Clinical Research

Intravenous magnesium sulfate *versus* intravenous meperidine to prevent shivering during spinal anesthesia

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ABSTRACT

BACKGROUND Shivering is a frequent event during neuraxial anesthesia due to impaired central and peripheral thermoregulation control. Meperidine and $MgSO_4$ are effective in lowering the shivering threshold. Hence, this study aimed to compare the efficacy of $MgSO_4$ and meperidine to prevent shivering in patients undergoing spinal anesthesia.

METHODS This was a double-blind randomized clinical trial of 100 patients divided into 2 groups. One group had $MgSO_4$ 30 mg/kg, and the other group had meperidine 0.5 mg/kg intravenously in 100 ml of 0.9% NaCl before undergoing spinal anesthesia. Participants were non-pregnant patients aged 18–65 years and had physical status I or II (based on the American Society of Anesthesiologist). Shivering was considered significant if it occurred in grade 3 or 4. Patient characteristics, shivering degree, tympanic membrane temperature, and side effects were recorded.

RESULTS Shivering occurred 10% in the $MgSO_4$ group and 19% in the meperidine group, with $p = 0.23$. Both groups had similar side effects of nausea, vomiting, and hypotension.

CONCLUSIONS $MgSO_4$ 30 mg/kg was not superior to meperidine 0.5 mg/kg intravenously in preventing shivering in patients undergoing spinal anesthesia.

KEYWORDS magnesium sulfate, meperidine, shivering, spinal anesthesia

Shivering is common in neuraxial anesthesia. The incidence of shivering in patients who underwent surgery with regional anesthesia was 40–70%. It is thought to be caused by vasodilatation below the level of neuraxial block and disturbance in the thermoregulation system.[1] It can also disturb electrocardiography, heart rate, blood pressure, and oxygen saturation monitoring because of the sympathetic system activation, which increases oxygen needs, carbon dioxide production, and metabolic rate four times higher. This should be considered, especially in patients with cardiac and lung diseases.[2]

Some drugs can be used to prevent and treat shivering during spinal anesthesia, such as ketamine, meperidine, clonidine, and tramadol. However, these drugs have adverse effects. Clonidine may cause hypotension and bradycardia. Ketamine may cause hypertension and tachycardia. Meperidine and tramadol, with their opioid properties, have side effects such as nausea, vomiting, pruritus, and dizziness.[3] Meanwhile, magnesium sulfate, a calcium competitor and noncompetitive antagonist N-methyl D-aspartate (NMDA) receptor, has been reported to lower the shivering threshold through central effect

and mild muscle relaxation but has side effects of nausea, vomiting, pruritus, and heat at the injection site.[4] Although meperidine has been thought of as a gold standard for the prevention and treatment of shivering due to its direct effect of opioid on the thermoregulatory center,[5] $MgSO_4$ is more cost-effective, easily accessible, and useful for anesthesia.[4]

A study showed a lower incidence of shivering in patients receiving intravenous (IV) $MgSO_4$ 50 mg/kg and followed by a maintenance dose of 0.5 mg/kg/min (28%), compared with patients receiving IV meperidine bolus of 0.5 mg/kg (68%) when undergoing spinal anesthesia for knee arthroscopy.[2] However, a higher dose of $MgSO_4$ would cause vasodilatation and subsequent hypotension.[2] Another study compared lower doses of $MgSO_4$ at 30 mg/kg IV with tramadol 0.5 mg/kg and placebo groups under spinal anesthesia. It was found that shivering was significantly lower in the $MgSO_4$ (39%) and tramadol groups (43.9%), compared with the placebo group (67.9%).[6] No study compared a low dose of $MgSO_4$ 30 mg/kg IV with meperidine 0.5 mg/kg IV. Therefore, this study aimed to compare the effectiveness of such doses of $MgSO_4$ and opioid meperidine to prevent shivering in patients undergoing spinal anesthesia.

METHODS

Study design

This was a double-blinded randomized clinical trial (registered at ClinicalTrials.gov identifier: NCT05110469) conducted in Cipto Mangunkusumo Hospital in February–June 2021. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia–Cipto Mangunkusumo Hospital (No: KET-1510/UN2.F1/ETIK/PPM.00.02/2020).

Subjects

The sample size needed for each group in this study was based on the sample size formula for two proportions. The assumption proportion of shivering in the $MgSO_4$ group was 0.39,[6] and in the meperidine group was 0.68.[2] Based on the calculation, the minimum sample size was 45 for each group plus the risk of dropping out of 10%, then a total of 100 subjects were required for this study.

