Original Article

Effect of adding magnesium sulfate to intrathecal low-dose of bupivacaine for patients with severe pre-eclampsia undergoing cesarean delivery

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Abstract: Background: Intrathecal magnesium sulfate, an NMDA antagonist, has been shown to prolong analgesia and potentiates spinal anesthesia without significant side effects in parturients. This study aimed to explore the hypothesis that adding magnesium sulfate to intrathecal low-dose of bupivacaine and sufentanil can prolong the spinal analgesia in patients with severe pre-eclampsia. Methods: Sixty patients with severe pre-eclampsia were enrolled in this prospective, double-blinded, placebo-controlled trial. Patients were randomly divided into two groups. Patients in Magnesium group received spinal anesthesia with 0.5% bupivacaine 6 mg + sufentanil 2.5 μg + 25% magnesium sulfate 50 mg and the other patients in Control group received the same dose of bupivacaine and sufentanil only. Characteristic of spinal anesthesia, duration of spinal anesthesia, postoperative analgesia requirements were recorded. Side effects were also recorded. Results: The duration of spinal analgesia was longer (183 ± 32 vs 138 ± 27 min) in Magnesium group than in Control group (P < 0.001). The consumption of postoperative fentanyl was significantly lower in the Magnesium group than that in the Control group (343 ± 42 vs 550 ± 49 µg, P < 0.001). No differences in side effects of spinal anesthesia were found between groups. Conclusion: In parturients with severe pre-eclampsia undergoing caesarean delivery, the addition of intrathecal magnesium sulfate to low-dose of bupivacaine and sufentanil prolongs the duration of analgesia and reduces postoperative analgesic requirements without additional side effects.

Keywords: Magnesium, sulfate, intrathecal, bupivacaine, pre-eclampsia, cesarean delivery, low-dose

Introduction

The perioperative pain could induce neuroendocrine response and catecholamine release, which could cause a transient but severe hypertension [1]. And the hypertension may cause maternal intracranial pressure, cerebral haemorrhage and cardiac failure with pulmonary oedema. These malignant events could result in increased morbidity and mortality in both mother and newborn [2], especially in patients with severe pre-eclampsia [3]. Therefore significantly effective pain relief is important to this patient population. Moreover, early ambulation and enjoying of the care of newborn is relevant to the effective of pain management.

Spinal anesthesia technique has the benefits to manage postoperative pain when compared with general anesthesia and systemic analgesia [4]. However, spinal anesthesia especially using low-dose of intrathecal local anesthetic (preventing spinal induced hypotension), is associated with short duration of analgesia. Recently, increasing studies have demonstrated that the addition of magnesium sulfate to intrathecal local anesthetics with or without opioids could prolong the duration of analgesia, reduce postoperative analgesic requirements, improve perioperative shivering and without significant side effects observed [5-12]. However, there were no studies on the effect of adding magnesium sulfate to intrathecal low-dose of bupivacaine combined with sufentanil spinal anesthesia for patients with severe pre-eclampsia have been reported. We therefore explored the effect of adding magnesium sulfate to intrathecal low-dose of bupivacaine combined with sufentanil spinal anesthesia for patients with severe pre-eclampsia.
Methods

After getting the agreement from the Ethics Review Board of the Jiaxing Maternity and Child Care Hospital, we registered this clinic trial in Chinese Clinical Trial Registry (ChiCTR) (registration number is ChiCTR-TRC-15006500). With written informed consent, seventy-three patients with severe pre-eclampsia, scheduled for elective cesarean section, were enrolled in the current study, which was accomplished between June 2015 and December 2015 in our hospital. Severe preeclampsia was defined by the presence of one of the following: systolic arterial blood pressure (SBP) ≥ 160 mmHg, diastolic arterial blood pressure (DBP) ≥ 110 mmHg, symptoms of imminent eclampsia, proteinuria ≥ 300 mg/dL. Patients with hemolysis elevated liver enzymes, and low platelets syndrome were eligible for inclusion if the platelet count exceeded 75 × 10^9/L. Exclusion criteria were as follows: any contraindication to combined spinal epidural anesthesia (CSEA), body mass index > 35 kg/m^2, chronic hypertension, coagulation abnormality, platelet count < 75 × 10^9/L, local or generalized sepsis, cord prolapsed, gestation < 28 weeks, twin pregnancy, active labor, or a non-reassuring fetal heart rate, patients whose sensory block level less than T_6 or needing epidural supplement during surgery. Antepartum management of patients was based on the established protocol of our hospital: labetalol was administered to control blood pressure when SBP was 160 mmHg or higher, or DBP was 105 mmHg or higher, and magnesium sulfate therapy was initiated for prophylaxis of seizures.

