THE EFFECT OF A SINGLE DOSE OF MAGNESIUM SULPHATE AS AN ADJUVANT TO EPIDURAL BUPIVACAINE FOR INFRAUMBILICAL SURGERIES: A PROSPECTIVE DOUBLE-BLIND, RANDOMIZED CONTROL TRIAL

Shruthi AH*, Sudheesh K**, Nethra SS***, Raghavendra Rao RS**** and Devika Rani D*****

Context: Epidural anesthesia provides the advantage of segmental blockade and many adjuvants have been added to shorten the onset of action, improve the quality of analgesia and prolong the duration of analgesia. Magnesium sulphate(MgSO₄) by virtue of its anti-nociceptive property has been administered by various routes.

Aim: To assess the effect of MgSO₄ on the duration of onset of action of injection bupivacaine for epidural anesthesia in infraumbilical surgeries.

Materials and methods: A prospective, double-blind, randomized control study was conducted in 40 patients. Group M received 15 ml of bupivacaine 0.5% + 1 ml of 50 mg MgSO₄ and Group C received 15 ml of bupivacaine 0.5% + 1 ml of normal saline via epidural route. Onset time of the sensory and motor blockade were the primary outcomes studied. Highest level of sensory block, time for two segment regression, hemodynamic parameters, side effects were the secondary parameters.

Results: There was a significant difference between the groups in the mean onset time of sensory blockade at T8, 12.85 ± 2.32 min in Group M and 16.75 ± 1.74 min in Group C. Median level of sensory blockade was comparable. Mean onset time of motor blockade was 13.85 ± 3.28 min in Group M and 23.25 ± 3.35 min in Group C which was clinically and statistically significant. Time for two segment regression of sensory blockade was 95.75 ± 11.84 min in Group M and 55.5 ± 8.57 min in Group C which was significant. Hemodynamic parameters and side effects were comparable.

Conclusion: Magnesium sulphate as an adjuvant provides rapid onset of epidural anesthesia and prolongs the duration of analgesia with minimal side effects.

Keywords: Magnesium sulphate, bupivacaine, epidural, infraumbilical surgeries

Introduction

Central neuraxial blockade is widely used for lower abdominal and lower limb surgeries. Epidural anesthesia being a safe technique, has a unique feature of segmental blockade and better control over hemodynamic variables and provision of prolonged post-operative analgesia. Effective

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treatment of perioperative pain blunts autonomic, somatic and endocrine responses. It is a common practice to use polypharmacy approach for treatment of intra-and post-operative pain as no single agent has yet been identified to specifically inhibit nociception without associated side effects. Search for a drug that provides optimal intraoperative anesthesia and prolonged postoperative analgesia with minimal side effects still continues.

Various adjuvants have been used with local anaesthetics via epidural route with the objectives of shortening the onset of action, improving the quality and prolonging the duration of analgesia and minimising the adverse events.

Magnesium is the fourth most plentiful cation in the body and the second most prevalent intracellular cation after potassium. Its antinociceptive property has been shown in animal and human models of pain. The anti-nociceptive effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors thereby preventing central sensitization induced by peripheral nociceptive stimuli. These effects have prompted the investigation of magnesium as an adjuvant agent for intra-and post-operative analgesia as it is an inexpensive, relatively harmless molecule. Most of the studies have used magnesium as a co-adjuvant to opioids for prolongation of post-operative analgesia, while few studies have investigated its effect as an adjuvant for surgical anesthesia, when used as sole agent.

We therefore conducted a prospective, double blind, randomised, controlled clinical study to assess the effect of magnesium as an adjuvant for epidural bupivacaine with respect to the onset time of sensory and motor blockade. Two segment regression, hemodynamic variables, respiratory rate and oxygen saturation were the secondary outcomes of the study.

Materials and Methods

A prospective double-blind, randomized study was conducted on 40 patients undergoing elective infraumbilical surgery at tertiary level medical college hospital, between January 2012 to December 2012.

