Magnesium Sulphate versus Neostigmine as an Additive to Bupivacaine In Spinal Anesthesia

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Background:
Spinal magnesium has been found to prolong the duration of analgesia in various surgical procedures. Spinally administered neostigmine causes analgesia in animals and humans by preventing the breakdown of synaptically released acetylcholine.
The present study was designed to compare the analgesic efficacy and side effects of either intrathecal magnesium sulfate or neostigmine added to bupivacaine in patients receiving spinal anesthesia.

Methods:
60 patients were randomised into three groups with 20 patients. Group “I” received 3 mL (15 mg) of hyperbaric bupivacaine + 0.1 mL normal saline. Group “II” received 3 mL (15 mg) of hyperbaric bupivacaine + 0.1 mL (50 mg) of magnesium sulfate. Group “III” received 3 mL (15 mg) of hyperbaric bupivacaine + 0.1 mL (50 mcg) of neostigmine. Onset of sensory and motor block, peak sensory level, time to peak sensory level, time to best motor block, intraoperative hemodynamics side effects, duration of analgesia, recovery of motor block, visual analogue score, time to first analgesic request and postoperative side effects were noted.

Results:
Patients characteristics and duration of surgery were comparable (P>0.5). Time of onset of sensory and motor blockade was significantly delayed in Group II compared with Group I and III. It was significantly shorter in Group III compared to Group I. The highest sensory level showed non significant difference in the three groups. A statistically significant longer duration of analgesia was observed in Group II and III compared with the control Group while in group III, it was significantly longer compared to group II. Also the recovery of both sensory and motor blockade was found to be statistically significantly longer in group II and III compared to Group I while group III showed significantly longer time compared to Group II. The hemodynamic parameters were comparable in the perioperative period in the three groups (P>0.05). The incidence of side-effects in the three groups were also comparable (P>0.05).

Conclusion:
The addition of 50 mg intrathecal magnesium or 50mcg neostigmine succeeded significantly and safely in prolonging duration of analgesia without increasing the incidence of side-effects. Also, there was a significant delay in the onset of both sensory and motor blockade in the magnesium group compared to the neostigmine group.

Keywords: magnesium sulfate, neostigmine, bupivacaine, spinal anesthesia

Introduction
Various drugs have been added to local anesthetic agents given intrathecally(IT) in an attempt to improve the analgesic effect of the local anesthetic agent, as well as its duration beside decreasing its dose in an attempt to decrease its systemic side effects (1). The aim of good post operative analgesia is to produce a long lasting continuous effective analgesia with minimal side effects.
These drugs included opioids midazolam, anticholinesterases, NMDA receptor antagonists, alpha2 receptor agonists and cyclooxygenase inhibitors. Unfortunately, non of these additive drugs is without side effects such as pruritus, hemodynamic instability, respiratory depression, urinary retention, nausea and vomiting.(1) Magnesium has antinociceptive effects in animal and human pain models.(2-4) These effects are primarily based on the regulation of calcium influx into the cell, natural physiologic calcium antagonism, and antagonism of the N-methyl-Daspartate (NMDA) receptor.(5) Although some Clinical reports(2,3) have demonstrated antinociceptive effects of systemically administered MgSO4, results are not consistent.(6,7) There are considerable evidences that intrathecally administered magnesium has antinociceptive effects in animals.(4,8,9) In addition, the safety profile has been evaluated, including histopathological analysis.(10) In the first randomized human study of intrathecal (IT) magnesium as an antinociceptive modulator, the addition of IT magnesium, acting as a noncompetitive NMDA antagonist, has shown prolongation of the analgesic effect of opioids in spinal analgesia.(11) Magnesium has also been shown to potentiate the nalgesic effect of bupivacaine when co-administered intrathecally in rats.(12)
Spinally administered neostigmine causes analgesia in animals and humans by preventing the breakdown of synaptically released acetylcholine, which acts on muscarinic and also nicotinic receptors in the spinal cord (13). Neostigmine is a quaternary amine, unable to cross the blood-brain barrier and therefore has to be administered intrathecally in order to reach the target organ, the spinal cord.

When injected intrathecally in volunteers, neostigmine produces dose dependent analgesia but also severe nausea and vomiting, probably due to cephalad spread and action in the brainstem.(14) This side effect can be reduced by injecting the drug in a hyperbaric solution and keeping the head of the bed elevated. Spinal neostigmine is advantageous over other currently used spinal drugs as it causes no hypotension (excitation of sympathetic outflow), no sedation, no respiratory depression, or neurological dysfunction.(13,15). In addition, neostigmine increases sympathetic outflow, thus countering the hypotension of IT local anesthetics (16).

