Study of Intrathecal Magnesium Sulphate as an Adjunct to Bupivacaine for Subarachnoid Block in Infraumbilical Surgeries - A Randomised Double-Blind Study

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ABSTRACT

BACKGROUND

To improve the quality and duration of subarachnoid block various adjuncts have been used. But they exhibit side effects like nausea, vomiting, pruritis, respiratory depression, urinary retention and haemodynamic instability. Magnesium does not cause adverse effects when used as an adjuvant in therapeutic doses.

METHODS

This was a prospective, randomized, double blind, controlled study. 50 patients belonging to ASA physical status I and II posted for infraumbilical surgery were randomized into two groups. Group I patients received Inj. bupivacaine 0.5% heavy 2.5 mL (12.5 mg) with Inj. normal saline 0.2 mL intrathecally. Group II patients received Inj. bupivacaine 0.5% heavy 2.5 mL (12.5 mg) with Inj. magnesium sulphate 25% 0.2 mL (50 mg) intrathecally. The onset and duration of sensory blockade, the onset and duration of motor blockade, haemodynamic parameters, Ramsay sedation score and Visual Analogue Scale were assessed. Rescue analgesia was given when VAS score was >3. Statistical analysis was performed by student's t-test for nominal data, Chi-square test or Fisher's exact probability test for categorical data.

RESULTS

When 50 mg of magnesium sulphate was added intrathecally, the duration of motor blockade was prolonged (p value of <0.001); the onset of motor blockade was significantly slower, and the duration of analgesia was prolonged (p value <0.001). The prolonged analgesia in magnesium sulphate group was accompanied by an average 24-hour postoperative visual analogue scale of 1 to 2 when compared to 3 to 4 in saline group ($p \leq 0.001$).

CONCLUSIONS

Intrathecal magnesium sulphate as an adjunct to bupivacaine in spinal anaesthesia prolongs the duration of spinal anaesthesia and postoperative analgesia, without adverse effects.

KEYWORDS

Subarachnoid Block, Intrathecal Adjuvant, Magnesium Sulphate, Analgesia, NMDA Receptor

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BACKGROUND

Spinal anaesthesia or subarachnoid block is the most commonly practiced anaesthetic procedure in our day to day anaesthesia routine. Local anaesthetics like lignocaine, bupivacaine or ropivacaine given intrathecally for spinal anaesthesia alone are associated with a relatively short duration of action and do not cover the postoperative analgesic needs.[1] Various additives have been used to improve the characteristics of subarachnoid block like opioids, clonidine, dexmedetomidine, ketamine, neostigmine, epinephrine, magnesium sulphate and other agents.[2-7] Magnesium sulphate is a non-competitive NMDA (n-methyl D-aspartate) receptor antagonist.[8,9] NMDA receptor antagonists prevent the induction of central sensitization attributed to peripheral nociceptive stimulation.[1,10] Intrathecal magnesium sulphate potentiates morphine antinociception at the spinal level in naive rats.[11] It increased the peak effect and area under the analgesic curve in morphine rats.[11] Intrathecal magnesium sulphate potentiates spinal anaesthesia by a localized action on spinal nociceptive pathways.[12] It reduces the activation of C-fibres by inhibiting slow excitatory post synaptic currents produced by NMDA receptor activation.[10] The binding and dissociation of non-competitive NMDA receptor antagonists is relatively slow, which may prolong anaesthesia into the postoperative period.[13] When magnesium sulphate was administered intrathecally, the time of maximum sensory block, time of onset of motor block and time for analgesic request were prolonged.[14] Postoperative pain is associated with neuroendocrine responses, catecholamine release and increased morbidity.[15] Intrathecal magnesium reduced morphine consumption at 24 hours postoperatively, and modestly reduced early postoperative pain scores without increasing risk of hypotension, bradycardia or sedation.[16] A limitation to the parenteral use of magnesium for modulation of antinociception via NMDA channel antagonism is insufficient blood-brain barrier penetration to achieve effective concentration.[17]

Magnesium in a dose of 50 mg to 100 mg with local anaesthetic for spinal anaesthesia has been used in various studies.[7,18,19,20] 50% of 100 mg intrathecal magnesium sulphate did not have more desirable effect than 75 mg and 100 mg of intrathecal magnesium sulphate.[20] Hence in our study, we used a dose of 50 mg magnesium sulphate intrathecally which was the minimum dose to prolong analgesia. The primary objective was to study the duration of spinal anaesthesia and time for rescue analgesic with the use of intrathecal magnesium sulphate as an adjunct to 0.5% hyperbaric bupivacaine. The secondary objective was to observe perioperative side effects following magnesium administration.

