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Research Article

Prophylactic vs. therapeutic magnesium sulfate for shivering during spinal anesthesia

Ibrahim T. Ibrahim, Soheir A. Megalla, Omyma Sh.M. Khalifa *, Hala M. salah El Deen

Department of Anesthesia, Faculty of Medicine, El-Minia University, Egypt

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KEYWORDS

Prophylactic;
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Abstract *Introduction:* Shivering is one of the most common complications of neuraxial blockade. Some patients find shivering sensation worse than surgical pain. Therefore, both prevention and treatment of established shivering should be regarded as clinically relevant intervention in the perioperative period. The aim of our study is to compare the efficacy of magnesium sulfate when used for prevention or treatment of shivering following spinal anesthesia.

Methods: In this prospective, double blind, placebo controlled study, 120 ASA I, II patients undergoing surgery under spinal anesthesia were randomized into 3 groups. Following intrathecal injection, Group P (prophylactic) was given $MgSO_4$, 50 mg/kg I.V. bolus + 2 mg/kg/h infusion. Group T (therapeutic) was given $MgSO_4$ 50 mg/kg I.V. bolus as a therapy when shivering occurred. If shivering persisted, they received 25 mg/kg I.V. bolus. Group C (control) received saline at identical times. Meperidine was given as rescue if shivering persisted. Shivering grade 3/4 was regarded as significant. Core temperatures, incidence of shivering, and side effects were recorded.

Main results: Total incidence of shivering, grade 3/4, was 15% in Group P, 45% in Group T, and 50% in Group C ($p < 0.01$). Magnesium sulfate significantly reduced the incidence and gain of shivering. The use of rescue meperidine was more in Group P (20%) and Group C (50%) compared to none in Group T ($p < 0.05$, $p < 0.01$, respectively). Significant reduction in core temperature occurred in the Mg groups compared to the control group $p < 0.05$. No correlation was found between patients who shivered and core temperature or ΔT. Hypotension was more frequent in Group P; nausea and vomiting were more in Mg groups than control group $p < 0.05$.

* Corresponding author. Tel.: +01061762894.
E-mail address: omyma.shehata44@yahoo.com (O.Sh.M. Khalifa).
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Conclusion: Following spinal anesthesia, prophylactic $MgSO_4$ infusion lowered incidence of shivering. When shivering did occur, $MgSO_4$ proved to be an effective treatment with minimal side effects.

1. Introduction

Shivering is a frequent complication following neuraxial anesthesia. It is an involuntary, oscillatory muscular activity that augments metabolic heat production. Shivering may occur as a response to hypothermia. However, it may also occur in normothermic patients [1].

Regional anesthesia impairs both central and peripheral thermoregulatory control. In patients becoming sufficiently hypothermic, shivering may appear and is often disturbing to both patients and medical staff [2]. Shivering may interfere with monitoring of heart rate, blood pressure, and oxygen saturation. It is associated with substantial adrenergic activation [3]. It increases oxygen consumption, lactic acidosis, carbon dioxide production, and metabolic rate by up to 400%; thus, it may cause problems in patients with low cardiac and pulmonary reserves [1].

Numerous studies have tested the efficacy of a large variety of interventions to prevent shivering in normothermic or hypothermic surgical patients, but the relative efficacy of these interventions, however, remains unclear [4].

As the incidence of hypotension is high during regional anesthesia, hypotensive agents including clonidine and urapidil 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 tachycardiac effects of ketamine limits its use [5].

The search continues for drugs that sufficiently improve thermoregulatory tolerance without simultaneously producing excessive sedation or respiratory depression.

Intravenous magnesium has been shown to suppress postoperative shivering suggesting that the agent reduces the shivering threshold [6]. Recently, the addition of intravenous magnesium sulfate to a pharmacological antishivering regimen increased the cooling rate in unanesthetized volunteers [7]. The drug not only exerts a central effect [8] but is also a mild muscle relaxant [9] and may thus simultaneously reduce the gain of shivering (incremental shivering intensity with progressing hypothermia) [10].

This study was designed to compare the effectiveness of magnesium sulfate when given prophylactically to that given as treatment in the control of shivering.

