Mann-Whitney-Wilcoxon tests were performed when normal tests failed. A p value < 0.05 was considered to be statistically significant. [Graph pad Instat Version 3.05, Graph Pad Software, San Diego, CA].

Results and Discussion

Table 1

Patient characteristics (Mean ± SD)

	Group M	Group P
Age (mean; range)	46.7 [35-65]	41.4 [35-65]
Sex (M:F)	21 : 9	23 : 7
Body weight	66.92 ± 10.78	64.88 ± 10.8
Duration of surgery (min)	111.28 ± 13.3	116.32 ± 11.56

The groups were comparable with respect to age, sex, bodyweight and duration of surgery.

Table 2

Comparison of block characteristic (Mean ± SD)

	Group M	Group P	Statistical Significance
Onset time of sensory block (min)	6.65 ±1.08	5.2± 1.21	P< 0.001, S
Time to achieve peak sensory block (min)	19.26 ±4.41	14.83 ±3.46	P< 0.001, S
Time for rescue analgesia	382.13 ± 46.9	180.76 ± 31.25	P< 0.001, S

S = Significant, NS = Not significant

The mean value of onset time of sensory block (assessed by loss of sensation by pin prick method) in group M was more than group P. This difference was found statistically significant ($p<0.001$) Mean time to achieve peak sensory level in group M was 19.26±4.41 minutes and 14.83 ±3.46 minutes in group P. The difference was again statistically significant ($p<0.001$). Time for rescue analgesia in group M was significantly prolonged in comparison to group P ($P<0.001$).

Table 3

Distribution of patients according to occurrence of adverse effects (Values are in number)

Adverse effects	Group M	Group P	Statistical Significance
Hypotension	8	6	P> 0.05 NS
Bradycardia	5	3	P> 0.05 NS
Nausea	5	7	P> 0.05 NS

S = Significant, NS = Not significant

Hypotension, bradycardia and nausea experienced by patients of both groups when compared, was statistically insignificant ($p>0.05$). There was no incidence of drowsiness and respiratory depression.

In this prospective, randomized, double blind, controlled trial; we found that onset of sensory block was slower in the group received intrathecal magnesium sulphate. Time to achieve peak sensory level was more than the control group. However, time for rescue analgesia is prolonged in group M.

Magnesium sulphate administered as an adjunct to bupivacaine in intrathecal route prolongs the duration of postoperative analgesia and this finding correlates with the knowledge on the pharmacological mechanisms underlying the anti-nocicetive action of magnesium ions. Magnesium ion blocks NMDA receptors associated channels in a voltage-dependent manner[10]. NMDA receptor channels are ligand-gated ion channels that generate slow excitatory post-synaptic currents at glutamatergic synapses. Some evidences suggest that sustained NMDA receptor activation promotes intracellular signaling that culminates in long-term plasticity, wind-up phenomenon and central sensitization [3].

Magnesium sulphate is being administered intravenously to reduce intra-operative consumption of hypnotic agents and analgesics and post-operative analgesic requirements [5]. Although this clinical observation could suggest in favour of the anti-nociceptive efficacy of the intravenously administered magnesium sulphate, it does not seem to be associated with a corresponding increase in cerebrospinal fluid (CSF) concentration of magnesium ion [11]. Makee JA and Brewer RP [12] observed the failure of intravenously administered magnesium sulphate to act on the spinal cord despite the activation of spinal NMDA receptor

gated channel, as the CSF concentration of magnesium ion in rats and human remain unchanged even when the plasma concentration of magnesium ion varies.

Direct administration of magnesium sulphate in the sub arachnoid space has been advocated to obtain a clinically effective and sustained action of magnesium ion on spinal cord NMDA receptors. Animal experiments have shown that direct intrathecal administration of magnesium sulphate causes prolongation of sub arachnoid anaesthesia [6, 7] This route of administration has been shown to be clinically safe in human being also after evaluating the safety profile by several experimental settings including histopathologic analysis [8, 9]. We hypothesized that, like local anaesthetics and opioids, magnesium sulphate administered directly into sub arachnoid space might reach and maintain therapeutic concentration in the CSF and thereby prolongs sub arachnoid anaesthesia by acting on spinal cord NMDA receptors.

Incidence of side effects like hypotension and bradycardia were almost similar in both groups (the difference is not statistically significant). Incidence of nausea was more in control group than in the magnesium group, although not statistically significant.

To conclude, addition of magnesium sulphate with bupivacaine (heavy) intrathecally delays the onset of sensory block but prolongs the period of analgesia without additional side effects.

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