METHODS

We performed a prospective, randomized, double blind study. Randomization was done using numbers generated from www.random.org. 25 patients were included in each group to detect a 10% difference in the duration of spinal anaesthesia, at a confidence interval of 95% and keeping the power of study 80%.

Inclusion Criteria

The inclusion criteria were patients aged 18 to 60 years, ASA physical status I and II, body mass index of 18.5 to 24.9, posted for elective infraumbilical surgery.

Exclusion Criteria

The exclusion criteria were patients with coagulation disorders, infection at site of lumbar puncture, neurologic and psychiatric disturbances, uncontrolled diabetes, hypertension, significant coexisting diseases, patients with opioid or analgesic abuse, history of hypersensitivity to magnesium, neuropathy, patients who refused to give consent.

After obtaining informed written consent from patients, 50 patients posted for infraumbilical surgery were randomly divided into two groups. Group I patients received Inj. bupivacaine 0.5% heavy 2.5 mL (12.5 mg) with Inj. normal saline 0.2 mL intrathecally. Group II patients received Inj. bupivacaine 0.5% heavy 2.5 mL (12.5 mg) with Inj. magnesium sulphate (preservative free) 25% 0.2 mL (50 mg) intrathecally. The study drug was measured using an insulin syringe.

After shifting the patient to operation theatre, intravenous (IV) line was secured. The patients were preloaded with 10 to 15 mL/Kg body weight of Ringer's lactate solution 15 to 20 minutes before the administration of spinal anaesthesia. Monitors like pulse oximeter, non-invasive blood pressure (NIBP) and electrocardiography (ECG) were connected. Baseline parameters were recorded. Patients were premedicated with Inj. midazolam 1 mg IV. The study drug syringes were prepared by a senior anaesthesiologist who was further not involved in the study. Patients and the anaesthesia provider were not aware of the study drug. Patients were randomly assigned to group I and group II. Under aseptic precautions, lumbar puncture was performed with the patient in lateral position at L_3 - L_4 interspace by midline approach using 25-gauge Quincke's needle and the respective study drug was administered. Patients were positioned in supine position.

The anaesthesiologist recorded the intraoperative parameters. Sensory blockade was noted by loss of sensation to temperature bilaterally along midclavicular line using a spirit swab. Motor blockade was noted by using the Bromage scale (Bromage 0 - Patient able to move hip, knee and ankle; Bromage 1 - Patient able to move hip and knee, but able to move ankle, Bromage 2 - patient not able to move hip, but able to move knee and ankle; Bromage 3 - Patient not able to move hip, knee and ankle). Time for onset of sensory blockade, time for onset of motor blockade, maximal height of sensory blockade, total duration of sensory blockade, total duration of motor blockade were

noted. Oxygen saturation (SpO_2), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiography (ECG), respiratory rate (RR), Ramsay sedation score (RSS) and any side effects were recorded at the baseline, at 0, 1, 2, 5 minutes of subarachnoid block and 5 minutes thereafter until 1 hour, 15 minutes thereafter until the end of surgery. If SBP was ≤90 mmHg or if MAP was <60 mmHg, Inj. mephentermine 6 mg IV stat was administered. If HR was <50 beats per minute, Inj. Atropine 0.6 mg IV stat was administered.

The onset of sensory blockade is defined as time for T_{10} dermatomal blockade. The duration of sensory blockade is defined as time for two dermatomal segments regression (from the highest dermatomal blockade). The time for onset of motor blockade was when Bromage score was 3. The duration of motor blockade is defined as time for recovery to Bromage 0. Duration of analgesia is the time from the administration of subarachnoid block to first rescue analgesics.

Ramsay sedation score, visual analogue scale (VAS) were assessed postoperatively immediately, 30 minutes, 1 hour, 1½ hour, 2-hour, 6-hour, 12-hour and 24-hour. Side effects like nausea, vomiting, respiratory depression, sedation were noted. Time for request of first analgesic was noted and rescue analgesic was given as Inj. diclofenac 75 mg intramuscular.

Features of magnesium toxicity like bradycardia, hypotension, arrhythmias, respiratory distress, drowsiness, hyperexcitability, decreased urine output (<0.5 mL/Kg/hour) and others if any were noted.

Statistical Analysis

After completing the study, our observations were tabulated and analysed by student's t-test for nominal data; by Chi-square test or Fisher's exact probability test for categorical data. A p-value of less than 0.05 was considered statistically significant. Version of software used was SAS 9.2, SPSS 15. In order to keep power of the test 80%, a sample size of 25 patients was decided.