2. Patients and methods

This randomized, double blind, placebo controlled study was carried out at the anesthesiology department in El-Minia University Hospital. We included 120 male and female patients, 18–60 years of age scheduled to undergo elective lower extraperitoneal abdominal or lower limb surgery using spinal anesthesia. Patients with ASA physical status > II, severe cardiopulmonary disease, renal or liver impairment, preoperative fever, history of seizures or peripheral neurological disease, contraindication to regional anesthesia, thyroid disease, parkinsonism, Raynaud's syndrome, allergy to the study medications, massive blood transfusion during surgery and those receiving vasodilators or medications that alter thermoregulation were excluded from the study.

The study was double blind (neither the investigator nor the patients knew the nature of the drugs given), and the unknown solutions were prepared and supplied to the investigator in 25 ml ampoules and coded as (A, B, C and D) for IV injection and infusion. The protocol was opened after the study was completed.

Randomization was done according to computer generated number.

The study drugs were administered as follows:

- 0.5 ml / kg was taken from ampoule A, diluted in 60 ml glucose 5% and injected IV over 10 min immediately after spinal injection.
- This is followed by 2 ml taken from ampoule B, diluted in 200 ml and given IV at a rate of 2 ml/kg/h.
- If shivering occurs, 0.5 ml/kg was taken from ampoule C, diluted in 60 ml glucose 5%, and injected IV over 10 min.
- If shivering continues, 0.25 ml/kg was taken from ampoule D, diluted to 60 ml glucose 5%, and injected IV over 10 min.
- If shivering persists, meperidine 25 mg was injected IV.

Drugs used in the study were the following: magnesium sulfate ampoule 25 ml 10%, 100 mg/ ml (Egypt Otsuka pharm. Co.); saline 0.9% ampoule 25 ml (Egypt Otsuka pharm. Co.); and meperidine (Pethidine) 50 mg/ml.

The patients admitted were blindly injected and classified into 3 equal groups (40 patients each), group P (Prophylactic group), received $MgSO_4$ 50 mg/kg IV bolus + 2 mg/kg/h infusion as prophylaxis (A and B ampoules were $MgSO_4$ and C and D ampoules were saline), Group T (Therapeutic group): received $MgSO_4$ 50 mg/kg IV bolus as therapy when shivering occurred, and if shivering persists, they received 25 mg/kg IV bolus of $MgSO_4$ (A and B ampoules were saline; C and D ampoules were $MgSO_4$) and group C (Control group) received 0.9% saline for injection as a placebo (A, B, C, and D ampoules were saline). In all groups if shivering of grade 3 or more persists, meperidine 25 mg IV was given as a rescue drug.

No premedication was given. In the operating room, after IV access, all patients received 500 cc lactated Ringer's solution maintained at room temperature. The ambient temperature was maintained at 22–24 °C.

Spinal anesthesia was performed at either L3/4 or L4/5 interspaces. Hyperbaric bupivacaine, 20 mg was injected using a 24 gauge spinal needle with the patients in the lateral decubitus position. Level of sensory blockade was assessed by pinprick and motor blockade by Bromage scale [11].

Supplemental oxygen was delivered via a nasal cannula (4 L/min) if needed. Intraoperatively, all patients were monitored and covered by one layer of surgical drapes.

HR, MAP, SpO2, respiratory rate (cycle/min), and temperature were measured by Advisor monitors (Smith Medical PM, Inc., Waukesha, WL, 53186). These parameters were recorded preoperative, after induction of anesthesia, every 10 min till the end of surgery, then every 10 min postoperative until 2 segments regression of the sensory blockade.

Tympanic (core) temperature was measured by an ear thermometer. The aural probe was inserted until the patient felt it touching the tympanic membrane, the probe was then securely taped in place, and the aural canal was occluded with cotton and a gauze bandage was positioned over the external ear. Axillary (skin) temperature was measured by an axillary thermometer. Temperature difference was measured (ΔT = core temperature – skin temperature). Core temperature less than 36 °C was considered hypothermia.

