Comparison of Intrathecal Magnesium Sulphate and Intrathecal Buprenorphine Used as Adjuvants to Hyperbaric Bupivacaine: A Prospective Randomized Double Blind Placebo Controlled Study

Kaushic A Theerth, MD 1*, Madhuri S Kurdi, MD 2

1 Department of Neuroanaesthesiology and Critical Care, NIMHANS, Bangalore, India
2 Department of Anaesthesiology, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

ABSTRACT

Magnesium has advantages compared to other adjuncts to local anaesthetics in spinal anaesthesia. This study is designed to compare the effects of intrathecal magnesium sulphate with buprenorphine as adjuvants to bupivacaine. 90 adult patients scheduled for below umbilicus surgeries were randomized into three groups of 30 each. They received 2.75ml of 0.5% hyperbaric bupivacaine mixed with either 0.5ml of 10% magnesium sulphate(50mg) or 0.5ml of buprenorphine(150µg) or 0.5ml of sterile water(placebo). Onset, duration of sensory and motor block and duration of total analgesia were studied. The duration of spinal anaesthesia did not increase with the addition of magnesium, but did so with buprenorphine. The time for first analgesic request was 493.33 > 313.1 > 234.17 mins (buprenorphine > magnesium > placebo) p<0.001. Addition of 50mg magnesium sulphate to bupivacaine did not demonstrate an effect on duration of spinal anaesthesia. However, it significantly prolonged the time for first analgesic request though to a lesser extent than buprenorphine, thus substantiating its use in postoperative analgesia.
INTRODUCTION

Spinal anaesthesia is the primary anaesthetic technique for many types of surgery. Recent developments in spinal anaesthesia have led to greater patient satisfaction and accelerated functional recovery. [1] Currently new ways of decreasing post-operative analgesic requirements are of special interest. The use of conventional local anaesthetics (LA) like bupivacaine has been unable to provide analgesia for longer duration. [2] Most patients require further analgesics during post-operative period. Various adjuvants are added to local anaesthetics for this purpose. Among the myriad list of LA adjuncts, magnesium seems to have many advantages. [1]

Magnesium blocks N-methyl d-aspartate (NMDA) channels in a voltage dependent fashion and such NMDA antagonism can prevent the induction of central sensitisation from peripheral nociceptive stimulation. [3] However, intravenous magnesium even at higher doses has limited passage across the blood brain barrier to act on NMDA channels. [4]

Intrathecal administration of magnesium has been reported to prolong duration of spinal anaesthesia, [5] potentiate opioid nociception [6] and reduce postoperative opioid consumption. [7] Unlike opioids it is not associated with pruritus, respiratory depression, sedation etc. [8] It has been used in different doses either alone or in combination with lipophilic opioids in spinal anaesthesia. [1] Keeping this in mind we conducted a study to compare the effects of intrathecal magnesium 50mg and intrathecal buprenorphine 150µg added to bupivacaine for spinal anaesthesia.

MATERIALS AND METHODS

Clearance was obtained from the hospital ethics committee for the conduct of the study. Informed consent was taken from all patients. 90 adult patients (25 – 60 years) of physical status I & II, scheduled to undergo elective surgical procedures below the level of umbilicus, under spinal anaesthesia, at our institute, from January 2012 to December 2012 were recruited. Patients with history of allergy to magnesium sulphate, bupivacaine or buprenorphine, history of opioid medication or magnesium treatment prior to surgery, history of central or peripheral neuropathies, history of seizures, patients having significant coexisting medical disease and parturients were excluded from the study. Sample size was estimated to be 90 based on the results of a pilot study conducted in our hospital (α – 0.05 β – 95 % σ – 43 δ – 42 minutes) where δ is the difference of mean duration of effective analgesia.

All the patients were assessed before the day of surgery. Oral premedication, tablet Diazepam 0.2mg/kg body weight, was given the night before surgery. The patients were fasted for eight hours before surgery. The patients were randomly assigned by a computer generated table into three groups A, B and C. The randomisation list was maintained by the pharmacist. The method of concealment was by sealed envelope technique. In the operating room, baseline blood pressure and pulse rate were recorded. Peripheral intravenous access was secured with an 18 gauge cannula and the patients were preloaded with ringer’s lactate solution 10 ml/kg body weight.
Ampoules of 0.5% hyperbaric bupivacaine (Sensorcaine from Astra Zeneca laboratories, Bangalore, India), buprenorphine 300µg/cc (Buprigesic from Neon laboratories, Mumbai, India) and magnesium sulphate 50% (Systochem laboratories, Loni, India) were used for the study.

