Original contribution

Magnesium sulfate infusion prevents shivering during transurethral prostatectomy with spinal anesthesia: a randomized, double-blinded, controlled study

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Received 16 June 2008; revised 3 June 2009; accepted 22 June 2009

Keywords:
Hypothermia; Magnesium sulfate; Shivering; Spinal anesthesia

Abstract
Study Objective: To determine whether magnesium sulfate (MgSO₄) infusion during surgery reduces shivering during spinal anesthesia.
Design: Double-blinded placebo-controlled, randomized trial.
Setting: Operation room of a university hospital.
Patients: 60 patients, aged 40 to 70 years, scheduled for elective transurethral resection of the prostate (TURP) during spinal anesthesia.
Interventions: Subarachnoid anesthesia consisting of hyperbaric bupivacaine three mL 0.5% was injected using a 25-G Quincke spinal needle. Patients received either saline (Group C, n = 30) or MgSO₄ (Group Mg, n = 30). Group Mg received an intravenous (IV) bolus of MgSO₄ 80 mg/kg via syringe pump over a 30-minute period, followed by a two g/hr infusion during the intraoperative period. Group C received an equal volume of saline.
Measurements: Motor blockade was evaluated by Bromage motor scale. Sensory block level was assessed by pinprick test. Shivering was assessed after the completion of subarachnoid drug injection. Side effects were recorded.
Main Results: Hypothermia was observed in all patients (100%) in Group Mg and in 24 patients (80%) in Group C (P = 0.024). The decrease in core temperature in Group Mg was significantly greater (P < 0.005). Shivering was observed in two patients (6.7%) in Group Mg and 20 patients (66.7%) in Group C (P = 0.0001).

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Conclusions: MgSO₄ infusion in the perioperative period significantly reduced shivering during TURP with spinal anesthesia. MgSO₄ infusion prevents shivering in patients receiving spinal anesthesia but increases the risk of hypothermia.
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1. Introduction

Regional anesthesia is known to significantly impair thermoregulation and predispose patients to hypothermia [1]. General and epidural anesthesia alter function of the autonomic nervous system, which plays a significant role in thermoregulation [2] and interferes primarily with peripheral vasoconstriction below the level of the sympathetic blockade.

Shivering associated with spinal anesthesia is common, occurring in up to 56.7% of patients [3]. Shivering may interfere with monitoring of the electrocardiogram, blood pressure, and oxygen saturation. Furthermore, shivering increases oxygen consumption, lactic acidosis, carbon dioxide production, and metabolic rate by up to 400% [4]. Thus, it may cause problems in patients with low cardiac and pulmonary reserves [5].

Shivering is an important problem for urologists, especially during transurethral resection of the prostate (TURP) surgery. Shivering may interfere with the surgeon’s ability to visualize resectable prostate tissue. Injury to the urethra, bladder, and rectum may occur during the procedure. As a result, shivering not only prolongs the operation time, it may also cause severe complications.

Magnesium sulfate (MgSO₄) has anti-shivering effects [6, 7] but it may enhance the rate of cooling because of its vasodilatory properties. Furthermore, it has potential neuroprotective effects [8], and experimental data suggest that the neuroprotective effect of hypothermia may be increased with the addition of MgSO₄ [9]. Although intravenous (IV) MgSO₄ suppresses shivering after general anesthesia, there are no data on perioperative IV MgSO₄ in the treatment of shivering associated with regional anesthesia. The aim of this study was to assess the effect of IV MgSO₄ administration on shivering associated with spinal anesthesia.

2. Materials and methods

After Fatih University Hospital Ethics Committee approval, written, informed consent was obtained from all patients participating in this randomized, double-blinded, placebo-controlled trial. Sixty patients, 40-70 years of age, who were scheduled for elective TURP during spinal anesthesia, were enrolled in the study. Patients with ASA physical status > II, obesity (BMI > 28 kg/m²), preoperative fever (temperature > 38°C), contraindications to regional anesthesia, allergy to the study medication, thyroid disease, Parkinson’s disease, dysautonomia or Raynaud’s syndrome, ischemic heart disease, or cerebrovascular disease requiring blood transfusion during surgery and/or receiving vasodilators or medications likely to alter thermoregulation, were excluded from the study.