Shivering was assessed after completion of subarachnoid injection until the patient was discharged after 2 segments regression of sensory blockade by a scale similar to that validated by Crossley and Mahajan [12] which is 0 = No shivering, 1 = Cyanosis and piloerection, 2 = Visible tremors only in one muscle group, 3 = Visible tremors in more than one muscle group, and 4 = Intense shivering, tremors of the head, arm. Side effects like hypotension, nausea and vomiting, respiratory depression, and diminished deep tendon reflexes in upper extremities were recorded. Hypotension was treated by crystalloid infusion and if necessary IV ephedrine 5 mg. Nausea and vomiting was treated by IV metoclopramide 10 mg. Postoperatively, all patients were transferred to postoperative care unit (PACU) and monitored every 10 min until discharge.

2.1. Statistical analysis

Data were analyzed by using SPSS (The Statistical Package for Social Sciences) version 17.0 software. Categorical data including total incidence of shivering and side effects were analyzed using Chi square. Independent *t*-test was used for quantitative data for comparison between two groups; paired *t*-test, for quantitative data within each group; one-way ANOVA, for quantitative data comparison between the 3 groups; Fisher's exact test, for categorical data between the study groups; Mann Whitney test, for quantitative nonparametric data between two groups; Kruskal–Wallis *H*-test, for quantitative nonparametric data between three groups; and Spearman correlation for correlation testing.

P-value $\leqslant 0.05$ was considered significant.

3. Results

A total of 120 patients completed this study, 40 in each group. The three groups were similar as regards age, weight, height, and ASA physical status (Table 1). They were also comparable in duration of anesthesia, surgery, and amount of crystalloid administered. Total dose of magnesium sulfate was significantly higher in Group P (3863 ± 544 mg) vs. (2425 ± 1941.8 mg) in Group T ($p < 0.05$) (Table 2).

There was insignificant change as regards mean heart rate, mean arterial blood pressure, oxygen saturation, and mean respiratory rate in the three groups throughout the study period.

Hypothermia occurred in $MgSO_4$ groups with respect to baseline temperature. Hypothermia began earlier in group P, 10 min after induction of spinal anesthesia compared to group T, after 20 min. Degree of hypothermia was greater in Group P than Group T. Also, reduction in tympanic membrane temperature was significantly greater in the Mg groups compared to the control group ($P < 0.01$). After receiving spinal anesthesia until 80 min, the core temperature was significantly lower in Group P than Group C ($p < 0.01$), from 20 to 60 min the core temperature was significantly lower in Group T than Group C ($p < 0.05$) (Fig. 1). There was no correlation between patients who shivered and core temperature (Table 3 and Fig. 3) or ΔT (ΔT = core – skin temperature) (Table 4).

Total incidence of shivering grade 3/4 was 15% in Group P, 45% in Group T, and 50% in Group C. Shivering was considered significant when the patient shivered at least to grade 3 [12]. Ten min after induction of spinal anesthesia, corresponding to the end of the bolus dose of $MgSO_4$ in Group P, only 5% had shivering grade 3/4 compared to 25% in Group T and 35% in Group C. Up to 40 min, there was significant difference in incidence of shivering between the 3 groups, being more in Groups T and C than Group P (Fig. 2). In the therapeutic group, a single dose of $MgSO_4$ was effective in controlling shivering as only 4 patients (20%) of the 18 patients who shivered required a second dose of Mg. Prophylactic $MgSO_4$ was effective in reducing the incidence of shivering, but when shivering occurred, therapeutic Mg was more effective in the control of shivering as evidenced by the use of rescue meperidine which was more in Group P (20%) and Group C (50%) compared to none in Group T ($p < 0.05$, $p < 0.01$,

Table 1 Demographic data and type of operation in the study groups.

Data	Group		
	Prophylactic $n = 40$	Therapeutic $n = 40$	Control $n = 40$
Age (yrs)	30.9 ± 11	31.6 ± 11.4	30 ± 10.4
Weight (kg)	73 ± 10.1	70.5 ± 12.7	73 ± 9.2
Sex males: *n* (%)	38 (95%)	32 (80%)	34 (85%)
Females: *n* (%)	2 (5%)	8 (20%)	6 (15%)
Type of operation			
General surgery: *n* (%)	16 (40%)	12 (30%)	12 (30%)
Orthopedic: *n* (%)	18 (45%)	20 (50%)	22 (55%)
Urologic: *n* (%)	6 (15%)	8 (20%)	6 (15%)

Data are presented as Mean ± SD. *n* = number.