All patients received no premedication. On arrival in operating theatre, all patients had an intravenous cannula inserted into a peripheral arm vein and 300 mL 37°C Ringer’s solution were carefully administered before anesthesia. Blood pressure, heart rate, oxygen saturation and electrocardiogram were monitored and recorded.

Combined spinal-epidural (CSE) using a needle-through-needle technique was performed with the patient in the left lateral position. An 18-G Tuohy needle was inserted into epidural space at L_3-L_4 using the method of loss of resistance to air technique. A 27G spinal needle with pencil tip was then passed through the Tuohy needle to enter the subarachnoid space. After ascertaining the emergence of cerebrospinal fluid, patients received one of two premixed solutions intrathecally at a speed of 3 mL/10 s. After intrathecal injection, the spinal needle was removed, and an epidural catheter was placed and advanced cephalad 3-4 cm into the epidural space. No drugs were injected via the epidural catheter. The patient was then placed on supine position with the right hip pad at 15 degrees. Surgery was permitted after T_6 with disappearing sensory of pain. Intraoperative pain was rescued by injecting 5 ml lidocaine via epidural catheter. Postoperative pain was rescued by intravenous fentanyl with patient controlled intravenous analgesia (PCIA). The PCIA was set with a bolus of 30 μg fentanyl and 10 min of locking time and without a background dose.

The mixed solutions for spinal anesthesia were prepared by an anesthesia assistant who had known the patient grouping, and administered by a second attending anesthesiologist who remained blinded to the mixed solution contents. The mixed solution for patients in Magnesium group is: 0.5% bupivacaine 1.2 mL + 2.5 μg sufentanil + 0.5 mL 10% Dextrose + 0.2 mL 25% magnesium sulfate (Wuxi Pharmaceutical Company, China; Production batch: 1307201.), diluted with 0.9% sodium chloride to a total volume of 3 mL. The mixed solution for patients in Control group is: 0.5% bupivacaine 1.2 mL + 2.5 μg sufentanil + 0.5 mL 10% Dextrose, diluted with 0.9% sodium chloride to a total volume of 3 mL. An insulin syringe was used to measure volumes less than 1 mL.

Sensory block level and motor block degree was assessed at 1-min intervals for the first 10 min after spinal injection and then at 10-min intervals until the end of the surgery and at 30-min intervals after surgery. Sensory level was assessed bilaterally along the mid clavicular line using a 17-G needle (patient was asked to report pain sensation, if the block was not even bilaterally, the lower side was chosen). The duration of spinal analgesia was defined as the period from spinal injection to the first requirement of rescued fentanyl postoperatively. The onset time of sensory block was defined as the time from intrathecal injection to a T_6 sensory block level. The duration of sensory block was defined as the time between the onset time of sensory block and the recovery of sensory level of T_12. Motor block in the lower
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Figure 1. Consort Diagram.

limbs was graded using the Bromage Scale [13] (0 = able to lift extended leg; 1 = able to flex knee but not lift extended leg; 2 = able to move foot only; and 3 = unable to move foot). The onset time of motor block was defined as the time from intrathecal injection to a Bromage Score of 1 reached. The duration of motor block was defined as the period between the time of motor block onset and a Bromage Score of 0.

Non-invasive arterial pressure (NIBP) was measured automatically at 2-min intervals from the start of anesthesia for 10 min, and then at 5-min intervals until the end of the surgery. Hypotension was defined as a systolic arterial pressure below 110 mmHg, or a decrease in systolic arterial pressure > 20% below baseline. Baseline of NIBP was defined as an average of three successive measurements at the time when patient arrived in operating theatre with a sitting position. Hypotension was treated with 40 μg i.v. boluses of phenylephrine. Bradycardia, defined as heart rate less than 55 beats per min, was treated with 0.5 mg of atropine intravenously.