As there are no studies that have compared the efficacy of intrathecally administered combination of either magnesium sulphate and neostigmine with bupivacaine in humans, this study was conducted to compare the quality of spinal anesthesia and the postoperative analgesia when using either of them with heavy bupivacaine 0.5%.

**Patients and methods:**

After obtaining hospital ethical committee approval and written informed consent, 60 ASA physical status I and II patients aged 18-65 years scheduled for elective surgery under spinal anesthesia were included in this prospective randomized, double-blinded study. Patients with a history of uncontrolled hypertension, patients with allergy to the study drugs, opium addiction, sedative drugs consumption, contraindication for spinal anesthesia were excluded from the study. Upon arrival of patients into the operating room, ECG, pulse oximetry (SpO2) and noninvasive blood pressure (NIBP) were monitored. Venous line was inserted, and patients were preloaded with 500 mL Ringer's solution. With the patient in the sitting position, lumbar puncture was performed at the L3-L4 level through a midline approach using a 25G Quincke spinal needle under complete aseptic technique.

The patients were allocated randomly into three groups:

Group I: received 15 mg hyperbaric bupivacaine (3ml) and 0.1 ml normal saline as a control group
Group II: received 15 mg hyperbaric bupivacaine (3ml) and 0.1 ml (50 mg) magnesium sulphate
Group III: received 15 mg hyperbaric bupivacaine(3ml) and 0.1 ml (50mcg neostigmine)

After intrathecal injection, patients were positioned in supine position The anesthesiologist performing the block was blinded to the study drug and recorded the intraoperative data. Sensory block was assessed bilaterally by using absence of pain to pin prick with a short hypodermic needle in the midclavicular line bilaterally. Motor blockade was assessed by using the modified Bromage scale (18) (Bromage 0, no block, the patient was able to move the hip, knee and ankle; Bromage 1, the patient was unable to move the hip but is able to move the knee and ankle; Bromage 2, the patient was unable to move the hip and knee but able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle). The time to reach T10 dermatome sensory block (onset of sensory block), peak sensory level (the time to reach this level and the time to Bromage motor block were recorded before surgery. The three groups were monitored preoperatively, intraoperatively every 2 minutes for the first 20 minutes, every 5 minutes till end of surgery and during shifting for heart rate, NIBP and SpO2. Hypotension was defined as systolic blood pressure 20% decrease in baseline values and was treated with intravenous fluids and ephedrine 5mg intravenous boluses. Bradycardia was defined as heart rate <50/min and was treated with intravenous atropine 0.5mg. Sedation was categorized as 1 = fully awake; 2 = somnolent and responds to call; 3 = somnolent and no response to verbal stimulation; and 4 = asleep and responds to only painful stimulation. Intraoperative nausea, vomiting, rigors, pruritus or sedation were recorded. Nausea and vomiting were treated with intravenous metoclopramide 10 mg. Rescue antiemetics were given if vomiting occurred more than once, for nausea lasting more than ten minutes, or at the patient’s request. The treatment was repeated if necessary.

The regression time for sensory and motor block were recorded in a post anesthesia care unit (PACU). All durations were calculated considering the time of spinal injection as time zero. Patients were discharged from the PACU after sensory regression to S1 dermatome and Bromage 0. The severity of postoperative pain was measured using a 10–cm visual analogue scale (VAS) (0=no pain; 10=the worst possible pain) during rest at four-hour intervals or whenever the patient requested analgesia. All patients were observed for 24 hours and rescue analgesic was given in the form of diclofenac sodium 75mg intramuscularly on demand or when VAS was more than 4. The time for first rescue analgesic was recorded. Duration of analgesia was taken as the time from the onset of subarachnoid block till the time of first rescue analgesic. Postoperative side effects like nausea, vomiting, pruritus, urinary retention and headache were recorded.

**Statistical analysis**

A number of 15 patients was needed to detect a difference of 25% in the duration of spinal analgesia till time of first rescue analgesic. A sample size of 15 patients per group was needed to detect an intergroup difference of at least 20% (α= 0.01, two-sided, power = 90%) with two sample t-test.