Table 2 Operative data.

Data	Group		
	Prophylactic $n = 40$	Therapeutic $n = 40$	Control $n = 40$
Anesthetic duration (min)	85.5 ± 17	81.5 ± 14.6	86 ± 18.2
Surgical duration (min)	61 ± 16	59.3 ± 13.9	62.75 ± 18.3
Crystalloid fluids (cc)	1550 ± 426.1	1325 ± 372.6	1553 ± 535.6
Drug administration			
None: *n* (%)	26 (70%)	34 (85%)	34 (85%)
Atropine: *n* (%)	0 (0%)	0 (0%)	2 (5%)
Ephedrine: *n* (%)	6 (15%)	0 (0%)	2 (5%)
Metoclopramide: *n* (%)	8 (20%)	6 (15%)	2 (5%)
Meperidine use: *n* (%)	8 (20%)*	0 (0%)	20 (50%) **
Total dose Mg (mg)	3863 ± 544*	2425 ± 1941.8	0

Data are presented as Mean ± SD, *n* = number.
* $p < 0.05$ Group P vs. Group T.
** $p < 0.01$ Group C vs. Group T.

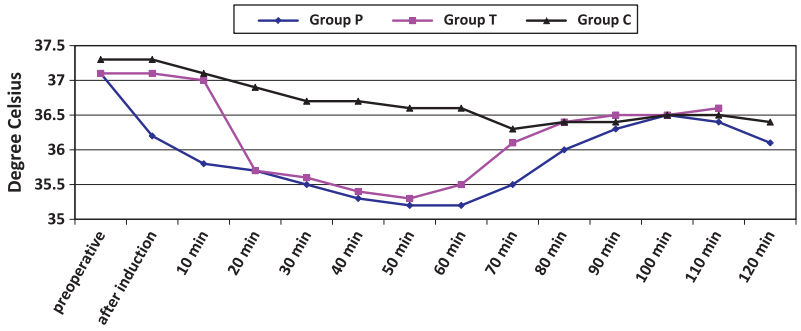

Figure 1 Changes in mean core temperature in the three groups.

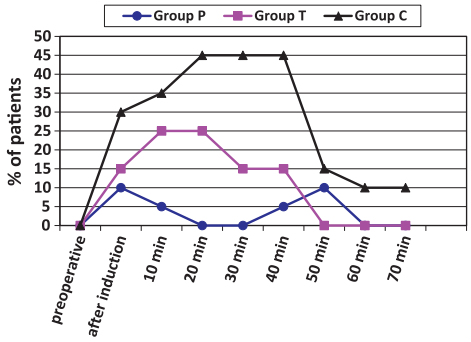

Figure 2 Changes in incidence of shivering grade 3/4 over time.

respectively). Hypotension occurred in 6(15%) in Group P and 2(5%) in Group C and none in Group T. Nausea and vomiting occurred in 8(20%) in Group P, 6(15%) in Group T, and 2(5%) in Group C (Table 5).

4. Discussion

Postanesthesia shivering is very common following neuroaxial anesthesia. In our study, shivering was reported in 45–50% of patients in the control and therapeutic groups similar to 57% incidence reported in earlier studies [13].

The exact mechanism of shivering during regional anesthesia has not been fully established. Postanesthesia shivering is probably a combination of both thermoregulatory and non-thermoregulatory shivering [1]. Thermoregulatory shivering is a response to hypothermia due to redistribution of body heat from the core to the periphery [14]. The resultant vasoconstriction and shivering are restricted to the upper body due to the sympathetic and somatic neural blockade below the level of spinal blockade [15].

In our study, we found that postspinal shivering may appear within minutes after injection of local anesthetic and long before sufficient time has elapsed for significant heat loss to have occurred; therefore, other mechanisms of shivering exist. The same finding led Bromage [11] to postulate that spinal cord response is secondary to misinterpretation of afferent thermal clues due to differential blockade of warm and cold sensation, which is also supported by Kaoy et al. [16].

Also, shivering has been reported in normothermic patients, suggesting that inhibited spinal reflexes, apprehension, decreased sympathetic activity, pyrogen release, adrenal gland suppression, and respiratory alkalosis are also involved [17].