Subjective pain was assessed using a 10 cm visual analogue scale (VAS), where 0 cm represented ‘no pain’ and 10 cm represented ‘most severe pain’, at the following timepoints: skin incision, fetal delivery, peritoneal closure, skin closure, and 2, 4, 8, 12, 24 h postoperatively. At the time of 24 h after surgery, a grading was used to assess patient satisfaction to analgesia (1 = excellent; 2 = good; 3 = bad).

Side effects and complications of spinal anesthesia including pruritus, shivering, severe sedation, nausea and vomiting, post dural puncture headache (PDPH) and respiratory depression (defined as breath rate < 12 bpm or SpO2 < 90%) during surgery and the first 24 h postoperatively were also recorded by a fixed anesthesia assistant. Sedation was measured as none = awake and alert, mild = awake but drowsy, moderate = asleep but arousable, severe = not arousable. Any symptoms and signs of neurological deficit were also recorded.

Umbilical arterial blood was drawn for blood gas analysis immediately after delivery. The neonatal Apgar score was assessed by a pediatrician who was not involved in this study.

Demographic data were collected and are presented as count or mean ± SD as appropriate. Nominal data were analyzed using the Chi-square test, and continuous data were analyzed using one-way analysis of variance (ANOVA) for intergroup comparison. Duration of spinal anesthesia was also analyzed using
Table 1. Patient’s demographic, obstetric and surgical data

<table>
<thead>
<tr>
<th></th>
<th>Magnesium group (n = 30)</th>
<th>Control group (n = 30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>25 ± 3</td>
<td>26 ± 3</td>
<td>0.41</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 ± 3</td>
<td>159 ± 3</td>
<td>0.42</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 ± 5</td>
<td>72 ± 4</td>
<td>0.84</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>0.60</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>45 ± 7</td>
<td>47 ± 7</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *Student t test.

Table 2. Characteristics and efficacy of spinal anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Magnesium group (n = 30)</th>
<th>Control group (n = 30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory block (to pinprick)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset time to T₆ (min)</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>123 ± 35</td>
<td>96 ± 27</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Motor block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset time (min)</td>
<td>4 ± 0</td>
<td>3 ± 0</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>139 ± 27</td>
<td>110 ± 21</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>183 ± 32</td>
<td>138 ± 27</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Consumption of fentanyl (µg)</td>
<td>343 ± 42</td>
<td>550 ± 49</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Patient Satisfaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent [number (%)]</td>
<td>24 (80)</td>
<td>16 (51)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Good [number (%)]</td>
<td>6 (20)</td>
<td>14 (49)</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (%). *Student t test, #Chi-square test.

Figure 2. Cumulative percentages of patient remaining no pain after spinal injection in the Magnesium group (solid line, yellow area) and in the Control group (dotted line, green area), obtained using the Kaplan-Meier survival analysis. Log-rank differences between the two groups were significant (P < 0.05).

Kaplan-Meier survival analysis. Statistical analysis was performed with Graphpad Prism 5 (Version 5.01). Statistical significance was defined as P < 0.05 (two-sided).

Results

The CONSORT diagram of the present study is showed in Figure 1. A total of 73 patients with severe pre-eclampsia were assessed for eligibility, among them 60 patients were enrolled and randomly assigned into the Magnesium group (n = 30) or Control group (n = 30). Three patients refused to participate in this study, two patients whose platelet was less than 75 × 10⁹/L, eight patients whose sensory block level less than T₆, 10 min after intrathecal injection or needing epidural supplement during surgery. All the 60 patients finished the study and were included into the final analysis.