All statistical analyses were performed using SPSS for windows 15.0. Parametric data were compared using analysis of variance (ANOVA). Within group comparisons at different time intervals were assessed by using paired t-test. All the categorical data were compared by using chi-square test. A value of P<0.05 was considered statistically significant. The results are expressed as mean (SD), median and interquartile range, or numbers and percentages.
Table 1: patients characteristics and surgery duration

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.31±9.23</td>
<td>48.22±10.24</td>
<td>48.33±9.65</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.63±4.65</td>
<td>62.34±5.45</td>
<td>61.89±4.78</td>
</tr>
<tr>
<td>Male/ female ratio</td>
<td>12/8</td>
<td>11/9</td>
<td>13/7</td>
</tr>
<tr>
<td>Surgery duration(min)</td>
<td>68.44±8.5</td>
<td>66.44±9.22</td>
<td>67.44±7.86</td>
</tr>
</tbody>
</table>

Values are mean ±SD except male to female ratio which are number or ratio

Table 2: Sensory and motor characteristic of spinal anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group I</th>
<th>Group I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time of sensory block(min)</td>
<td>2.43±1.15</td>
<td>4.05±1.04</td>
<td>1.37±1.12*</td>
</tr>
<tr>
<td>Peak sensory level</td>
<td>T8</td>
<td>T7</td>
<td>T7</td>
</tr>
<tr>
<td>Peak sensory level time (min)</td>
<td>5.15±2.67</td>
<td>6.32±2.23</td>
<td>3.45±1.34*</td>
</tr>
<tr>
<td>Onset time of motor block(min)</td>
<td>2.49±1.19</td>
<td>3.24±1.34</td>
<td>1.56±0.57*</td>
</tr>
<tr>
<td>Time to best motor block(min)</td>
<td>5.43±2.53</td>
<td>7.23±2.52</td>
<td>4.48±1.46*</td>
</tr>
<tr>
<td>Sensory regression to S1 time (min)</td>
<td>194.45±56.15</td>
<td>254.54±55.15</td>
<td>341.45±55.32*</td>
</tr>
<tr>
<td>Time to Bromage score (h/min)</td>
<td>155.43±32.11</td>
<td>244.44±48.25*</td>
<td>325.43±35.24*</td>
</tr>
<tr>
<td>Time to first analgesic request(h)</td>
<td>3.43±2.45</td>
<td>7.36±2.45*</td>
<td>8.43±1.12**</td>
</tr>
</tbody>
</table>

Values are mean ± SD

* denotes significance (p < 0.05)

Table 3: Incidence of side effects

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group I</th>
<th>Group I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>3(15%)</td>
<td>3(15%)</td>
<td>2(10%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2(10%)</td>
<td>2(10%)</td>
<td>2(10%)</td>
</tr>
<tr>
<td>Desaturation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2(10%)</td>
<td>2(10%)</td>
<td>3(15%)</td>
</tr>
<tr>
<td>Rigors</td>
<td>4(20%)</td>
<td>3(15%)</td>
<td>3(15%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

Values are number (percentage)

Table 4: Post operative VAS:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0</td>
<td>0.62±0.09*</td>
<td>3.02±0.13*</td>
<td>3.52±0.18*</td>
<td>3.42±0.16</td>
<td>3.07±0.09</td>
<td>2.58±0.15</td>
<td>3.22±0.12</td>
<td>3.45±0.12</td>
</tr>
<tr>
<td>Group II</td>
<td>0</td>
<td>0.15±0.08</td>
<td>1.19±0.17</td>
<td>2.52±0.12</td>
<td>3.82±0.15</td>
<td>3.46±0.18</td>
<td>2.52±0.15</td>
<td>3.12±0.12</td>
<td>3.35±0.12</td>
</tr>
<tr>
<td>Group III</td>
<td>0</td>
<td>0.07±0.02</td>
<td>1.02±0.09</td>
<td>1.46±0.12</td>
<td>1.52±0.25</td>
<td>3.52±0.12</td>
<td>3.88±0.23</td>
<td>3.03±0.12</td>
<td>3.25±0.26</td>
</tr>
</tbody>
</table>

* denote significance

Results

60 patients were included and randomly assigned to the treatment groups.
There were no significant differences as regards age, weight and sex, among the three groups. The duration of surgery was also similar (Table 1).

As shown in Table 2, the mean onset time of sensory block in groups III was significantly shorter than group I and II (p < 0.001) and while in group II it was significantly longer than group I. The maximum sensory level comparison between the three studied groups showed non significant difference .The time to reach this level was significantly shorter in group III compared to either group I or II while it was significantly longer in group II compared to group I.(p<0.05%) Table 2 also shows a significant difference in duration of sensory block between groups II and III (95% CI 148±162.5; p < 0.001) compared to group I. Group III time of sensory analgesia was significantly longer than group II (p < 0.001). In addition, as demonstrated in Table 2, there was a significant difference in mean onset time of motor block between groups II and III (p < 0.001) compared to group I; it was longer in group II and shorter in group III (p < 0.001). Group II had significantly longer mean onset time of motor block than group III.