This study was conducted on 100 patients aged 18–65 years and had physical status I or II (based on the American Society of Anesthesiologist) undergoing spinal anesthesia after receiving informed consent. Patients were excluded if they had a history of allergy to the drugs used in the study, pregnancy, neuromuscular disease, hyperthyroid, severe cardiopulmonary diseases, liver and/or renal disorders, used drugs that interact with $MgSO_4$ such as nifedipine, and preoperative body temperature less than 36°C or more than 37.5°C. Subjects were dropped out if there were any complications such as systemic allergic reaction, anaphylaxis, cardiac arrest, failure of spinal anesthesia, respinal, surgery duration less than 30 min, and conversion to general anesthesia during evaluation.

Interventions and outcomes

Patients who met the eligibility criteria were randomized into two groups using a randomization software at randomizer.org by an anesthesiologist outside the research team. The same anesthesiologist also prepared the drug solution and labeled it as "research drug" without mentioning it. The treatment group was administered 30 mg/kg of $MgSO_4$ intravenously in 100 ml of 0.9% NaCl, while the control group received 0.5 mg/kg of meperidine intravenously in 100 ml of 0.9% NaCl before undergoing spinal anesthesia. The subjects and investigators who administered the drug and made the observation were kept unaware of the drug solution. Drugs were given in 10 min while monitoring the side effects such as hypotension, bradycardia, nausea, vomiting, itch, allergy, drowsiness, and respiratory depression. If hypotension occurred or blood pressure decreased by >20% from baseline, subjects would be treated with a crystalloid solution and ephedrine 5–10 mg IV.

Afterward, subjects were given 10 ml/kg of room temperature crystalloid for 10 min before spinal anesthesia. Pre-spinal and post-spinal tympanic membrane temperature were measured as early tympanic membrane temperature. Spinal anesthesia was performed at the lumbar vertebrae 3–4 or 4–5 interspaces, with 15 mg of hyperbaric bupivacaine and fentanyl 25 mcg. Room temperature was maintained between 19–24°C. Subjects were covered with one layer of a blanket, which covered the chest and upper arm, and other areas outside the operating area. They were given maintenance fluid of 2 ml/kg/hour crystalloid and oxygen supplementation of 2–3 l/min by nasal cannula. They were managed in the state of Ramsay sedation scale 2 (co-operative, oriented, and tranquil) or 3

(appears asleep but responds to verbal command), and some of them needed midazolam IV.

Mean arterial pressure, heart rate, and respiratory rate were closely monitored as the standard monitoring during the procedure, while the incidence of shivering and tympanic membrane temperature were observed every 5 min during the first 15 min and every 15 min within the next 120 min. The degree of shivering was measured with Crossley and Mahajan scale (0 = no shivering; 1 = piloerection or peripheral vasoconstriction; 2 = muscular activity in only one muscle group; 3 = muscular activity in more than one muscle groups but not generalized; 4 = intense shivering involving the whole body, except in the muscle affected by spinal block).[6] Drugs were considered effective if there was no incidence of the 3rd or 4th degree of shivering. Meperidine 25 mg IV was given if the 3rd or 4th degree of shivering occurred. Nausea and vomiting were treated using metoclopramide 10 mg IV. Postoperatively, the subjects were transferred to a recovery room and monitored for any adverse events for an hour until discharged. Hypotension, bradycardia, and respiratory depression were observed using a bedside monitor, while nausea, vomiting, pruritus, allergy, and drowsiness were complained directly by the subjects if available. Any serious adverse events such as anaphylactic or cardiac arrest during monitoring would be managed immediately and reported to the ethics committee.

Statistical analysis

All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., USA). Chi-square test or Fisher's exact test were used to compare the difference in the proportion of shivering between the two groups. For numerical data, T-test and Mann–Whitney test were used. $p<0.05$ was considered statistically significant.

RESULTS

Of 108 eligible patients, 5 were excluded because of having cardiopulmonary disease, 1 refused the procedure, 2 were canceled, and 5 were dropped out because of respinal and converted to general anesthesia. Hence, a total of 95 patients completed this study (Figure 1).