RESULTS

25 patients were enrolled in each group. The age, sex, weight, BMI, ASA physical status, type of surgery and duration of surgery were comparable in the two groups.

Demography	Group I	Group II	P Value
Age (Years)	40.6 ± 8.53	39.84 11.29	
Sex (M: F)	12: 13	18: 07	
Weight (Kg)	64.52 ± 9.71	55.20 ± 13.74	0.008
Duration of surgery (min)	62.00 ± 27.12	68.40 ± 31.91	0.449

Table 1. Demographic Data

Our observation was that the onset of sensory blockade was significantly faster in magnesium group when compared to saline group (p <0.05). The onset of motor blockade was significantly slower in magnesium group when compared to saline group (p <0.05). Duration of sensory and motor blockade was significantly longer in magnesium group with p value <0.001. The time for first analgesic request also known as the duration of analgesia was significantly prolonged with the addition of intrathecal magnesium with p value <0.001. The mean time for rescue analgesic was 136.80 ± 37.83 min in saline group versus 228.20 ± 101.56 min in magnesium group.

Parameters	Group I (n=25)	Group II (n=25)	P Value
Onset of sensory blockade (seconds)	168 ± 71.4	124.8 ± 62.2	0.027
Onset of motor blockade (seconds)	245.71 ± 110.47	379.2 ± 241.69	0 .016
Duration of motor block (minutes)	136.8 ± 37.82	215.4 ± 49.11	<0.001
Time for rescue analgesia (minutes)	107.2 ± 22.67	238.2 ± 116.98	<0.001

Table 2. Characteristics of Sensory and Motor Blockade

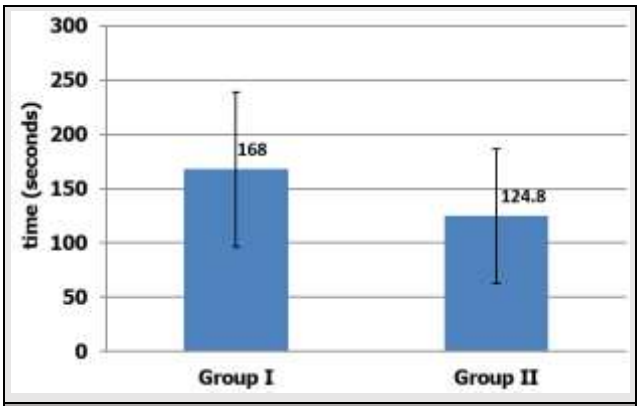

Figure 1. Comparison of Mean Time for Onset of Sensory Blockade

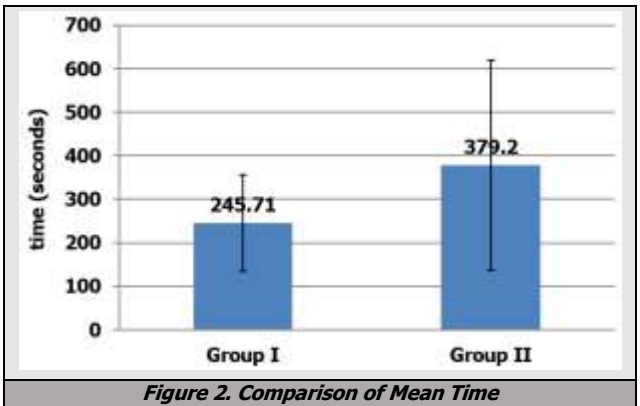

Figure 2. Comparison of Mean Time for Onset of Motor Blockade

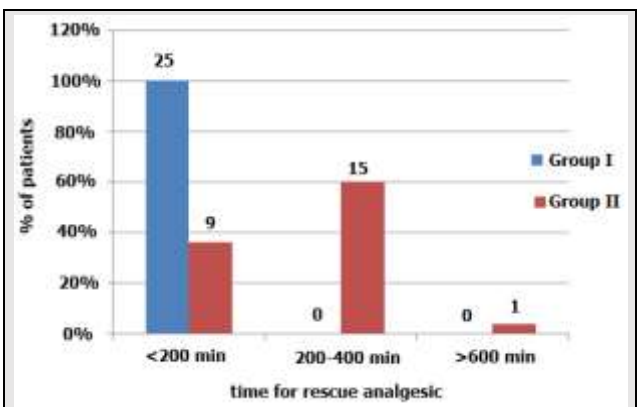

Figure 3. Comparison of Time for Rescue Analgesia

Visual Analogue Scale	Group I	Group II	P Value
30 mins	1.52 ± 0.77	0.04 ± 0.20	<0.001**
60 mins	2.88 ± 0.45	0.04 ± 0.20	<0.001**
90 mins	3.04 ± 0.35	0.24 ± 0.52	<0.001**
2 hours	3.76 ± 0.66	0.48 ± 0.92	<0.001**
6 hours	2.64 ± 0.49	0.20 ± 0.41	<0.001**
12 hours	2.28 ± 0.61	0.12 ± 0.44	<0.001**
24 hours	1.44 ± 0.51	0.08 ± 0.28	<0.001**