Institutional ethical committee approval was taken. Patients belonging to American Society of Anesthesiology (ASA) physical status I and II, aged between 18 to 50 years of either gender and those with a BMI less than 30 kg/m² were included in the study. Those with contraindication to central neuraxial blockade like patient refusal, local site and systemic infections, patients on anticoagulant therapy, those with spinal deformities, with neurological illness or cardiac failure; with history of adverse reaction to study medication and history of chronic pain syndrome and long term analgesic use were excluded.

Pre-anesthetic check up was done on the day prior to surgery. Written informed consent was obtained. Patients were advised fasting for 6-8 hours and pre-medicated with ranitidine 150 mg and alprazolam 0.5 mg per orally on the previous night of surgery. After shifting the patient to the operating room, standard monitors like pulse oximeter, noninvasive arterial blood pressure (NIBP) and electrocardiography were attached and baseline vital parameters recorded. An intravenous access was obtained and preloading done with 10 ml/kg of lactated ringer’s solution. Midazolam 0.03 mg/kg intravenous was the premedicant administered.

Patients were divided into 2 groups of 20 patients each based on software-derived random number sequence (www.random.org). The patient and the anesthesiologist administering the drug and collecting the data subsequently, were unaware of the group to which the patient was allotted. Group M (n=20) received 15 ml of bupivacaine 0.5%+ 50 mg of magnesium sulphate (MgSO₄) made up to 1 ml. Group C (n=20) received 15 ml of bupivacaine 0.5%+ 1 ml of normal saline (placebo). Both the solutions were prepared under sterile conditions by an anesthesia technician as per instructions of principal investigator, who was not assisting the monitoring anesthesiologist.

Under aseptic precautions and local anesthesia, epidural space was identified at L1-L2 or L2-L3 intervertebral space with a 16G Tuohy needle by loss of resistance technique to air and an 18G epidural catheter was threaded 3-4 cm into epidural space. A test dose of 3 ml of lignocaine 2% with adrenaline (1:2,00,000) was administered after negative aspiration
for blood and cerebrospinal fluid (CSF) and patient was monitored for intravascular/intrathecal placement of catheter for 2 minutes, epidural catheter was fixed and secured with tapes. The patients then received epidural medications as per randomization.

Pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), peripheral oxygen saturation (SpO₂) and level of sedation as per Ramsay Sedation Scale (RSS) were recorded preoperatively, every 5 minutes intraoperatively, postoperatively every 30 minutes for next 2 hours, and every 4th hour till 12 hours and at 24 hours.

Sensory block was assessed by loss of sensation to temperature (by cold swab method) bilaterally along the midclavicular line every minute. Onset time of sensory block was defined as the time interval between the injection of anesthetic to the loss of sensation at T8 dermatome. Sensory blockade was checked 15 minutes after attainment of T8 level to note the cephalad spread beyond T8 dermatome. This was continued till two segment regression from the cephalad level was reached. This was also taken as the time for the first epidural top up and a bolus of bupivacaine 0.5% (3 ml) was administered via epidural route with no supplemental dose of magnesium sulphate intraoperatively.

Motor blockade was assessed using ‘Modified Bromage Scale’⁹. The assessment was done every minute till Bromage Scale 3 was attained. Surgeons were allowed to proceed with surgery once level of sensory block reached T8 and motor block was complete. Complications or side effects, if any were noted.

Patients in whom there was a failure to achieve adequate level of sensory or motor blockade were managed with general anesthesia and excluded from the study.

Hypotension was defined as SBP <90 mmHg or >30% decrease from baseline values and was treated with ephedrine 6 mg IV. Bradycardia was defined as HR <60 beats per minute (bpm) and was treated with atropine 0.02 mg/kg intravenous. Respiratory depression was documented when RR <8 breaths per minute or SpO₂ <85% and was managed with mask ventilation, endotracheal intubation and intermittent positive pressure ventilation, if necessary. Vomiting was managed with injection ondansetron 0.1 mg/kg and shivering was managed with administration of warm intravenous fluids and warming blankets.

Postoperative analgesia was managed with epidural bolus of bupivacaine 0.125% 8 ml boluses and/or Paracetamol 1 gm infusion as per discretion of treating consultants.

