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A systematic review on considering the role of magnesium in preventing post-anesthesia shivering

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ABSTRACT

Shivering following anesthesia is caused by disturbed regulation of body temperature and causes an increase in tissue oxygen consumption and cardio-pulmonary activity. Choosing the right medicine to reduce shivering with the most negligible side effects in surgery is essential. Magnesium is prescribed intravenously, epidurally, or intra-peritoneally. Each of these methods can have different effects in different surgical operations. In this review, we are looking for randomized clinical trials that compared preoperative magnesium administration with a control group and included studies that evaluated the degree of shivering as a primary outcome variable. This study aimed to evaluate pre-operative magnesium's effect in preventing shivering after surgery. This article was a systematic review type, in which all quality articles published until the end of 2021 were searched with the keywords magnesium, shivering, surgery, and prevention via different databases, including PubMed, Cochrane Central Register of Tested Controlled, EMBASE and Web of Science. In the initial search, 3294 publications were identified. 64 articles were included in this study. The results indicated that shivering in the magnesium group with IV epidural injection inside the peritoneum was significantly reduced compared to the control group. It was also identified in the examination of symptoms. Variants such as extubation time, length of stay in PACU, magnesium serum concentration, spinal c-*fos* mRNA expression, nausea or vomiting, sedation, itching, pressure drop, and bradycardia were significantly less reported than the control group. In general, the results showed that the preventive use of magnesium could decrease the intensity and number of post-anesthesia shivering and other post-anesthesia symptoms.

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Introduction

Shivering is a common complication in the postoperative period. This complication can increase the body's oxygen demand and induce myocardial ischemia. Despite careful efforts to prevent hypothermia, many patients suffer from shivering after surgery. Young age, endoprosthetic surgery, low body temperature, and longer duration of surgery have been considered risk factors for postoperative shivering in previous studies (1). A drug intervention can reduce the incidence of shivering. It has been proven that drugs such as dexmedetomidine, 5-hydroxytryptamine receptor antagonists, and meperidine have anti-shivering effects, but their cost is very high, and their safety is questioned. Magnesium may reduce the need for anesthetics, neuromuscular relaxants, and opioids during surgery. In a previous meta-analysis, five combined data from 3 studies showed that magnesium reduces the degree of shivering (2). The results of other meta-analyses are contradictory. It may be because meta-analyses have included only a few studies that evaluated primary outcomes. In many studies, shivering has been evaluated as one of the secondary outcomes. However, its side effects have not been evaluated. The quality of evidence in this data has not been evaluated. Therefore, it is still unclear how effectively preoperative magnesium prevents postoperative shivering (3, 4).

In addition, magnesium is prescribed intravenously, epidurally, or intraperitoneally. Each of these methods can have different effects in different surgeries (5). In this review, we are looking for randomized clinical trials that compared preoperative magnesium administration with a control group and included studies that evaluated the degree of shivering as a primary outcome variable. This study's main goal was to assess preoperative magnesium's effect in preventing shivering after surgery.

Materials and Methods

This study is a systematic review with sequential analysis of randomized controlled trial studies. Based on the statement of Meta-Analyzes13 and the Cochrane guidebook, we followed this study based on PubMed, Cochrane Central Register of Tested, Web of Science and Controlled, and EMBASE databases until the end of 2021 without a time limit. Two of the authors independently reviewed the titles and abstracts of the articles. The irrelevant articles were deleted, and those articles included in this study that was eligible for the agreement of the two authors. The papers that met the inclusion criteria were evaluated separately by two authors. We looked for randomized clinical trials that assessed the degree of shivering after magnesium administration compared with placebo or no medi-

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cation in patients expected to have to shiver after surgery.

We excluded studies in which patients underwent cardiopulmonary bypass surgery. We excluded studies that did not report shivering or compared oral magnesium with a placebo. We also removed data from case reports, observational studies, and letters to the editor, reviews, and animal studies.

The immediate result was shivering after the operation or during the process. We only assessed postoperative shivering for patients who underwent general anesthesia because intraoperative nerve-blocking agents or other drugs can mask intraoperative shivering. We estimated total shivering during the surgical and postoperative periods for patients who were not placed under general anesthesia. Suppose the number of patients with tremors is recorded several times, and the total amount of tremors is not reported. In that case, we consider tremors for the first time after surgery as tremors. If shivering was written intraoperatively at different time points, we used the last time point during surgery. We did not limit the observation time of shivering because shivering in the entire postoperative period is a significant result. It is also unpleasant for patients and can cause cardiopulmonary problems. Secondary outcomes included:

- Serum magnesium concentration before and after surgery.
- Intubation time after surgery.
- Length of stay in the post-anesthesia care unit (PACU).
- Length of stay in the hospital.
- Side effects.