Table 3. VAS in the First 24 Hours of Postoperative Period

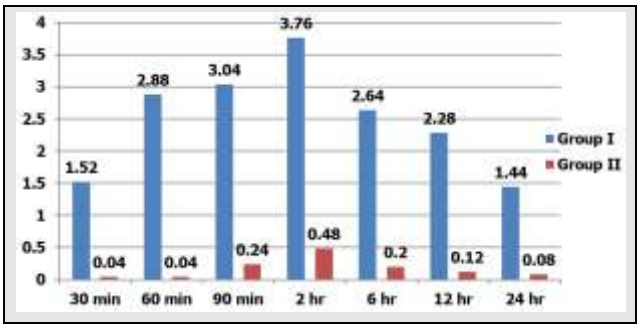

Figure 4. Comparison of VAS in the First 24 Hours of Postoperative Period

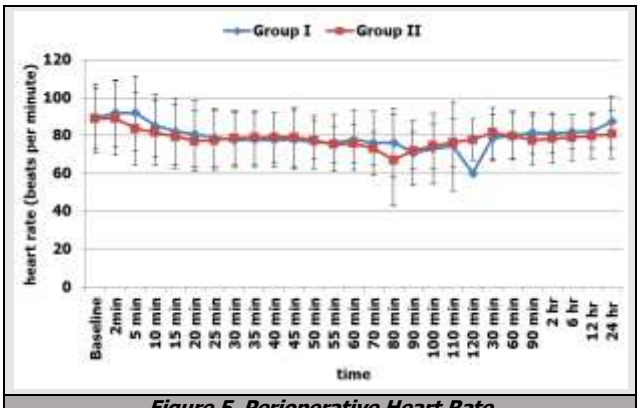

Figure 5. Perioperative Heart Rate (0 Minute Corresponds to the Time of Subarachnoid Block)

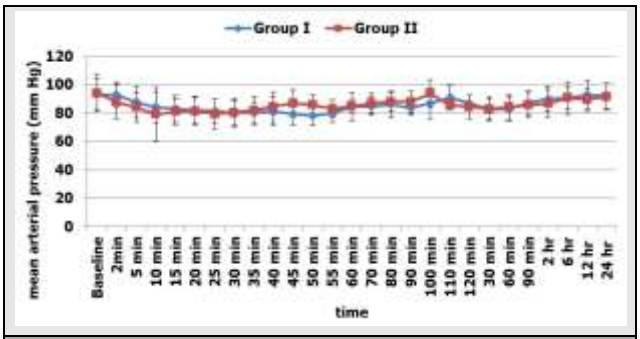

Figure 6. Perioperative Mean Arterial Pressure (0 Minute Corresponds to the Time of Subarachnoid Block)

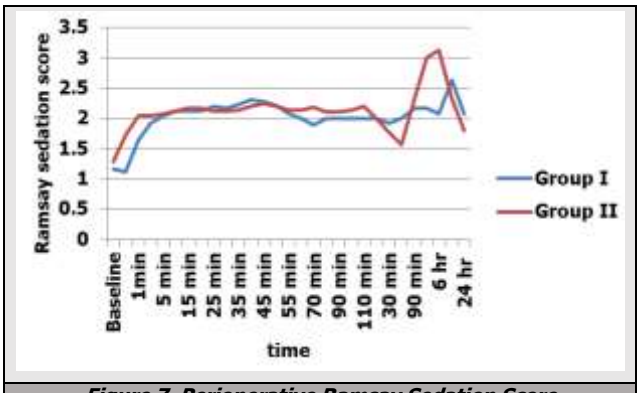

Figure 7. Perioperative Ramsay Sedation Score (0 Min Corresponds to the Time of Subarachnoid Block)

The average visual analogue scale (VAS) in first 24 hours of postoperative period was 1 to 2 in group II versus 3 to 4 in group I. The p value was highly significant at all intervals: ≤0.001. There was no difference in the haemodynamic parameters among the two groups. The sedation scores are comparable among the two groups. Sedation does not occur with the addition of magnesium sulphate in a dose of 50 mg.