With aseptic precautions, under local anaesthesia, lumbar puncture was performed in the sitting position, through midline or paramedian approach using a Quincke 25 gauge lumbar puncture needle inserted through the L₃–L₄ inter vertebral space. Patients in group A received 2.75ml of 0.5% heavy bupivacaine + 0.1ml of 50% magnesium sulphate (50mg) + 0.4ml of sterile water. Patients in group B received 2.75ml of 0.5% heavy bupivacaine + 150µg of buprenorphine (0.5ml). Patients in group C received 2.75ml of 0.5% heavy bupivacaine + 0.5ml of sterile water (placebo). The total drug volume in all three groups was the same (3.25ml). All injections were made at a rate of about one ml in four to five seconds and solutions were at room temperature. The drugs were loaded by an independent colleague. Both the patient and the anaesthetist were blinded to the procedure. After injection of the drug the patients were made supine immediately. Standard monitoring was carried out in the perioperative period which included pulse oximetry, electrocardiography, non-invasive arterial blood pressure and respiratory rate monitoring.

Heart rate and blood pressure (BP) were recorded, every five minutes throughout the procedure and every fifteen minute till the onset of pain, by an anaesthetist blinded to the patient group.

Time of intrathecal (IT) injection, time taken for onset of analgesia, time taken to attain maximal level of sensory block, time taken for regression of analgesia by two segments, duration of sensory block, time of onset of complete motor block, time taken for complete recovery of motor block were recorded. Pain scores were monitored from the onset of pain after the procedure and rescue analgesic (Inj. Diclofenac 75mg or Inj. Tramadol 100mg) was given intramuscularly, if visual analogue scale (VAS) score for pain was less than or equal to four.

Onset of analgesia was defined as time taken from subarachnoid injection to time taken to obtain analgesia for pinprick at T₁₀. Duration of sensory block was defined as the time taken for analgesia to regress till S₂. Onset and recovery of motor block were assessed using modified Bromage scale. Duration of spinal anesthesia was defined as time taken from intrathecal drug administration to the first complaint of pain. Duration of effective analgesia was defined as time taken from intrathecal drug administration to the time of first analgesic request.

Adverse effects like hypotension, which is defined as a systolic BP of < 90mm of Hg or fall in BP>20% of basal value, bradycardia (heart rate <60 beats/min), respiratory depression, sedation, nausea, vomiting, paresthesia, neurological deficits and pruritus were recorded. A follow-up telephone call was made one month later and patients were asked about symptoms suggestive of neurological deficit.

The results were analyzed using (Statistical Package for Social Sciences) SPSS package (version 20, Chicago). Results were represented as mean and standard deviation for parametric data and as median and range for categorical data. Continuous variables were tested for normality using Kolmogorov – Smirnov test. Analysis of Variance (ANOVA) test was used for parametric data. Intergroup comparisons were done using
one way ANOVA and Tukeys post hoc test. Chi-square test was used for categorical data. Results were considered statistically significant if p-value<0.05.

RESULTS

The possible confounding factors which might affect the results are age, sex, height, weight, dermatomal level of surgical pain & American Society of Anaesthesiologists (ASA) physical grades. These were statistically compared between the groups and were found to be similar (Table 1).

The mean time of onset of analgesia to T10 was 6.67 minutes in the magnesium group, 4.28 minutes in the buprenorphine group and 4.42 minutes in the distilled water group. The mean time of onset of complete motor block was 7.06 minutes in the magnesium group, 4.53 minutes in the buprenorphine group and 4.52 minutes in the distilled water group (Fig 1).

[FIGURE: 1]

[Figure 1: Comparison of the three groups Magnesium (M), Buprenorphine (B) and Distilled Water (DW) with respect to onset of sensory and motor block.]

The onset of analgesia and complete motor block were significantly delayed in the magnesium group compared to the buprenorphine and the distilled water groups. There was no significant difference between buprenorphine and control groups.

With respect to highest level of sensory block achieved, the median was T7 in distilled water and buprenorphine group and T6 in magnesium group. The range was T6-9 in magnesium and distilled water
groups and T6-10 in buprenorphine group. On pair wise comparison the difference in levels obtained was found to be significant between buprenorphine and distilled water group.