Patients received no premedication. Heart rate (HR), mean arterial pressure (MAP), oxygen saturation as measured by pulse oximetry (SpO₂), and core temperature (First Temp Genius; Sherwood-Davis, Gasport, UK) were recorded using standard, noninvasive monitors (AS/3; Datex Ohmeda, Bromma, Sweden).

Operating room (OR) temperature was maintained at 21°-22°C. Irrigation and IV fluids were preheated at room temperature and given without inline warming. All patients were covered with one layer of surgical drapes over the chest, thighs, and calves during the operation, and one cotton blanket over the entire body postoperatively. No other warming device was used. Core temperature below 36°C was considered hypothermia. Before performing spinal anesthesia, each patient received 10 mL/kg/hr of lactated Ringer’s solution over 30 minutes. The infusion rate was then reduced to two mL/kg/hr. Subarachnoid anesthesia was instituted at either the L₃-L₄ or L₄-L₅ interspaces. Hyperbaric bupivacaine three mL 0.5% (Marcaine Spinal Heavy 0.5%; AstraZeneca, Istanbul, Turkey) was injected using a 25-G Quincke spinal needle (Tyco Healthcare UK, Ltd., Gasport, UK). Patients were randomized by sealed envelope assignment to receive saline (Group C, n = 30) or MgSO₄ (Group Mg, n = 30). An investigator who was not otherwise involved in the study prepared syringes containing saline or MgSO₄; thus, the study was double-blinded. Just after intrathecal injection, all drugs were infused intravenously. MgSO₄ was diluted to a volume of 60 mL and prepared in coded syringes by an anesthesiologist. Group Mg received an IV bolus of MgSO₄ 80 mg/kg via syringe pump (Perfuser compact; B. Braun, Melsungen, Germany) over a 30-minute period. This action was followed by an infusion of two g/hr during the intraoperative period. Group C received an equal volume of saline. Supplemental oxygen (4 L/min) was delivered via face mask during the operation.

Motor blockade was evaluated by Bromage scale. Sensory block level was assessed by pinprick test. Degree of motor and sensory blockade were assessed intraoperatively and also in the recovery unit.

Shivering was assessed after completion of the subarachnoid drug injection. Shivering was graded using a scale similar to that validated by Crossley and Mahajan [10], where 0 = no shivering, 1 = piloerection or peripheral vasoconstriction but no visible shivering, 2 = muscular...
activity in only one muscle group, 3 = muscular activity in more than one muscle group but not generalized, and 4 = shivering involving the whole body. During the surgery, shivering scores were recorded at 5-minute intervals. If scores were 3 or greater 15 minutes after spinal anesthesia, the treatment was regarded as ineffective and IV pethidine 25 mg was administered.

Side effects such as hypotension, nausea, vomiting, and deep tendon reflexes of the upper extremities were recorded. If HR decreased below 50 bpm, IV atropine 0.5 mg was given. Hypotension was defined as a decrease in MAP of more than 20% from baseline (baseline MAP was calculated from three measurements taken on the ward before surgery). Hypotension was treated with IV boluses of ephedrine 10 mg and additional IV infusion of lactated Ringer’s solution, as needed. The amount of ephedrine given in each group was recorded. If patients developed nausea and vomiting, IV metoclopramide 10 mg was administered.

Postoperatively all patients were monitored, receiving oxygen via facemask, and covered with one layer of drapes and one cotton blanket. Postoperative care unit (PACU) temperature was maintained at 25°C to 26°C with constant humidity. If shivering scores were greater than or equal to 3, IV pethidine 25 mg was administered.

2.1. Statistical analysis

Power analysis was performed using NCSS 2000 and PASS 2000 (NCSS Statistical & Power Analysis Software; NCSS, Kaysville, UT, USA). To provide 80% power to detect such a difference using 2-sided t test, with alpha = 0.05, a sample size of 30 patients per group was needed. SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the statistical data. Student’s t-test or Mann-Whitney U-test was used for comparison of numeric variables depending on the distribution of data. Within-group data were analyzed using repeated-measures analysis of variance followed by Bonferroni’s post-hoc testing. Chi-square test was used for comparison of ratios. Results are medians (ranges), exact numbers, or proportions expressed as a percentage. A $P$-value $< 0.05$ was considered statistically significant.

