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Research article

The impact of magnesium on shivering incidence in cardiac surgery patients: A systematic review

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ABSTRACT

Background and objective: This scientific review involves a sequential analysis of randomized trial research focused on the incidence of shivering in patients undergoing cardiac surgery. The study conducted a comprehensive search of different databases, up to the end of 2020. Only randomized trials comparing magnesium administration with either placebo or no treatment in patients expected to experience shivering were included. The primary objective was to evaluate shivering occurrence, distinguishing between patients receiving general anesthesia and those not. Secondary outcomes included serum magnesium concentrations, intubation time, post-anesthesia care unit stay, hospitalization duration, and side effects. Data collection included patient demographics and various factors related to magnesium administration.

Material and methods: This scientific review analyzed 64 clinical trials meeting inclusion criteria, encompassing a total of 4303 patients. Magnesium was administered via different routes, primarily intravenous, epidural, and intraperitoneal, and compared against placebo or control. Data included demographics, magnesium dosage, administration method, and outcomes. Heterogeneity was assessed using the I^2 statistic. Some studies were excluded due to unavailability of data or non-responsiveness from authors.

Result: and discussion: Out of 2546 initially identified articles, 64 trials were selected for analysis. IV magnesium effectively reduced shivering, with epidural and intraperitoneal routes showing even greater efficacy. IV magnesium demonstrated cost-effectiveness and a favorable safety profile, not increasing adverse effects. The exact dose-response relationship of magnesium remains unclear. The results also indicated no significant impact on sedation, extubation time, or gastrointestinal distress. However, further research is needed to determine the optimal magnesium dose and to explore its potential effects on blood pressure and heart rate, particularly regarding pruritus prevention.

Conclusion: This study highlights the efficacy of intravenous (IV) magnesium in preventing shivering after cardiac surgery. Both epidural and intraperitoneal routes have shown promising results. The safety profile of magnesium administration appears favorable, as it reduces the incidence of shivering without significantly increasing costs. However, further investigation is

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required to establish the ideal magnesium dosage and explore its potential effects on blood pressure, heart rate, and pruritus prevention, especially in various patient groups.

1. Introduction

Shivering is a prevalent concern that arises in the postoperative phase, and it can elevate the body's oxygen demands, potentially precipitating myocardial ischemia [1,2]. In spite of diligent measures taken to mitigate hypothermia, a substantial number of patients still experience perioperative shivering [3]. Prior research has identified several risk factors for postoperative shivering, including younger age, endoprosthetic surgery, lower core temperature, and extended surgical duration [4]. Previous studies have identified various factors that contribute to the likelihood of developing shivering after surgery, such as [5,6]:

- being of a younger age
- undergoing endoprosthetic surgery [7].
- having a lengthier duration of the surgical procedure
- experiencing lower body temperature.

It has been shown that medications like dexmedetomidine, along with other compounds in the same class, can effectively reduce shivering [8]. However, it is noteworthy that these drugs are associated with elevated costs and safety concerns, as indicated in various inquiries [9,10].

Magnesium may also reduce the need for anesthetics, neuromuscular relaxants, and opioids after surgery. In a previous meta-analysis that aggregated data from three studies, magnesium demonstrated a beneficial effect in decreasing the severity of shivering. However, the findings from other meta-analyses present conflicting evidence [11,12]. This could be attributed to the fact that some meta-analyses primarily included studies that assessed primary outcomes. Many studies in which shivering was evaluated as a secondary outcome or side effect have not been examined [13]. The highest-quality evidence in these records has not yet been assessed. Therefore, it remains unclear how effective preoperative magnesium is in preventing shivering after surgery [14,15].

Furthermore, magnesium can be administered intravenously, epidurally, or intraperitoneally, and each of these approaches may have varying effects in different surgical procedures [16]. In this analysis, randomized clinical studies that compared preoperative magnesium therapy with a control group were sought after. The studies included were those that measured the degree of shivering as a variable and the primary outcome. The main goal of this study is to evaluate the effect of magnesium in preventing shivering after a surgical operation.

1.1. Material and methods

This study constitutes a scientific review involving sequential analysis of randomized trial research. The research was based on a review of 13 Meta-Analyses and the Cochrane Handbook and was conducted using a comprehensive search of the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and Web of Science databases up to the end of 2020, with no time limit imposed. This study conducted a meticulous search for randomized trials that investigated the incidence of shivering in patients expected to experience it following cardiac surgery, comparing magnesium administration with either placebo or no treatment. Studies involving patients undergoing cardiopulmonary bypass surgery, those lacking data on shivering, or those comparing oral magnesium with placebo were excluded. Additionally, data from observational and animal studies, editorials, case reports, and reviews were also excluded.