The mean time to attain maximum level of sensory block was 10.32 minutes in the magnesium group, 6.96 minutes in the buprenorphine group and 7.05 minutes in the distilled water group in our study. The time taken to achieve maximum sensory level was significantly delayed in the magnesium group compared to other two groups.

In the present study, the mean duration of regression of sensory block by two segments, from the highest level attained, was 132.5 minutes in the magnesium group, it was 138.33 minutes in the buprenorphine group and 127 minutes in the distilled water group. The difference in mean values was found to be significant only between buprenorphine and distilled water groups.

Also, in the present study, the mean duration of regression of analgesia to S1 was 244.67 minutes in the magnesium group, 287.47 minutes in the buprenorphine group and 235.33 minutes in the distilled water group. The difference in mean values was found to be significant only between buprenorphine and distilled water groups (Fig 2).

In our study, the mean duration of motor block was 236.5 minutes in the magnesium group, 253.5 minutes in the buprenorphine group and 227.67 minutes in the distilled water group. The difference in mean values was not statistically significant between the groups (Fig 2).

[FIGURE: 2]

[Figure 2: Comparison of the three groups Magnesium (M), Buprenorphine (B) and Distilled Water (DW) with respect to duration of sensory and motor block.]
The mean duration of spinal anaesthesia was 171.63 minutes in the magnesium group, 229.43 minutes in the buprenorphine group and 159.5 minutes in the distilled water group. The difference in mean values was found to be significantly prolonged in buprenorpine group compared to magnesium and distilled water groups. The mean duration was similar between magnesium and distilled water groups.

In our study, the mean duration of effective analgesia was 313.1 minutes in the magnesium group, 493.33 minutes in the buprenorphine group and 234.17 minutes in the distilled water group. The differences in mean values were found to be significant between every other group (Fig 3). The mean values of heart rate, systolic and diastolic blood pressure were comparable between the groups at all time points. p values of all statistical comparisons are given in table 2. Adverse effects are given in table 3.

[FIGURE: 3]

[Figure 3: Comparison of the three groups Magnesium (M), Buprenorphine (B) and Distilled Water (DW) with respect to duration of total analgesia.]
### TABLE 1

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>GROUP A (n = 30)</th>
<th>GROUP B (n = 30)</th>
<th>GROUP C (n = 30)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>42.23 ± 9.19</td>
<td>42.63 ± 9.21</td>
<td>37.80 ± 9.73</td>
<td>0.57784</td>
</tr>
<tr>
<td>Male:Female (n)</td>
<td>17:13</td>
<td>16:14</td>
<td>17:13</td>
<td>0.7950</td>
</tr>
<tr>
<td>ASA 1:2 (n)</td>
<td>22:8</td>
<td>20:10</td>
<td>23:7</td>
<td>0.67863</td>
</tr>
<tr>
<td>Height in centimeters</td>
<td>161.47 ± 5.42</td>
<td>161.37 ± 4.45</td>
<td>163.53 ± 6.18</td>
<td>0.2202</td>
</tr>
<tr>
<td>Weight in kilograms</td>
<td>55.5 ± 6.56</td>
<td>56.1 ± 6.32</td>
<td>54.63 ± 7.54</td>
<td>0.7056</td>
</tr>
<tr>
<td>Duration of surgery in minutes</td>
<td>75 ± 26.42</td>
<td>71 ± 25.31</td>
<td>72.5 ± 23.59</td>
<td>0.8241</td>
</tr>
</tbody>
</table>

(Data are expressed as mean and standard deviation unless specified)