Also, Table 2 is indicative of a significant longer mean duration of motor blockade time in group II and III compared to group I (p < 0.001). Moreover, a significant difference in duration of motor block between groups III and II was found . Patients who were given neostigmine demonstrated a significantly prolonged duration of anesthesia compared with the control (p < 0.001) and magnesium groups (Table 2). With the duration of anesthesia, there was a significant difference in mean time to first analgesic request between groups II and III compared to group I (p < 0.001) (Table 2). A significant difference in mean time to first analgesic request between groups II and III was observed (table. 2).

The first rescue analgesic was related to the visual analogue scale which was 4 or more. The VAS showed significant difference between group I compared to either group II or III at 2,3, and 4 hours After receiving the rescue analgesic there were non significant changes between the three groups at 6,8,12 and 24 hours.(table 4)

The time of regression of both sensory block to S1 dermatome level and motor block to Bromage scale 0 were significantly longer in both group II and III compared to group I, also it was significantly longer in group III compared to group II. The total analgesic consumption during the first 12 hours after surgery was devoid of any significant difference between groups II and III. (table 2)

Several studies have demonstrated the benefits of intravenous magnesium sulphate in the perioperative period. In this study, it was found that magnesium sulphate 50mg and neostigmine 50mcg injected intrathecaically with 15 mg heavy bupivacaine successfully improved the quality and duration of spinal anesthesia with minimal side effects.

In this study, it was found the onset of both sensory and motor blockade were longer in the magnesium group compared with the neostigmine and control groups. This is supported by the study of Unlugence et al.(21) who found that the addition of magnesium sulphate 50mg and neostigmine 50mcg in 15 mg heavy bupivacaine prolonged the duration of sensory analgesia calculated from the time of intrathecal block till the time of sensory regression to S1 dermatome and then to the time of first analgesia request was significantly longer than the control group but shorter than the neostigmine group. This is in consistence with the study of Maleeswaran et al.(22) who found that the addition of magnesium sulphate 50mg to bupivacaine and fentanyl prolonged the onset and the duration of analgesia and reduced the analgesic requirements with minimal side effects. In contrary to our results in a study of Kherzi et al.(23), the difference in duration of sensory block time between the magnesium and control group was shown to be insignificant. The difference between the results of the two studies may be caused by different doses of magnesium sulfate or the baricity of bupivacaine.

As regards to hemodynamic changes there was hemodynamic stability in the perioperative period and a non significant number of patients in the magnesium group demonstrated a hypotensive episode requiring treatment. This finding may be attributable to the gradual onset of sympathetic blockade in the magnesium group in our study. This is in agreement with previous studies. Studies with 50 and 100 mg magnesium sulphate with resultant satisfactory analgesia without significant added adverse effects(21,24). With 50 mg of intrathecal magnesium, we observed increased duration of analgesia and motor blockade as compared with previous studies without...
increasing any adverse effects. The time to first rescue analgesic was significantly prolonged than the control group but it was significantly shorter than the neostigmine group. This was in agreement with previous studies. In contrary to our results Kherzi et al (23) found that the addition of magnesium did not prolonged the time to first analgesic request. Use of intrathecal magnesium did not find any signs of systemic toxicity, such as arterial hypotension, cardiac arrhythmias, somnolence, double vision, slurred speech or weakness, either intraoperatively or during the postoperative course in patients treated with magnesium sulfate who underwent major orthopedic surgery. [24] We too did not find any of the above-mentioned complications during the intraoperative or in the postoperative periods. As regards to the incidence of side effects, it was comparable between the magnesium and control group. The selected dose of intrathecal magnesium in the current study was based on previous studies.(21,25,26)

Saecki et al(26) claimed that a dose of 1 mg/kg represents the maximum tolerable dose in rabbits from a neurotoxic standpoint and hence the selection of a dose of 50 mg intrathecal MgSO4 in our study was based on the fact that several previous studies have shown that the use of such a dose could prolong the duration of intrathecal opioid analgesia without additional side effects. [21, 22, 27]