A wide variety of agents with different mechanisms of action including opioids, nonopioid analgesics, 5-HT3 antagonists, α_2 adrenoreceptor agonists, and cholinomimetic agents have been studied in an attempt to prevent or treat shivering, but unfortunately, there is no "gold-standard" drug for the

Table 3 Correlation between incidence of shivering and core temperature.

Period	Group											
	Group P				Group T				Group C			
	Shiv grade 3/4 (%)	Core temp M ± SD	*r*	*P*	Shiv grade 3/4 (%)	Core temp M ± SD	*r*	*p*	Shiv grade 3/4 (%)	Core temp M ± SD	*r*	*p*
After induction	10	36.2 ± 0.3	−0.53	0.17	15	37.1 ± 0.5	−0.19	0.41	30	37.3 ± 0.4	−0.18	0.46
After 10 min	5	35.8 ± 0.3	−0.36	0.13	25	37 ± 0.4	−0.24	0.29	35	37.1 ± 0.4	−0.12	0.61
After 20 min	0	35.7 ± 0.4	−0.29	0.21	25	35.7 ± 0.4	−0.3	0.2	45	36.9 ± 0.4	−0.19	0.43
After 30 min	0	35.5 ± 0.3	−0.22	0.35	15	35.6 ± 0.4	−0.38	0.1	45	36.7 ± 0.4	−0.17	0.46
After 40 min	5	35.3 ± 0.3	−0.19	0.41	15	35.4 ± 0.35	−0.1	0.69	45	36.7 ± 0.5	−0.13	0.58
After 50 min	10	35.2 ± 0.4	−0.13	0.26	0	35.3 ± 0.37	−0.01	0.99	15	36.6 ± 0.4	−0.16	0.77
After 60 min	0	35.2 ± 0.3	−0.54	0.08	0	35.5 ± 0.3	−0.02	0.94	10	36.6 ± 0.3	−0.16	0.62
After 70 min	0	35.5 ± 0.5	−0.43	0.34	0	36.1 ± 0.4	−0.01	0.99	10	36.3 ± 0.3	−0.13	0.72

Spearman correlation, for nonparametric quantitative data. Shiv (%): Incidence of shivering by percentage. Core temp: Core temperature. M ± SD: mean ± standard deviation. *r*: Correlation coefficient. *p*: *p*-value.

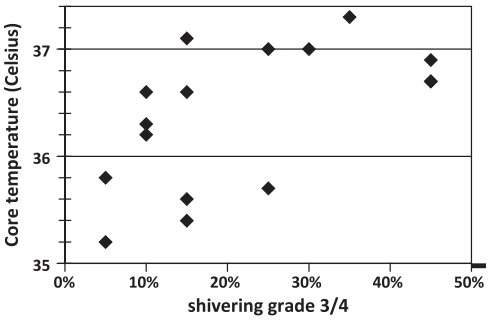

Figure 3 Correlation between core temperature and shivering.

treatment of postoperative shivering. The search continues for drugs that sufficiently reduce the shivering threshold and improve thermoregulatory tolerance without simultaneously producing excessive sedation or respiratory depression [4].

Magnesium is a naturally occurring calcium competitor and a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors [18]. The exact protective mechanism of $MgSO_4$ remains uncertain; Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the release of acetylcholine at the motor nerve terminals [19]. Parenteral magnesium sulfate is the drug of choice for the prevention and treatment of eclamptic convulsions [20]. It is an effective treatment for postoperative shivering following general anesthesia [6]. Magnesium has been reported to reduce shivering threshold in healthy volunteers [21], as treatments that reduce the shivering threshold by a few tenths of a degree Celsius may be sufficient to attenuate postoperative shivering [22]. In our study, core hypothermia occurred in all Mg groups being more evident in the prophylactic group than the therapeutic group. It is likely that larger doses of $MgSO_4$ would produce greater thermoregulatory effects but carries a greater risk of complications as the thermoregulatory response to most IV drugs is linear with plasma concentration [23].

Patients receiving prophylactic magnesium in our study had a lower incidence of shivering than the other groups. This is due to its mild muscle relaxant effect, thereby reducing the gain of shivering (incremental shivering intensity with progressing hypothermia). Magnesium has been suggested as a possible means of resolving muscle rigidity and spasm in tetanus [24].