[Table 1 Demographic and other basic data of patients]
<table>
<thead>
<tr>
<th>Groups</th>
<th>Magnesium (M)</th>
<th>Buprenorphine (B)</th>
<th>Control (C)</th>
<th>M-B*</th>
<th>M-C*</th>
<th>B-C*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to T10 analgesia</td>
<td>7.06 ±0.79</td>
<td>4.53 ±1.15</td>
<td>4.52 ±1.11</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Onset of complete motor block</td>
<td>6.67 ±1.57</td>
<td>4.28 ±1.03</td>
<td>4.42 ±1.06</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Time to maximum sensory block</td>
<td>10.32 ±1.01</td>
<td>6.96 ±0.82</td>
<td>7.05 ±0.84</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Maximum sensory level †</td>
<td>8(T6-9)</td>
<td>7(T6-10)</td>
<td>7(T6-9)</td>
<td>-</td>
<td>-</td>
<td>0.028</td>
</tr>
<tr>
<td>Time to 2 segment regression of sensory block</td>
<td>132.17 ±11.94</td>
<td>138.33 ±16.83</td>
<td>127.00 ±13.36</td>
<td>-</td>
<td>-</td>
<td>0.007</td>
</tr>
<tr>
<td>Time to regression of sensory block to S1</td>
<td>244.67 ±51.56</td>
<td>287.47 ±97.11</td>
<td>235.33 ±55.78</td>
<td>-</td>
<td>-</td>
<td>0.015</td>
</tr>
<tr>
<td>Duration of total analgesia</td>
<td>171.63 ±34.45</td>
<td>229.43 ±45.42</td>
<td>159.50 ±31.52</td>
<td>&lt;0.001</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of effective analgesia</td>
<td>313.10 ±64.43</td>
<td>493.33 ±82.85</td>
<td>234.17 ±47</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

[Table 2: Comparison of the parameters observed between the three groups.]
(Data are expressed as mean and standard deviation unless specified)
* p values which are significant, † Data expressed as median and range (in brackets)
[Table 3]

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Magnesium</th>
<th>Buprenorphine</th>
<th>Distilled water</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shivering</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

[Table 3: Adverse effects in three groups]

**DISCUSSION**

Safety of intrathecal magnesium sulphate has been studied in animal models. Though earlier studies encouraged the use of intrathecal magnesium concurrent animal research[^9^-^12] published recently has raised questions regarding safety of intrathecal magnesium. However, IT magnesium has been used in significant number of humans and there were no documented neurological complications.[^13] Histopathological and ultrastructural human spinal cord studies may sound interesting but are practically next to impossible. In such circumstances off label use of magnesium intrathecally is supposed to thrive because of its availability, affordability and advantages.
Optimum dose and concentration of IT magnesium for antinociceptive action is an untrodden area in research. In the first human study [7] on IT magnesium the dose was fluked out from within the safety range extrapolated from animal studies. Recently, few studies [8,14-17] have used higher doses and shown antinociceptive action but regression analysis of dose response relationship has not been performed and there is still scope for further higher doses. Nevertheless 50mg was the lowest dose studied [5] which showed antinociceptive potential and so it was used in our study.

In the present study buprenorphine was chosen for comparison because prolongation of spinal analgesia by buprenorphine is well studied [28,18] and hence it can be used as an active control to gauge the efficacy of magnesium sulphate. No other study has compared the effect of magnesium with buprenorphine. This study was designed to identify the possibility of magnesium replacing buprenorphine as an adjuvant in spinal anaesthesia.

In our study, magnesium significantly prolonged the onset of analgesia and complete motor block. The difference between mean time of onset of analgesia was 2.25 minutes (Mg vs control) and mean time of onset of complete motor block was 2.54 minutes (Mg vs control) which might not be clinically significant. This delayed onset might be due to difference in pH of the solution injected. [19] Our study results concur with those done by Paul et al [5], Shukla et al [20] and Khezri et al [21]. They demonstrated a delay in onset of block using 50mg of magnesium sulphate. The difference in mean values of onset of sensory block and complete motor block obtained by Khezri was 3.16 minutes and 4.37 (Mg vs control) respectively which is nearly similar to our results.

The mean duration of the regression of sensory block by two segments was similar between magnesium and distilled water groups. Magnesium did not prolong the duration of sensory block unlike buprenorphine. The mean duration of regression of analgesia to S₁ was similar between magnesium and distilled water groups. Magnesium did not prolong the duration of regression of analgesia to S₁ unlike buprenorphine. Similar results were obtained in the study done by Khezri et al [21]. Here, it may be apt to mention that NMDA channels are involved in pain modulation and hence NMDA blockers may not be expected to prolong sensory block. But it has been shown that an intrathecal injection of a large dose of magnesium sulfate (MgSO₄) (1260 mg) causes a complete sensory and motor block (e.g. spinal anaesthesia) lasting for 60 minutes. [22] However, the mechanisms were not elucidated. Sanad et al [23] in his study showed that 50mg magnesium prolonged the regression of sensory block. However, we cannot suggest a satisfactory explanation for this prolongation and further studies and clinical trials are required.