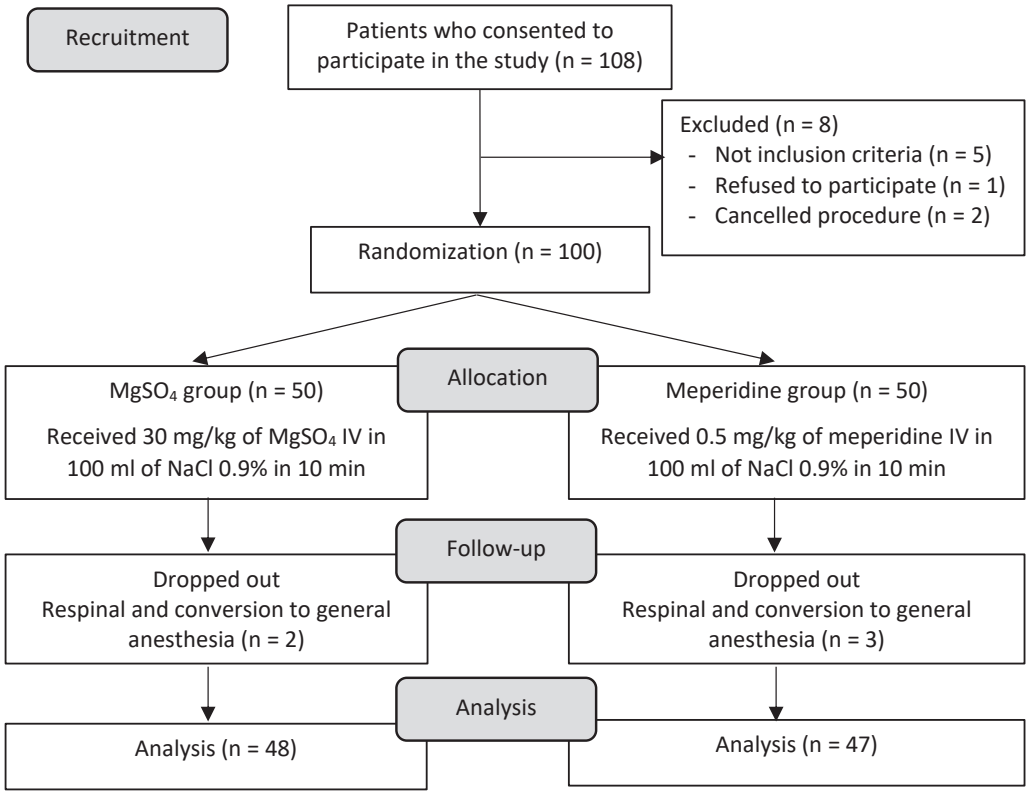

Figure 1. Research flow diagram. IV=intravenous

Table 1. Demographical and baseline characteristics of the subjects

Variables	$MgSO_4$, mean (SD) (N = 48)	Meperidine, mean (SD) (N = 47)
Age (years)	44.69 (12.98)	45.28 (15.82)
Weight (kg)	64.10 (13.53)	61.30 (11.12)
Height (m)	1.59 (0.09)	1.59 (0.08)
BMI (kg/m^2)	25.19 (4.21)	24.08 (3.91)
Block height (segment of thoracal vertebra), median (min–max)	8 (6–10)	8 (4–10)
Pre-anesthesia tympanic membrane temperature (°C)	36.32 (0.24)	36.39 (0.29)
Post-anesthesia tympanic membrane temperature (°C)	36.19 (0.26)	36.24 (0.31)
Operating room temperature (°C)	22.67 (1.56)	22.28 (1.65)
Bleeding (ml), median (min–max)	20 (2–600)	40 (2–700)
Volume of IV fluid given (ml)	928.13 (425.75)	913.21 (381.98)
Duration of fasting (hour)	7.08 (2.93)	7.87 (3.10)
Duration of surgery (min)	113.69 (3.34)	125.53 (72.70)

BMI=body mass index; IV=intravenous; SD=standard deviation

The types of surgery included in this study were lower abdominal, lower extremity, and urological surgeries under spinal anesthesia. Demographic and baseline characteristics of the subjects are shown in Table 1. Subjects' demographic and baseline characteristics were similar between the two groups.

The frequency of shivering is shown in Figure 2. There was no difference in significant shivering between the $MgSO_4$ and meperidine groups. The absolute risk reduction of significant shivering was 8.7% favorable to $MgSO_4$, and 11 subjects needed a treatment.

It is shown in Figure 3 that the early temperature of the tympanic membrane in the $MgSO_4$ group was lower than in the meperidine group, but it was not statistically significant, as shown in Table 1. Shivering started to occur at 10th min in subjects with meperidine and at 30th min in subjects with $MgSO_4$ when the temperature at those minutes was still higher in subjects with meperidine. The shivering occurred at 35.3–35.9°C in the $MgSO_4$ group and 35.7–36°C in the meperidine group.

Adverse reactions found in this study were nausea, vomiting, and hypotension. These were not significant between the two groups (Table 2).