In this study, it was found that the onset of sensory and motor block in the neostigmine group was significantly shorter than either the magnesium or the control group while the duration of spinal anesthesia and postoperative analgesia was longer. This is in consistent with the previous reports and studies of Liu et al(14) and Pan et al(29) who demonstrated similar prolonged durations of sensory block in their studies. The highest sensory level achieved was compared and was observed not to reach a statistically significant difference. The time for regression of sensory block to S1 was significantly prolonged in the neostigmine group as compared to the control group. Liu et al(14) and Pan et al(29) demonstrated similar prolonged durations of sensory block in their studies. Duration of motor block was significantly prolonged in the neostigmine 50μg group as compared to the bupivacaine control group. This comparison being statistically significant was shown by similar dose neostigmine studies of Liu et al(14) Pan et al(29) and Tan et al(30). Intrathecal neostigmine causes motor block by acetylcholine mediated reduction in motor neuron outflow with no reduction in spinal cord blood flow or histopathological changes. In addition increased spinal levels may augment motor block of spinal bupivacaine(28,31).

Analgesia provided by intrathecal neostigmine as assessed by visual analogue scale was also observed. VAS scores were compared at 1, 2, 3, 4, 6, 8, 12 and 24 hour durations and showed a statistically significant (p<0.05) value when compared with the control group at the times from 1–4 hours. Our results are in agreement with Chung et al(15) and Lauretti et al(17) who demonstrated statistically significant lower visual analogue scale scores in the doses ranging from 25-75μg neostigmine group compared to control group. Studies done by Hood et al (13) and Klam et al (16) founded same results. Hemodynamic changes in the neostigmine group were stable and comparable perioperatively and few non-cardiac patients showed transient hypotension and bradycardia and non of the patients developed hypoxemia or sedation. This is in agreement with previous reports of Lauretti et al(17) and in contrast to that of Hood et al(13) who found that IT neostigmine increased blood pressure and heart rate and this can be explained with the higher dose used in their study which was 500-750 mcg neostigmine while we used only 30mcg in this study.

Side effects slightly nausea and vomiting which are the most distressing showed non significant changes in the neostigmine compared to the control group and this can be explained by the low dose used in this study, the use of heavy bupivacaine and the supine position which limited the rostral spread of neostigmine to the brainstem which is the cause of nausea and vomiting, this is in agreement with the study of Yoganarashima et al(31). In contrary to our results Hood et al Klam et al and Lauretti et al found higher incidence of nausea and vomiting with IT neostigmine. Also in previous studies it was found that The addition of neostigmine 6.25 - 50 mcg prolonged duration of sensory and motor block but produced a high incidence of side effects, especially nausea and vomiting. This has limited its use in clinical settings (32,33).

Studies in volunteers and patients undergoing surgery showed that IT neostigmine provided analgesia when given at doses 10 μg for surgical patients, at doses 50 μg for volunteers, and induced few side effects at doses 50 μg(13,14). For the purpose of this study, the dose was chosen to maximise the analgesic efficacy whilst minimizing the potential side effects of neostigmine in view of the route of administration and to limit the extent of side effects. The 50 μg dose of neostigmine in this age group was therefore chosen to minimize peroperative side effects, in particular, nausea and vomiting. Spinal cord toxicity resulting from IT neostigmine has not been reported.(12,13,14,16)

In this study it was found that intrathecal neostigmine significantly prolonged the effect of spinal anesthesia, in terms of both the duration of complete analgesia and the time until postoperative analgesic was first requested, relative to the control group. Compared with the magnesium group, the duration of complete analgesia and the time until the first request for analgesic in the neostigmine group were significantly longer. When analgesic was first requested in the three groups after surgery, patients made one or two requests for doses of diclofenac 75mg intramuscularly to achieve adequate analgesia. Since the overall 24-hr VAS pain scores were significantly higher in the control group relative to the magnesium and neostigmine groups, it would seem that there was some residual
analgesic effect in the magnesium and neostigmine groups over that period. This is in agreement with previous reports of Tan et al who compared neostigmine with morphine as additives to bupivacaine in total knee replacement surgery. (34)

In contrast 100 µg of intrathecal neostigmine was unable to provide adequate analgesia for patients undergoing more painful surgery such as abdominal hysterectomy. (35) From these studies, it seems that the dose-dependency of IT neostigmine-induced postoperative analgesia depends on the nature of the noxious stimuli, the type of anesthesia used, the methods of analgesic administration and the assessment of analgesic effect.

Conclusion

Based on the data found in our study, it could be concluded that addition of either MgSO4 (50 mg) or neostigmine (50mcg) intrathecally with 15 mg of 0.5% hyperbaric bupivacaine succeeded safely in prolonging the duration of spinal anesthesia and postoperative analgesia. However neostigmine was superior to magnesium in having shorter onset of both sensory and motor blocks and having more prolonged time of request of first analgesia.

References