There were no significant differences in the demographic and obstetric characteristics between the Control group and the Magnesium group (Table 1). Characteristics of spinal anesthesia are presented in Table 2. The onset and duration of sensory and motor blockade were longer in the Magnesium group than in the Control group (P < 0.05) (Table 2). Moreover, the duration of spinal analgesia was significantly longer in the Magnesium group than in the Control group (183 ± 32 vs 138 ± 27 min, P < 0.05) (Figure 2). The consumption of fentanyl during the first 24 hours postoperatively were significantly less in the Magnesium group than in Control group (343 ± 42 vs 550 ± 49 µg, P < 0.05) (Table 2). The Magnesium group has higher rate of excellent satisfaction of patient to spinal anesthesia than that in the Control group (80% vs 51%, P < 0.05) (Table 2).

Side-effects, neonatal Apgar score and umbilical artery pH were similar between the two groups (Table 3).

Discussion

Although study showed patients with severe preeclampsia experience less hypotension during spinal anesthesia for elective cesarean delivery than healthy parturients [14], reducing
Magnesium for spinal anesthesia

Table 3. Side effects of anesthesia and neonatal Apgar score and umbilical arterial pH

<table>
<thead>
<tr>
<th></th>
<th>Magnesium group (n = 30)</th>
<th>Control group (n = 30)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>6 (20.0)</td>
<td>8 (26.7)</td>
<td>0.76*</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>12 (40.0)</td>
<td>9 (30.0)</td>
<td>0.59*</td>
</tr>
<tr>
<td>Shivering</td>
<td>5 (16.7)</td>
<td>6 (20.0)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (26.7)</td>
<td>7 (23.3)</td>
<td>1.00*</td>
</tr>
<tr>
<td>PDPH</td>
<td>0 (0%)</td>
<td>1 (3.3)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Severe sedation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Apgar score</td>
<td>10.0 ± 0.0</td>
<td>10 ± 0.0</td>
<td>1.00*</td>
</tr>
<tr>
<td>Umbilical artery pH</td>
<td>7.22 ± 0.04</td>
<td>7.28 ± 0.06</td>
<td>0.22*</td>
</tr>
</tbody>
</table>

Data are presented as number (percent) or mean ± SD. PPDH = post dural puncture headache. *Student t test, #Chi-square test.

or avoiding spinal induced hypotension, which could worsen the outcomes of newborns, is still a focus task while we choose spinal anesthesia for patients with severe preeclampsia. The main limitation of spinal anesthesia, when use a traditional intrathecal dose (10 mg advocated by the text book), is the high incidence of hypotension. Therefore several studies use low-dose of bupivacaine spinal for cesarean delivery got the conclusion that lowering the dose of spinal bupivacaine can prevent the incidence of hypotension, but associated with the risk of short duration of anesthesia and analgesia [15, 16]. Moreover, our previous study showed that 6 mg of bupivacaine could be a relatively ideal initial spinal dose (along with epidural anesthesia as a back-up) for cesarean section with a lower incidence of hypotension for patient with severe preeclampsia, when considering the balance of the conflicting demands of avoiding patient discomfort and avoiding adverse effect [17]. Therefore, in this study, we expect that adding 50 mg of magnesium sulfate to intrathecal 6 mg of bupivacaine combined with 2.5 µg sufentanil spinal anesthesia for patients with severe pre-eclampsia could prolong the duration of anesthesia and analgesia. To our knowledge, this is the first time to study the effect of intrathecal magnesium on low-dose of spinal bupivacaine.

The main finding in the present study was that the addition of magnesium sulfate (50 mg) to intrathecal hyperbaric low-dose (6 mg) bupivacaine and 2.5 µg sufentanil could prolong the duration of spinal analgesia. The results of our study are consistent with several previous findings that also showed the duration of spinal analgesia was significantly prolonged by intrathecal magnesium sulfate [9, 11, 18, 19]. Moreover, consumption of postoperative fentanyl was found in the present study to be decreased by adding intrathecal magnesium sulfate. Our findings reinforced that magnesium sulfate can be used in intrathecal place as an effective adjuvant since it has analgesic properties.