Adverse effects of magnesium like bradycardia, hypotension, arrhythmias, respiratory distress, drowsiness, decreased urine output were absent in both the groups.

Side Effects	Group I		Group II	
	Number	%	Number	%
nil	25	100	24	96
bradycardia	0	0	1	4
total	25	100	25	100

Table 4. Comparison of Side Effects Found in the 24 Hours Postoperative Period

DISCUSSION

NMDA receptor with second messenger effectors plays a role in the development of chronic pain after an acute injury.[21] Magnesium ion blocks NMDA receptor associated channels in a voltage dependent manner.[22] Noxious stimulation leads to the release of neurotransmitters like glutamate and aspartate, which bind to various subclasses of excitatory amino acid receptors including the N-methyl d-aspartate (NMDA) receptor. Activation of NMDA receptors leads to calcium and sodium influx into the cell, with an efflux of potassium and initiation of central sensitization and wind-up phenomena and long-term synaptic plasticity.[23,24] Magnesium is a natural physiological calcium antagonist and its antinociceptive effect is regulated by calcium influx into the cell. This prevents the induction of central sensitization.[1] Magnesium improves recovery from spinal cord ischemia when administered intrathecally in rat and dog models.[9,25] Ischemic injury appears to be related to increased levels of excitatory amino acids and magnesium blocks this dorsal horn NMDA receptor activation.[8,26,27,28] In several studies, intrathecally administered magnesium prolonged spinal opioid analgesia both in rats and humans. Magnesium has been reported as an effective analgesic and an adjunct to intrathecal opioid analgesia as per findings by Kroin and colleagues.[12] It reduces opioid induced side effects like sedation, pruritis, respiratory depression, nausea and vomiting, urinary retention, haemodynamic instability.[12,29]

Intravenous administration of magnesium, even at high doses undergo limited transfer across the blood-brain barrier.[17] The cerebrospinal fluid (CSF) concentration of magnesium does not vary with variation in plasma concentration of magnesium.[30,31]

Intrathecal magnesium was first used in humans in 1906[32] in which 1000-2000 mg of intrathecal magnesium produced spinal anaesthesia with profound sensory and motor block but without any permanent untoward effect. Lejuste described an inadvertent intrathecal injection of

1000 mg of magnesium that produced a dense motor block followed by a complete resolution within 90 minutes and no neurological deficit at long term follow-up.[33] Buvanendran et al. were first to perform study on 50 mg of intrathecal magnesium used as adjuvant with intrathecal fentanyl in labouring parturients and its effect on prolonging duration of analgesia, compared to plain intrathecal fentanyl.[34]

Our results are comparable to a study by Binesh K et al. who observed decreased postoperative analgesic consumption with the use of 50 mg and 75 mg of intrathecal magnesium sulphate to bupivacaine in lower limb orthopaedic surgeries.[19] Paul et al., [25] Jaiswal R et al.[35] too observed similar results in lower limb orthopaedic surgeries. Jabalameli M et al. conducted study by adding 50, 75, 100 mg magnesium sulphate as an adjuvant for spinal anaesthesia in caesarean section.[20] There was a delay in sensory and motor blockade in all the groups. Intraoperative side effects like hypotension, nausea and vomiting were more when 100 mg of magnesium was used. 75 mg of the drug was enough to achieve the desired effect without increasing major side effects. In many studies performed by Khemakhem et al.,[36] Ozalevli M et al.,[37] Malleeswaran S et al.,[38] Bidyut and Kumar[39] using magnesium sulphate as an intrathecal adjunct during caesarean section, they noted prolongation of sensory and motor blockade, prolongation in the time of analgesia request, reduced postoperative analgesic requirement without additional side effects; and the results were similar to the results of our study.

In our study the onset of motor blockade was delayed in magnesium group. This was similar to the results of study conducted by Arora B and co-workers who conducted study with intrathecal magnesium sulphate as adjuvant for spinal anaesthesia for caesarean section in pre-eclampsia.[18]

Limitation

We could not obtain serum magnesium levels of our patients.

CONCLUSIONS

Intrathecal magnesium sulphate added to bupivacaine prolongs the duration of spinal anaesthesia and duration of postoperative analgesia without haemodynamic instability or any other adverse effects. Magnesium sulphate can be used as an efficient and safe intrathecal adjuvant to reduce postoperative analgesic requirements and to minimize use of opioids, as well as opioid related undesirable side effects.

Financial or Other Competing Interests: None.

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