With the power of study at 90%, keeping alpha error at 5%, a minimum of 20 patients in each group was needed to detect an intergroup difference of at least 20% with respect to time for onset of sensory block. We included 20 patients in each group. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 17.0. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Student’s t-test was used for differences in hemodynamic variables between the groups and repeat measures of ANOVA for intergroup evaluation. Nominal data was analysed using the Chi-Square test or Fisher Exact test. P value <0.05 was considered statistically significant.

Results

Table 1 shows that the demographic data between the two groups were comparable. Epidural block was effective in all patients and none of the patients required additional supplementation.

<table>
<thead>
<tr>
<th>Table 1: Demographic characteristics. Data is presented as mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>37 ± 7</td>
</tr>
<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>ASA(I/II)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
</tr>
<tr>
<td>Type of surgery(orthopedic/gynecologic)</td>
</tr>
</tbody>
</table>
Mean time taken to achieve T8 dermatomal level sensory blockade was earlier in group M (12.85 ± 2.32 minutes) than group C (16.75 ± 1.74 min) (P <0.001). Similarly time for maximum motor block of Modified Bromage scale 3 was 13.85 ± 3.28 min in group M and 23.25 ± 3.35 min in group C which was clinically and statistically significant (P <0.001). The median height of sensory blockade (T8) though was similar in both the groups with group M showing higher level of blockade (T6) in few patients, but the comparison was not statistically significant (P = 0.358). Time for two segment regression was significantly prolonged in group M (95.75 ± 11.84 min) when compared to group C (55.5 ± 8.57 min) which was significant (P <0.001). Six patients in group M required additional top up, whereas 18 patients in group C required additional top up (P <0.001, odds ratio 0.09) (Table 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group M (n=20)</th>
<th>Group C (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time for sensory block (min)</td>
<td>12.85 ± 2.32</td>
<td>16.75 ± 1.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset time for motor block (min)</td>
<td>13.85 ± 3.28</td>
<td>23.25 ± 3.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Two segment regression (min)</td>
<td>95.75 ± 11.84</td>
<td>55.5 ± 8.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients requiring additional top ups</td>
<td>6</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean baseline heart rate was comparable in both groups. There was no statistically significant difference in heart rate between the groups throughout the study period (P >0.05) (Fig 1). Systolic, diastolic and mean arterial blood pressures (SBP, DBP, MAP) were comparable between the two groups at all time intervals during the study (Fig 2).

None of the patients in either group had any episode of respiratory depression or desaturation.

Median sedation score was 2 in group M and group C intraoperatively and postoperatively in both groups.

There were no significant differences between the two groups with respect to hypotension, need for vasopressor or bradycardia (Table 3). Five patients in group C while none of the patients in group M had shivering, but this was statistically insignificant.

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>4</td>
<td>8</td>
<td>0.451</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6</td>
<td>7</td>
<td>1.000</td>
</tr>
<tr>
<td>Shivering</td>
<td>0</td>
<td>5</td>
<td>0.231</td>
</tr>
<tr>
<td>Need for vasopressor</td>
<td>4</td>
<td>6</td>
<td>0.638</td>
</tr>
</tbody>
</table>

**Discussion**

The present study using magnesium sulphate (MgSO₄) 50 mg as an adjuvant to epidural bupivacaine showed that the time for the onset of sensory and motor blockade was significantly shortened and time for two segment regression was significantly prolonged with no clinically significant difference in hemodynamic parameters and adverse events.

Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters which bind to various excitatory receptors like N-Methyl D-Aspartate (NMDA). Activation of NMDA receptors causes an influx of calcium and sodium ions into the cells and efflux of potassium ions, and initiation of central sensitization. Central sensitization has an important role in pain perception and is considered to be one of the mechanisms implicated in the persistence of postoperative pain. NMDA receptor signalling may be important in determining the duration of acute pain. Hence NMDA receptor antagonists will be effective in prevention and treatment of pain. Magnesium is a non-competitive antagonist of NMDA receptor and causes voltage-dependent blockade of ion channels producing a dramatic reduction of NMDA-induced currents thereby preventing central sensitization resulting from peripheral nociceptive stimuli.