3. Results

The two groups were similar with regard to regarding age, body weight, height, ASA physical status, duration of

| Table 1 Demographic and intraoperative variables in the two groups |
|----------------|----------------|----------------|----------------|
|                | Group C (n = 30) | Group Mg (n = 30) | $P$-value  |
| Age (yrs)      | 70 (64-71)      | 65 (56-74)      | 0.240        |
| Weight (kg)    | 80 (73-83)      | 80 (65-81)      | 0.480        |
| Height (cm)    | 172 (170-175)   | 170 (165-175)   | 0.612        |
| ASA (I/II)     | 9/21            | 11/19           | 0.584        |
| Anesthesia time (min) | 117.5 (100-150) | 135 (120-154) | 0.224        |
| Surgery time (min) | 86 (64-131)    | 104 (83-131)    | 0.138        |
| Crystalloid infusion (mL) | 1550 (1500-2000) | 1750 (1500-2000) | 0.121        |
| Irrigation (L)  | 44 (20-65)      | 63 (25-72)      | 0.005        |
| Total dose of Mg (g) | —              | 8.6 (6.7-10.1) |             |

Data are medians (ranges).
Group C = control (saline) group, Group Mg = magnesium sulfate group, ASA = ASA physical status.
Bradycardia developed in three Group C patients (Table 3). Nausea. Heart rate and MAP were similar between groups. One Group Mg patient and two patients in Group C had vomiting were not significantly different between the groups. Side effects such as altered deep tendon reflexes, nausea, and vomiting were not significantly different between the groups. Bradycardia developed in three Group C patients (Table 3).

### Table 3: Bradycardia, nausea and vomiting, and sedation frequency of the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Group C (n = 30)</th>
<th>Group Mg (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>3 (% 10)</td>
<td>0 (% 0)</td>
<td>0.076</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2 (% 6.67)</td>
<td>1 (% 3.34)</td>
<td>0.554</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Group C = control (saline) group, Group Mg = magnesium sulfate group.

Table 3 Number of patients with different shivering scores perioperatively

<table>
<thead>
<tr>
<th>Shivering score</th>
<th>Group C (n = 30)</th>
<th>Group Mg (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>28 *</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Group C = control (saline) group, Group Mg = magnesium sulfate group. * P < 0.001, vs. Group C (Chi-square test).

Surgery and anesthesia, and amount of crystalloid received. In Group C, the intraoperative administered irrigation solution was significantly less than in Group Mg (P = 0.005; Table 1).

Hypothermia was observed in all patients (100%) in Group Mg and in 24 Group C patients (80%; P = 0.024). The decrease in core temperature seen in Group Mg was significantly greater than in Group C (P < 0.005; Fig. 1). Two patients (6.7%) in Group Mg and 20 patients (66.7%) in Group C experienced shivering (P = 0.0001). Two Group Mg patients had grade 1 shivering. The shivering scores of patients in both groups are shown in Table 2.

Sedation was not observed in any patient. Frequency of side effects such as altered deep tendon reflexes, nausea, and vomiting were not significantly different between the groups. One Group Mg patient and two patients in Group C had nausea. Heart rate and MAP were similar between groups. Bradycardia developed in three Group C patients (Table 3).

### 4. Discussion

Intravenous MgSO4 infusion effectively prevented shivering related to regional anesthesia in TURP but it also reduced core temperature. The exact mechanism of shivering during regional anesthesia has not been fully established. The possible mechanisms of shivering during spinal anesthesia are cessation of central thermoregulation [11,12] and internal redistribution of body heat lost to the environment [11,13]. Redistribution of core temperature during regional anesthesia is typically restricted to the legs, and therefore core temperature decreases about half as much during regional anesthesia as it does during general anesthesia [1,14].

Vasoconstriction and shivering are inhibited below the level of spinal anesthesia through sympathetic and somatic neural blockade [13]. In contrast to these changes, vasoconstriction and shivering are restricted to the upper body during spinal anesthesia. In regional anesthesia, shivering develops in up to 56.7% of all patients [15], similar to what was observed in the control group of our study (66.7%).