Magnesium did not prolong the duration of spinal anaesthesia unlike buprenorphine. Similar results were obtained in the studies done by Jabalameli et al [15] and Khezri et al [20]. Though Jabalameli showed that higher doses (75 and 100 mg) caused prolongation of spinal anaesthesia, it was contrasted by Khalili [14] who showed that 100mg did not cause prolongation of spinal anaesthesia. Recent meta-analysis on effect of intrathecal magnesium sulphate ± LA ± lipophilic opioids done by Morrison et al [1] commented on the lack of evidence in subgroup analysis (magnesium added to LA alone) to support the prolongation.

The duration of effective analgesia was significantly prolonged in the magnesium group compared to the control group but to a lesser degree than in the buprenorphine group. Similar results were obtained by
Paul et al \cite{5} and Sanad et al \cite{23} using 50mg of magnesium sulphate. However Khezri \cite{21} et al showed that 50mg IT magnesium did not prolong the duration of effective analgesia. They had conducted this study in patients undergoing surgery for fracture femur and hence the role of magnesium in preemptive analgesia was overlooked and might have led to the negative results. However they did demonstrate a reduction in post-operative opioid consumption with the use of IT magnesium. The actual duration of prolongation was 78.93 minutes. Duration of motor block was not prolonged with the use of magnesium or buprenorphine. This is because the IT dose of magnesium is relatively miniscule to get absorbed systemically and act upon the neuromuscular junction to cause paralysis. Studies done by Khezri et al \cite{21} and Sanad et al \cite{23} have also demonstrated that 50mg of IT magnesium does not affect duration of motor block but Shukla et al \cite{20} using similar dose contrasted these results. Though IT magnesium has produced spinal anaesthesia including motor blockade in both human and animal studies, the dose used was extremely high and the mechanism of action was not elucidated \cite{24}. Further studies are needed to explain the motor blockade caused by IT magnesium.

In the present study, the variations in heart rate, arterial blood pressure and respiratory rate were comparable in both the groups and the differences were not statistically significant thus showing that IT magnesium is hemodynamically stable. Katiyar et al found that intrathecal magnesium sulphate in a dose of 100mg was associated with better haemodynamic stability compared to 25µg of intrathecal fentanyl. Other studies showed similar findings \cite{20,21}.

In the present study, the incidence of complications was very minimal (Table 3). Others studies conducted using 50mg of intrathecal magnesium did not show any increased incidence of complications \cite{5,14,19,20,22}. However Jabalameli et al \cite{15} showed that 100mg of intrathecal magnesium is associated with increased incidence of intraoperative and postoperative complications like hypotension, nausea, vomiting compared with lower doses and with placebo. However they did not find any difference in the requirements of ephedrine or atropine. In our study, no patient had neurological complications postoperatively and in the one month follow-up period \cite{17}.

The present study has few limitations. In inclusion criteria, patients undergoing infraumbilical surgeries were selected. This was done to have a bigger sample size. This could have been narrowed down to specific surgeries like hip replacement surgery, arthroscopy, etc. Postoperative opioid consumption was not compared between the groups because of technical problems. Comparison of VAS scores in the late postoperative period (more than six hours) was not feasible. Prolonged follow up of patients (more than a month) for neurological deficits was not possible for us.

Nevertheless, there is scope for further studies related to this topic. Different doses of magnesium can be studied and compared. Continuous infusion of magnesium using IT catheters can be studied. Synergism of the combination, magnesium with buprenorphine can be evaluated. Concurrent use of IT magnesium along with magnesium intravenously or by wound infiltration can be done to study the effect of blocking both peripheral and central sensitization and thereby evaluate its optimal role in reducing postoperative analgesic requirements.
CONCLUSION

We conclude that the addition of 50mg of intrathecal magnesium sulphate to spinal anaesthesia induced by bupivacaine significantly delayed the onset of sensory and motor blockade with no demonstrable effect on the duration of spinal anaesthesia. However, intrathecal magnesium sulphate significantly prolonged the time for first analgesic request though to a lesser extent than buprenorphine, thus substantiating its use in postoperative analgesia. Higher doses of magnesium sulphate might be helpful in more prolongation of analgesia.

REFERENCES