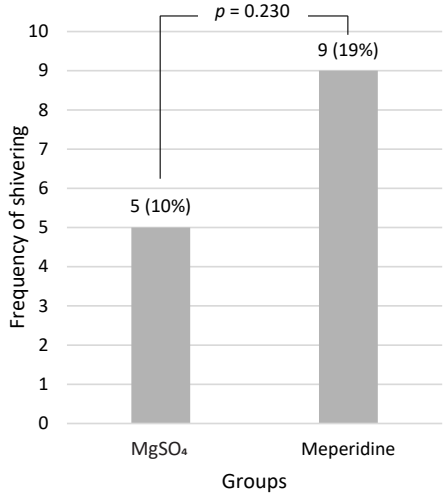

Figure 2. Incidence of significant shivering. Shivering was measured using Crossley and Mahajan scale and was considered significant if the scale was 3 and 4

DISCUSSION

The incidence of shivering in regional anesthesia without prophylaxis use is around 40–70%.[6] This study showed that the overall incidence of shivering was 10% in the $MgSO_4$ group and 19% in the meperidine group, with no statistical difference (Figure 2). Shivering is influenced by many factors, such as age, weight, height, level of the anesthesia block, operating room temperature, amount of IV fluid given, amount of bleeding, duration of fasting, and duration of surgery.[6,7] All of these factors in this study were homogenous in both groups (Table 1). Previous studies also showed that IV fluid temperature could influence the incidence of shivering[8]; hence, we only used IV fluid at room temperature (22–23°C). This indicated that $MgSO_4$ 30 mg/kg was as effective as meperidine 0.5 mg/kg in the prophylaxis of shivering during spinal anesthesia.

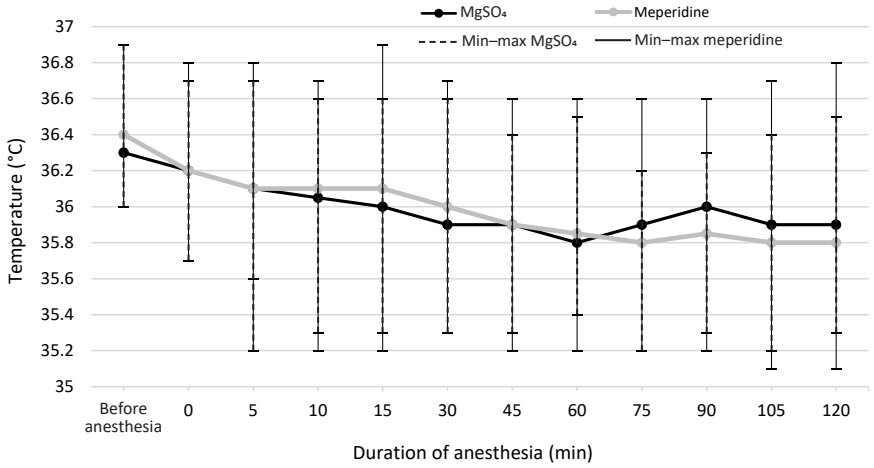

Figure 3. Tympanic membrane temperature in subjects given meperidine and $MgSO_4$. Data were shown as median

Table 2. Incidence of adverse reaction

Adverse reaction	$MgSO_4$, n (%) (N = 48)	Meperidine, n (%) (N = 47)	*p*
Nausea	5 (10)	5 (11)	1.000
Vomiting	2 (4)	1 (2)	1.000
Hypotension	10 (21)	8 (17)	0.635

p<0.05 was considered significant

The incidence of shivering in this study was in line with a study conducted by Elsonbaty et al[2] that showed 28% of patients had shivering when given $MgSO_4$ 50 mg/kg IV bolus over 20 min followed by a 0.5 mg/kg/min infusion, compared with 68% of patients who had shivering when given meperidine 0.5 mg/kg during spinal anesthesia. This difference might be due to a higher dose of $MgSO_4$ in that study that was associated with peripheral vasodilation due to increased synthesis of prostacyclin and nitric oxide which can lead to hypotension.[9] Another study that compared IV $MgSO_4$ 30 mg/kg with placebo found a significant decrease in shivering with $MgSO_4$ (39% *versus* 67.5%).[6]

Those studies might be due to different population and timing of the drug administration. The drugs in previous studies were given after spinal anesthesia, while the prophylaxis drugs in this study were given about 10 min before spinal anesthesia to achieve the onset of $MgSO_4$ in about 10 min and meperidine in about 5–10 min.[10,11] Shivering in spinal anesthesia may appear within minutes after local anesthetic injection and long before sufficient time has elapsed for a significant heat loss to occur.[3] The higher incidence of shivering in previous studies may happen because the patient might have shivered after spinal anesthesia but before the drug ran out or reached onset after being administered within 10 min. Hence, we suggest to administer $MgSO_4$ or meperidine before spinal anesthesia.