Abdel-Halim JMK found that co-administration of magnesium sulphate 50 mg with epidural bupivacaine and morphine preoperatively as a
MgSO₄ AS AN EPIDURAL ADJUVANT

single bolus dose provides a profound decrease in intraoperative and postoperative narcotic consumption, and in VAS pain scores with no significant side effects. Co-administration of epidural magnesium for postoperative epidural analgesia provided a pronounced reduction in patient-controlled epidural fentanyl consumption without any side effects. In these studies supplementation of magnesium, a non-competitive NMDA receptor antagonist resulted in enhancement of analgesic effect of opioids and by delaying development of tolerance probably caused a significant reduction in postoperative opioid consumption. However, the studies evaluating the effect of co-administration of magnesium alone with local anaesthetic in surgeries done under epidural anesthesia are very few.

Shahi V and colleagues showed that the time to achieve T6 block was 15.4 ± 2.1 minutes in epidural magnesium adjuvant group and 19.7 ± 2.1 minutes in control group, which is comparable with the observations of the present study.

There was statistically significant prolongation of time for two segment regression in patients receiving magnesium sulphate. This is in contrast with observations of Ghatak T and colleagues who found no statistically significant difference between the two groups. This was probably due to the volume of local anesthetic used, variations in performance of the block, drug preparations and patient characteristics.

Studies by Koinig H et al and Tramer MR et al have shown that systemic administration of magnesium is associated with smaller analgesic requirement and less discomfort in the postoperative period. A limitation to the parenteral application of magnesium for modulation of antinociception via NMDA channel antagonism is insufficient blood-brain barrier penetration to achieve effective cerebrospinal fluid concentrations. Similar finding was observed by...
Ko SH et al and no postoperative analgesic effect of magnesium was seen4.

The clinical efficacy of magnesium and its safety in humans by intrathecal route has been shown by Buvanendran and colleagues25. Shoeibi G et al26 demonstrated that magnesium sulphate administered intrathecally with lignocaine, prolongs the duration of spinal analgesia in those undergoing caesarean section. Similarly in our study, magnesium as an epidural adjuvant resulted in prolongation of analgesia. It is possible that the analgesic effect occurs at the supra-spinal level and may be related to its systemic absorption. The epidural dose of magnesium in our study was too low for the systemic effect. The probable mechanism may have been diffusion of magnesium from the dura18.

Shivering occurred in five (20%) patients in the control group whereas none of the patients of the magnesium group developed shivering. Though this was not of statistical significance, it may have clinical significance since it has been proven that hypomagnesemia can occur in patients under anesthesia and perioperative magnesium supplementation can prevent postoperative hypomagnesemia and decreases the incidence of postoperative shivering1.

In two cases reported by Goodman and colleagues27 larger doses (8.7 g and 9.6 g) of magnesium inadvertently administered into the epidural space did not cause any neurologic injury. However, we preferred to use a smaller dose of magnesium that would not cause any side-effects.

The present study has limitations. The overall 24 hour post-operative analgesic consumption was not studied and hence its effect on post-operative analgesia could not be ascertained. However, a study done with single dose of MgSO4 in labour analgesia has shown to reduce the need of top ups and hence, the epidural bupivacaine and fentanyl consumption28. Also, further studies are needed to evaluate the efficacy and safety of higher doses of magnesium sulphate with larger sample sizes and in different surgical settings and in patients with ASA physical status 3 and beyond.

**Conclusion**

Magnesium sulphate a NMDA receptor antagonist when used in a dose of 50 mg as an adjuvant to epidural bupivacaine not only hastens the onset of sensory and motor blockade but also prolongs the time for two segment regression thereby necessitating lesser need for top ups.
References

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- 97% of BRIDION patients recovered to a TOF* ratio of 0.9 from 1 to 2 PTCs* within 5 minutes

Rapid reversal

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- BRIDION rapidly reversed patients from 1 to 2 PTCs in 2.7 minutes

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Volunteer studies indicate a slight (17%-21%) and transient (<30 minutes) prolongation of the perioperative monitored time PTCT (case study) with BRIDION. However, clinical studies have demonstrated no clinically relevant effect on postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulants for a pre-surgical or general condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, drug interactions were observed in clinical trials. Prednisolone data suggest that clinically significant drug interactions are unlikely with the possible exceptions of terfenadine, lidocaine, and the oral contraceptives.

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