As shivering is a response to hypothermia, body temperature should be normally maintained within limits of 36.5°-37.5°C [16]. A number of factors including age, level of sensory block, and temperatures of the local anesthetic, the OR, and IV solution are risk factors for hypothermia in regional anesthesia [4]. In our study, OR temperature was maintained at 21°-22°C, and all fluids and drugs administered were at room temperature during the surgery. However, it was not always possible to maintain body temperature within normal limits, and shivering may be seen even in normothermic patients undergoing regional anesthesia [17].

Various drugs have been used to treat or prevent postoperative shivering, but the ideal treatment has yet to be determined. Pharmacological therapies such as pethidine, tramadol, physostigmine, clonidine, ketamine, and MgSO4 have been used to prevent shivering [18,19]. Because the incidence of hypotension is high during regional anesthesia, hypotensive agents including clonidine [18] and urapidil [19] may not be appropriate in preventing shivering. In addition, meperidine (the most widely used agent) and tramadol may cause nausea and vomiting and respiratory depression during and after regional anesthesia. The hypertensive and tachycardic effects of ketamine also have been reported [20]. The search continues for drugs that sufficiently improve thermoregulatory tolerance without simultaneously producing excessive sedation or respiratory depression. In practice, this constitutes a search for drugs that reduce the shivering threshold (triggering core temperature) to a value approximating the target therapeutic core temperature [21].

Magnesium (Mg2+) is a naturally occurring calcium antagonist and a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors [22]. The exact protective mechanism of MgSO4 remains uncertain; however, it provides excellent neuroprotection and cardioprotection in various experimental models of ischemia, and it is an effective treatment for postoperative shivering following general anesthesia. Intravenous MgSO4 suppresses postoperative shivering [6], suggesting that this agent reduces the shivering threshold. The drug not only exerts a central effect [23] but is also a mild muscle relaxant [24] and thus may simultaneously reduce the gain of shivering (incremental shivering intensity with progressing hypothermia). MgSO4 causes peripheral vasodilatation, which probably improves the cutaneous circulation, thus decreasing the incidence of shivering [6]. It also confers substantial neurological and cardiac protection in several animal models [25]. Thus, MgSO4 is an especially attractive candidate for inducing thermoregulatory tolerance since it may also protect against...
tissue ischemia. We tested the hypothesis that MgSO₄ reduces the threshold without causing clinically significant sedation or muscle weakness.

Unlike general anesthesia, regional anesthesia alters the afferent conduction of thermal signals as a result of spinal anesthesia; efferent thermoregulatory responses may be terminated as a result of sensory block below the intervention level. The sympathetic blockade that results in peripheral vasodilatation, increased cutaneous blood flow, and subsequent increased heat loss via the skin, may cause heat loss in patients during regional anesthesia [26]. MgSO₄ seems to induce thermoregulation tolerance because it is an effective treatment for postoperative shivering [26,27]. In a study of the effect of MgSO₄ on postoperative analgesic need, Usmani et al. observed no post-anesthetic shivering in patients receiving MgSO₄ [27]. Many postoperative patients have core temperatures only slightly below the normal shivering threshold. Treatments that reduce the shivering threshold by a few tenths of a degree Celsius may be sufficient to attenuate postoperative shivering [28].

It is likely that larger doses of MgSO₄ would produce both greater thermoregulatory effects and a greater risk of complications. Nonetheless, the thermoregulatory response to most IV drugs is a linear function of plasma concentration [29]. Thus, an even larger, potentially hazardous, dose of MgSO₄ seems unlikely to produce a useful reduction in the shivering threshold. A limitation of our study was that we did not assess Mg²⁺ levels.

Magnesium sulfate is associated with a high rate of minor side effects such as feeling warm and flushed; nausea and/or vomiting; muscle weakness; dizziness; and irritation at the injection site. The reported rates of these effects in randomized trials ranged from 15% to 67% [30]. Magnesium sulfate is also associated with major side effects such as respiratory depression [30]. Thus, an even larger, potentially hazardous, dose of MgSO₄ seems unlikely to produce a useful reduction in the shivering threshold. A limitation of our study was that we did not assess Mg²⁺ levels.

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In conclusion, MgSO₄ infusion in the perioperative period significantly reduced shivering associated with spinal anesthesia in TURP in the perioperative period. MgSO₄ infusion is an alternative for preventing shivering in patients during regional anesthesia; however, hypothermia also occurs.

References