Data collection

The data includes the number of patients in the study, age, physical condition based on the criteria of the American Society of Anesthesiology, type of anesthesia, anesthetic drugs used, type of surgery, route of magnesium administration, magnesium dose, continuous magnesium dose, time of magnesium kiss, time of urination. Continuous injection, number of cases with chills, serum magnesium concentration, time to remove the chip tube, length of stay in PACU, length of hospitalization, and side effects. Using the available form, the authors independently extracted the data from the studies and reviewed the data. When the prevalence of shivering was not general in a study, even if it was recorded, we tried to contact the corresponding author. Heterogeneity was investigated with the I2 statistic. An I2 value of 30-60 indicates moderate heterogeneity, while a value greater than 60 indicates significant heterogeneity.

Results

In the initial search, 3294 articles were identified. Sixty-four clinical trials were included in this study. Since we could not get the full text of some articles, we tried to contact the magazine offices. However, the full text of 11 articles was not available. Some studies showed that the amount of shivering was the same in both intervention and control groups, and in other studies, the number of patients with shivering was not reported. Some authors stated that the occurrence of shivering will be reported, but then they did not manage to do so, or they only reported that the occurrence was similar. We tried to contact the corresponding authors of these articles to inquire about the number of patients suffering from tremors and other relevant information. Two authors responded, and the rest did not, so four clinical trials were removed from the study because the authors did not respond. All the entered articles are written in English.

The evaluated studies included the data of 4303 people. 2300 of them had received magnesium. These patients received magnesium by IV prescription (in 23 studies) (1, 6-27), by epidural medication (in 17 studies)(28-44), by intraperitoneal injection (in 13 studies) (45-57), and through other routes (in 4 studies)(58-61). All studies compared magnesium sulfate with a placebo or no drug. Two studies compared several ways of magnesium administration. About the magnesium sulfate drug factory, it should be mentioned that in none of the articles published until 2014, the name of the manufacturer of the used drug was not mentioned. In other articles that mention the manufacturing factory, all the drugs are supplied from the factory of the researchers' country and are not supplied from outside the country. For example, in the Iranian studies, the magnesium sulfate was purchased from the Pasteur Institute of Iran, the Egyptian study provided the magnesium sulfate from the Egyptian Al-Sharki Company, the Chinese studies used the Chinese Infusion Medicines Pharmaceutical Company, etc.

Since there were a sufficient number of studies, a subgroup analysis was performed according to the ordering method. The incidence of shivering in the magnesium group was significantly reduced by IV injection (risk: 0.39; CI 95%; 0.54-0.299; I2 = 50%; n = 2124), Epidural injection (risk: 0.24; CI: 95%; 0.43-0.13; I2: 2%; n=880), intra-intestinal administration (risk: 0.64; CI: 95%; 0.43-0.96; I2:14%; n=1120), and intra-articular administration (risk: 1.01; CI: 95%; 0.46-2.19: I2:81%; n=880).

Extubation time and Length of stay in PACU

Extubation time was determined in 4 trials, but in all 4 studies, there was no significant difference in terms of extubation time (15, 22, 33, 39). In one study (26), the duration of PACU stay was shorter in the IV magnesium group compared to the placebo group (53 minutes vs. 63 minutes, P=0.04). In an article entitled "Effect of magnesium sulfate on extubation time and acute pain in coronary artery bypass surgery" (62), a significantly shortened postoperative time for extubation and reduced acute post-operative pain scores by intravenous MgSO4 infusion during elective CABG surgery (Table 1).

Serum magnesium concentration

It was reported in 9 clinical trials that used IV magnesium. From a statistical point of view, there was no significant difference in concentrations before the operation (18-26). Post-operative measurements were performed in the first hour after surgery. One study was removed from the present review because the concentration reporting unit

Table 1. Pain scores in the two groups (based on a maximum VAS od 10)(62).