On the contrary, there were several studies reported that intrathecal magnesium sulfate failed to prolong the duration of analgesia which were inconsistent with our results [20, 21]. Moreover, Morrison et al pointed out in the obstetric population there was not statistically significant difference in the prolongation of spinal analgesia with intrathecal magnesium sulfate in a recent meta-analysis [10]. Contributing to this discrepancy, that opioid was involved in our study may be a dominating factor we suspected. That Kroin [22] et al found intrathecal magnesium sulfate enhanced peak antinociception and widen the area under time-response curve of morphine can further enhance our suspicion. The potentiation of opioid antinociception by magnesium sulfate may continue into the post-operative period, explaining the decrease in consumption of postoperative fentanyl found in the present study. However, two studies demonstrated that intrathecal magnesium without opioids, even intrathecal magnesium alone, can prolong the duration of analgesia of spinal anesthesia [23, 24]. To explain the phenomenon, that the dose of intrathecal magnesium sulfate may be the critical cause. Larger dose of intrathecal magnesium sulfate were used in these studies compared with our study. We choose 50 mg magnesium sulfate as the adjuvant was based on several previous studies on clinical investigation of intrathecal magnesium sulfate for cesarean delivery publically published so far [6, 9, 10, 12, 21, 25]. Therefore no matter what the mechanism was, we recommended this adjuvant for the patients could get profits from it.

NMDA-receptor antagonists can diminish the activation of C-fibers which leads to neuronal excitation and prevent central sensitization elicited by peripheral nociceptive stimulation.
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[26, 27]. Magnesium sulfate, a noncompetitive NMDA-receptor antagonist, has analgesic properties. Mercieri et al. found that systemic magnesium sulfate infusion (i.e. intravenous route), even with large doses, did not increase cerebrospinal fluid (CSF) magnesium concentrations, suggesting magnesium sulfate exhibits insufficient blood-brain barrier penetration [28]. Kroin et al. demonstrated in an animal study that intrathecal magnesium sulfate potentiated the antinociceptive effect of morphine to noxious thermal and mechanical stimulation at an incisional pain site at the level of the spinal cord in a dose-dependent fashion [22]. Hence, intrathecal route would be better for magnesium sulfate administration to potentiate spinal anesthesia than systemic route by which effective CSF concentrations of magnesium required large doses that may result in severe side effects.

The onset of sensory and motor blockade in the present study was delayed in Magnesium group which was found in previous studies [11, 29]. The clinical significance of this delay is questionable because the delayed time was only about 1 min for both sensory and motor blockade onset in the present study. It is not easy to explain this phenomenon using available understanding of mechanism of magnesium action on central nervous system. The effect of adding magnesium sulfate on the pH and baricity of the spinal solution might be considered as a possibility for this delay [18, 30]. As the onset time of sensory in Magnesium group was delayed nearly 1 minute, we did not suggest adding magnesium to intrathecal local anesthetic for emergent cesarean delivery which requiring a rapid onset. The duration of motor block in the present study was 30 min longer in Magnesium group, and this delay of motor recovery was not clinically relevant in the patients, due to they were restrict to bed during this period in our hospital.

In the current study, we found there were no additional side effects in Magnesium group, and our results may demonstrate magnesium sulfate is a safe intrathecal adjuvant. In clinical studies, intrathecal magnesium sulfate 50 mg was found to be safe and effective [9-11, 19-21], which are similar to the findings of the present study, in which we also did not find any obvious symptoms and signs of dysfunction in nervous system, reinforcing the safety of maternal intrathecal magnesium. However, safety of intrathecal magnesium sulfate would be argued because our study is a small study and no specific assessments to assess safety were done. Hence, the safety of intrathecal magnesium sulfate with larger sample size and specific assessment variables, or with large dose should be carefully evaluated in both animals and humans, especially in pregnant populations.

In conclusion, in patients with severe pre-eclampsia undergoing cesarean delivery with spinal anesthesia, the addition of intrathecal magnesium sulfate (50 mg) to spinal hyperbaric low-dose of bupivacaine combined with sufentanil prolonged the duration of spinal analgesia, reduced the consumption of post-operative fentanyl, delayed the onset of both sensory and motor blockade of spinal anesthesia. No obvious additional side effects were found. And we do not recommend this drug to use in emergent cesarean delivery.

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Disclosure of conflict of interest

None.

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