An earlier study by Gozedemir et al., achieved a lower incidence of shivering 6.7% compared to 15% in our study. This is probably due to the higher dose of magnesium in their study 8.6 g (80 mg/kg bolus then 2 g/h) compared to 3.9 ± 0.54 g

Table 4 Correlation between ΔT measurements and incidence of shivering.

Period	Group											
	Group P				Group T				Group C			
	Shiv (%)	ΔT M ± SD	*r*	*p*	Shiv (%)	ΔT M ± SD	*r*	*p*	Shiv (%)	ΔT M ± SD	*r*	*p*
After induction	10	0.67 ± 0.24	−0.03	0.9	15	0.76 ± 0.24	−0.06	0.93	30	0.78 ± 0.22	−0.09	0.73
After 10 min	5	0.62 ± 0.2	−0.11	0.66	25	0.75 ± 0.27	−0.26	0.27	35	0.77 ± 0.28	−0.12	0.68
After 20 min	0	0.59 ± 0.2	−0.27	0.25	25	0.6 ± 0.2	−0.3	0.2	45	0.74 ± 0.22	−0.2	0.41
After 30 min	0	0.55 ± 0.24	−0.31	0.19	15	0.58 ± 0.2	−0.24	0.32	45	0.73 ± 0.24	−0.22	0.34
After 40 min	5	0.51 ± 0.27	−0.27	0.25	15	0.55 ± 0.2	−0.12	0.68	45	0.72 ± 0.24	−0.25	0.3
After 50 min	10	0.51 ± 0.16	−0.31	0.19	0	0.54 ± 0.1	−0.01	0.99	15	0.7 ± 0.23	−0.26	0.28
After 60 min	0	0.52 ± 0.2	−0.14	0.58	0	0.57 ± 0.1	−0.02	0.94	10	0.68 ± 0.2	−0.18	0.61
After 70 min	0	0.53 ± 0.18	−0.08	0.87	0	0.61 ± 0.1	−0.01	0.99	10	0.64 ± 0.2	−0.14	0.72

Spearman correlation, for nonparametric quantitative data. Shiv (%): Incidence of shivering grade 3/4. ΔT: Temperature difference. *r*: Correlation coefficient. M ± SD: mean ± standard deviation. *p*: *p*-value.

Table 5 Complications during the study period.

Side effects	Group					
	Prophylactic (P) $n = 40$	Therapeutic (T) $n = 40$	Control (C) $n = 40$	p Value		
	n (%)	n (%)	n (%)	P vs. T	P vs. C	T vs. C
Absent	26 (65%)	34 (85%)	34 (85%)	0.2	0.2	1
Bradycardia	0 (0%)	0 (0%)	2 (5%)	–	0.3	0.3
Hypotension	6 (15%)	0 (0%)	2 (5%)	0.2	0.6	0.3
Nausea and vomiting	8 (20%)	6 (15%)	2 (5%)	0.9	0.3	0.6

n = number. No significant difference between the 3 groups.

in our study [25]. Kizilirmak et al., used 30 mg/kg bolus as the treatment for postoperative shivering following general anesthesia and found that it was as effective as meperidine but meperidine stopped shivering slightly faster than magnesium [6].

We found no correlation between incidence of shivering and core temperature, and this finding is supported by the review of fifteen trials by Kranke et al., who found no relationship between shivering and average core temperature [4].

Minor side effects as hypotension, nausea, and vomiting were more frequent in the prophylactic group but not statistically significant. Cumulative data from 8 studies showed nausea, arterial hypotension, and bradycardia occurred more often with magnesium. None of the differences, however, was statistically significant [26]. Hypotension is due to the vasodilating effect of $MgSO_4$. This property was used by Ryu et al., to induce controlled hypotension in middle ear surgery [27] and also reduce blood loss during endoscopic sinus surgery [28].

From our study, we can conclude that following spinal anesthesia, prophylactic $MgSO_4$ infusion lowered incidence of shivering. It also proved to be an effective treatment when postspinal shivering occurred with minimal side effects.

Conflict of interest

No conflict of interest.

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