	Magnesium	Control	P-value
6th	2.6 (0.6)	3.7 (0.7)	<0.0001
12th	3.0 (0.5)	3.6 (0.6)	<0.0001
18th	2.5 (0.6)	3.3 (0.4)	<0.0001
24th	2.4 (0.4)	3.1 (0.5)	<0.0001

was not documented, and the corresponding author could not be reached. In other cases, the concentration in the magnesium group was significantly higher, and there was significant heterogeneity (I2=100%, 0.28-0.50, CI=95%). Serious side effects such as nerve damage, permanent nerve damage, or fatal dysrhythmias were not reported in any trial.

Spinal c-*fos* mRNA Expression

Tourniquet-induced hypertension (TIH) is by and large characterized as a dynamic increment of more than 30% in blood vessel blood weight after tourniquet swelling beneath general anesthesia. It should be mentioned that unmyelinated, slow-conducting C strands are likely dependable for tourniquet-induced torment and TIH. Several studies showed that expression of c-*fos* is diminished in reaction to the organization of ketamine in dorsal horn neurons after harmful boosts. A study by Lee et al. (63) showed that during anesthesia, magnesium and ketamine are similarly viable in weakening tourniquet-induced hypertension and spinal c-fos mRNA expression, proposing that this impact may be due to diminished torment transmission (Figure 1).

Nausea or vomiting

It has been reported in 54 clinical trials (11-66). The incidence in the IV magnesium group was lower than the control group (risk: 0.83; 0.99-0.69; CI: 95%; I2=4%), but there was no difference between the epidural (risk: 0.66; CI: 95%; 0.44-1.00; I2=0%) or intraperitoneal administration groups (risk: 0.98; CI: 95%, 0.74-1.29; I2=0%).

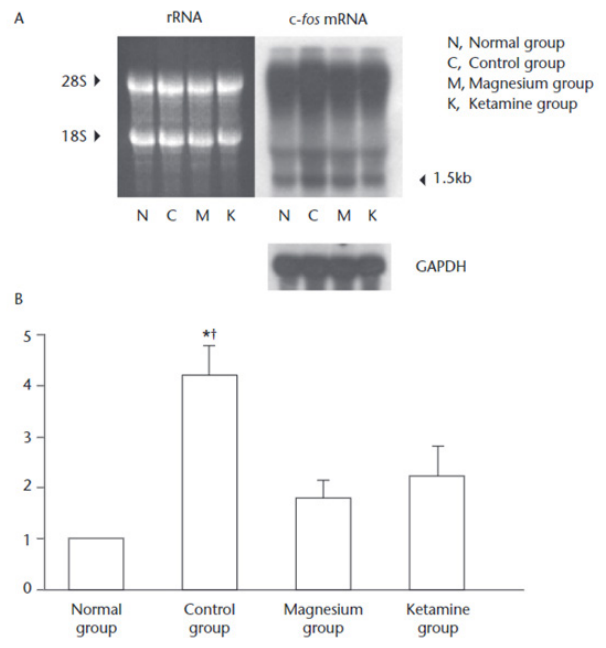

Figure 1. (A) Northern blot analysis of c-fos mRNA expression. C-fos mRNA expression increased in the control (0.1ml saline IV) compared with the normal (baseline values for c-fos mRNA expression), magnesium (50mg/kg magnesium sulfate IV) and ketamine (1mg/kg ketamine IV) groups. (B) Relative c-fos mRNA expression measured by real-time polymerase chain reaction. Values are fold changes in c-fos mRNA expression levels compared with the normal group and are expressed as mean ± SEM (n= 8 per group). *P< 0.01compared with the normal group; †P< 0.05 compared with the magnesium or ketamine group (63).

Relaxation

In 15 studies, 4 cases of sedation were reported, and in 11 cases, no patients in any groups had sedation. Our study showed that there is no significant difference between the groups (risk: 1.54; CI: 95%; 0.81-2.95; I2=0%). Eight studies reported sedation scores for each group. One study reported that the sedation score was higher in the magnesium group, and another reported higher in the control group. The remaining six studies reported no significant difference.

Itching

Itching has been reported in 22 studies (31-52). The incidence rate was lower in the magnesium group with IV prescription (risk: 0.48; CI: 95%; 0.30-0.75; I2=0%). But there was no difference with an epidural (risk: 1.49; CI: 95%; 4.46-4.89; I2=0%) or intraperitoneal administration (risk: 1.03; CI: 95%; 0.72-1.46; I2=0%).