Shivering might happen as a response to hypothermia but also occur in normothermic patients.[1] There are three mechanisms of hypothermia and loss of thermoregulation control that eventually cause shivering in neuraxial anesthesia. The first phase is the redistribution of body heat to the peripheral area. The second phase is the inhibition of the thermoregulation center. The third phase is an autonomic disturbance, followed by vasodilatation and loss of heat.[12] Antishivering mechanism of $MgSO_4$ is by blocking NMDA receptors at the thermoregulation center, such as the hypothalamus and spinal cord which interfere with thermoregulation, and also by blocking the calcium receptor which in turn reduces the release of acetylcholine at the presynaptic nerve endings, causing muscle relaxation.[2,4] Meanwhile, the antishivering effect of meperidine is caused by its property as opioid agonist of μ- and *k*-receptors that modulate the thermoregulatory center.[2] Even so, both antishivering drugs did not prevent the drop in body temperature or hypothermia. Tympanic membrane temperature monitoring in this study showed a drop in temperature during the first 60 min in the $MgSO_4$ group and 75 min in the meperidine group after spinal anesthesia (Figure 3). This is in accordance with a previous study that

found a significant body temperature drop in 40–60 min after spinal anesthesia.[13]

Figure 3 shows lower temperature in the $MgSO_4$ group than in the meperidine group in the first hour. This is caused by the vasodilatation property from $MgSO_4$, which causes a faster drop in temperature, but still has an antishivering effect.[14] Meanwhile, meperidine has a lower vasoconstriction threshold than its antishivering effect, which causes a slower temperature drop.[15] The incidences of shivering in this study occurred at 35.3–35.9°C in the $MgSO_4$ group and 35.7–36°C in the meperidine group, indicating that $MgSO_4$ has a lower shivering threshold than meperidine. Previous studies have shown that $MgSO_4$ and meperidine could lower the shivering threshold, but no study compared the threshold decrease on both drugs. $MgSO_4$ loading dose of 80 mg/kg with a maintenance dose of 2 g/hour could lower the shivering threshold by 0.3°C.[16] Meanwhile, meperidine with a plasma target of 0.6 µg/ml could lower the shivering threshold by 0.4°C.[15] Although $MgSO_4$ is better for patient comfort because it reduces the incidence of shivering, the lower shivering threshold in $MgSO_4$ can increase the risk of hypothermia. The higher shivering threshold in meperidine can detect hypothermia earlier than $MgSO_4$, although the risk of shivering is also higher.

Adverse reactions found in both groups were similar. Hypotension in the $MgSO_4$ group might be caused by its vasodilatation effect. Elsonbaty et al[2] compared $MgSO_4$ (50 mg/kg followed by 0.5 mg/kg/min) with meperidine (0.5 mg/kg) and found some adverse reactions such as hypotension, pruritus, and local allergy. However, their study also did not show a significant difference between the incidence of hypotension and pruritus but a significantly higher incidence of local allergy in the meperidine group.[2] Other adverse reactions of $MgSO_4$ include dizziness and bradycardia.[3] Severe adverse reactions of meperidine such as respiratory depression and anaphylaxis are also anticipated.[1,2,6] However, none of them occurred in this study.

Shivering prophylaxis may be considered for patients who have any experiences and complaints of discomfort due to shivering during previous spinal anesthesia. Administration of these drugs can increase the comfort of patients undergoing surgery, especially if given before spinal anesthesia. Our study showed that $MgSO_4$ could be used as an alternative prophylactic for shivering because it is an efficacious, easily available, and cost-effective drug. The use of this prophylaxis also needs caution that the decreased shivering due to the administration of $MgSO_4$ or meperidine could decrease the body heat formation, so patients were more prone to hypothermia.

This study also had limitations. First, most patients often experienced anxiety or restlessness during surgical procedures under regional anesthesia, so sedation was necessary for some patients to achieve the state of Ramsay sedation scale 2 or 3. It is known that sedative drugs have properties that might reduce the shivering threshold at different levels.[17] Second, this study did not exclude patients who underwent procedures using irrigation fluid, such as transurethral resection, and we did not have data on the irrigation fluid temperature. Different temperatures (room temperature or warm) of irrigation fluid influenced body temperature and incidence of shivering.[18,19]

In conclusion, $MgSO_4$ IV with a dose of 30 mg/kg can prevent shivering and is considered safe, similar to meperidine IV with a dose of 0.5 mg/kg. Further research needs to control other biases that might affect the shivering incidence, such as administration of sedation drugs (e.g., midazolam) or procedures with irrigation fluid.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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