Hypotension

Hypotension has happened in 36 studies (20-55), and the overall incidence rate was similar in all studies (risk: 0.91; CI: 95%; 0.79-1; I2=0%). No difference was observed in subgroup analysis according to the route of prescription. In 15 studies, no drop in blood pressure was reported, but blood pressure was recorded after prescribing the study drug. In 10 cases of the studies, the blood pressure was similar between the groups, and in 5 patients, the blood pressure in the magnesium group was lower at some point.

Bradycardia

Bradycardia has been reported in 32 studies (12-43). The overall incidence did not change, and no difference was observed in subgroup analysis according to the route of administration (risk: 0.85; CI: 95%; 0.66-1; I2=0%). In 12 studies, bradycardia was not reported, but heart rate (HR) was compared between groups. In 9 of them, HR had no significant difference. The remaining 3 cases reported that HR was lower in the magnesium group after prescribing the study drug.

Discussion

Our study showed that IV magnesium effectively reduces the degree of shivering. Of course, epidural and intraperitoneal administration methods were also influential (25, 35). Postoperative magnesium did not increase the occurrence of side effects. IV magnesium was effective in preventing shivering. Also, the review of the quality of the articles showed that I2 was equal to zero, indicating little heterogeneity. More studies are not needed to prove that IV magnesium effectively prevents shivering (39).

Only a few studies on this topic were included in the previous review studies (6, 29). In our opinion, the quality of the evidence was not evaluated, and their weaknesses were eliminated in our research.

This study of ours can be considered an update of the previous systematic review by Chang *et al.* (44). But some aspects were different between the studies. First, the word "shivers" was not used to search for texts in their analysis, while we reviewed all randomized control trials compa-

ring magnesium and control. In addition, our search had no time limit. While they limited the publications to the last ten years, our search not only included the latest publications, but its scope was broader.

The cost of prescribing magnesium is low, and our study showed that IV magnesium is not associated with an increased incidence of adverse outcomes (12). Therefore, magnesium should be considered for patients at risk of shivering, such as those who are young or undergoing long-term surgery, to prevent unpleasant shivering. In addition, patients who have limited cardiac reserve and suffer from cardiac compromise due to shivering benefit from active rewarming and pharmacological prevention of shivering (9, 49). Even if there is no difference in the amount of blood pressure reduction with magnesium administration in existing trials, it will be essential to be careful about administering magnesium to people with heart problems because small expansions in blood vessels can cause significant changes in the hemodynamics of patients (60). The mechanism by which magnesium exerts its anti-distortion effect is unclear (32). During general or neuraxial anesthesia, body temperature tends to decrease due to the dilation of blood vessels (16).

Vasoconstriction and shivering are automatic temperature regulation mechanisms to prevent hyperthermia. Shivering causes an increase in oxygen consumption and carbon dioxide production, and it requires oxygenation of the surrounding organs and causes blood vessels to dilate, which counteracts vascular contraction (23, 47). It may not be as effective in preventing hypothermia, but it can still be detrimental to patients with limited cardiac reserve. It has been reported that general anesthesia and spinal anesthesia decrease the shivering threshold of patients. The dose-response relationship between magnesium to prevent shivering is unclear. Analysis of subgroups according to IV dose showed that less than 60 mg/kg of magnesium sulfate would not increase the degree of shivering, but we cannot determine the optimal dose from our results. The lowest intravenous injection dose among the included studies was 2mmol (300 mg of magnesium sulfate)(51). Although there was no statistical difference, the amount of shivering was less in the magnesium group. Of note, only 12 studies compared magnesium with IV magnesium showed a significant reduction in the occurrence of shivering. We cannot conclude that IV magnesium sulfate up to 300 mg effectively reduces shivering.

The occurrence of side effects was not found with magnesium supplementation. It has been reported that magnesium has a sedative effect, but the administration of magnesium after the operation did not lead to sedation in our study (24, 48, 50). However, magnesium has been shown to prolong the effects of neurodepressant drugs. However, the tube removal time in patients prescribed magnesium was not significantly longer (37). Magnesium has been associated with nausea or vomiting in some patient populations. But this relationship was not observed in the postoperative period. This may be due to saving on the consumption of opioids (8).

Some studies have reported that blood pressure or HR is significantly lower after magnesium administration (36, 44, 53, 64). Some showed that the increase in HR and blood pressure is less, but the rate of drop in blood pressure or bradycardia in the magnesium group does not decrease significantly (38, 54, 58). Neither the previous meta-analysis nor ours included all the studies that evaluated the effect of itching prevention. It may be worth investigating in the future.

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