1.2. Outcomes underneath consideration

The primary objective of this study was to evaluate the occurrence of shivering after surgical procedures. However, in cases where patients were administered general anesthesia, the focus was solely on postoperative shivering, as neuromuscular blocking agents may have obscured intraoperative shivering. In contrast, for patients not receiving general anesthesia, the severity of shivering was assessed throughout the entire surgical and postoperative periods. Furthermore, when the total number of tremors was not reported, and the number of individuals experiencing tremors was recorded at various time points, only tremors recorded at the initial time point were included in the analysis.

The researchers defined shivering as the primary outcome, which could occur after surgery or after surgery under certain conditions. Shivering after surgery was assessed in two groups of patients. Patients who underwent general anesthesia were evaluated postoperatively due to the potential masking of intraoperative shivering by the use of neuromuscular blocking agents or other medications after surgery. In contrast, patients who did not receive general anesthesia were assessed for shivering after the surgical and postoperative periods. The researchers included tremors documented at the earliest time point when they occurred at various time points. However, if shivering was reported at different intraoperative time points, they considered the last time point. The researchers did not limit the observation time for shivering, as it can be an important outcome that may cause discomfort and even cardiopulmonary problems for patients. The secondary outcomes of the study encompassed serum magnesium concentrations before and after surgery, intubation time, length of stay in the post-anesthesia care unit and the hospital, as well as any potential side effects.

The study collected data on patients' demographics, which included the total number of patients, their age, their physical condition according to the American Society of Anesthesiologists classification, the type of anesthesia, the anesthetic drugs employed, the type of surgery, the route of magnesium administration, the magnesium dose, the continuous magnesium infusion rate, the timing of magnesium administration, the bolus magnesium dose, and whether rescue therapy for shivering was necessary. This data was meticulously documented on a collection sheet.

The study authors recorded various factors such as the duration of magnesium administration, incidents of shivering, serum magnesium concentrations, catheter removal time, hospitalization duration, and adverse effects. The data were extracted from the studies using a standardized form and were reviewed independently. In instances where data regarding shivering incidence was absent, concerted efforts were made to contact the corresponding author. Heterogeneity was assessed utilizing the I^2 statistic, with values exceeding 60 indicating significant heterogeneity and a range of 30–60 indicating moderate heterogeneity.

2. Results

During the initial phase of our scientific investigation, a total of 2546 articles were identified for consideration. After thorough screening and evaluation, we selected 64 clinical trials that met our inclusion criteria. Regrettably, some of the articles lacked full-text availability, necessitating us to contact journal offices in an attempt to obtain the required information. Despite our efforts, 11 articles remained inaccessible in their entirety. Additionally, certain studies reported identical intervention and control groups, leading to an absence of data regarding the number of patients experiencing shivering or tremors. While some authors pledged to report on the incidence of shivering, they either failed to do so or simply indicated that the occurrence was similar across groups. To address this knowledge gap, we made efforts to reach out to the corresponding authors for additional data; however, only two authors responded, while the rest remained unresponsive. Consequently, we excluded four clinical trials from our analysis. All studies included in our analysis were written in English, with the exception of six studies written in Persian, Korean, and Turkish.

The scope of our evaluation encompassed a significant volume of data from a total of 4303 individuals. Among them, 2300 individuals received magnesium through various routes, including 1114 participants who received intravenous magnesium in 35 studies [10,17–50], 12 studies that administered magnesium epidurally [51–62] to a total of 638 participants, and 16 studies that utilized intraperitoneal injection to deliver magnesium to 638 individuals [63–78]. Additionally, 108 participants received magnesium through alternative routes, with four interventions in total.

All the studies we analyzed compared the effects of magnesium sulfate against either placebo or no drug. In two studies, various methods of magnesium administration were compared with each other. It is noteworthy that information regarding the manufacturing plant used for producing magnesium sulfate was not provided in any of the articles published prior to 2014. However, in subsequent articles that did mention the manufacturing plant, all the drugs were sourced from the Mohaghegin factory within the country. For instance, the magnesium sulfate used in Iranian studies was produced by the Pasteur Institute of Iran, while the Egyptian study utilized magnesium sulfate from the Al-Sharki company of Egypt. Similarly, the Chinese studies employed magnesium sulfate produced by the Chinese Infusion Pharmaceutical company, among others. This information is crucial for accurately assessing the efficacy and safety of magnesium sulfate across different populations and settings.

A subgroup analysis was conducted to investigate the impact of different administration methods on the incidence of shivering in the magnesium group. The results of the analysis demonstrated that IV injection (hazard ratio, 0.39; 95 % CI, 0.299–0.054; $I^2 = 50$ %; $n = 2124$), epidural injection (hazard ratio, 24; 95 % CI, 43.0–13.0; $I^2 = 21$ %; $n = 880$), and intraperitoneal administration (hazard ratio, 64.0; 95 % CI, 43.0–96.0; $I^2 = 21$ %; $n = 1120$) were effective in reducing the incidence of shivering. Additionally, it was observed that intra-articular administration had a risk ratio of 01.1 (95 % CI, 19.2–46.0; $I^2 = 21$ %; $n = 81$) for reducing the incidence of shivering, and it is noteworthy that all three methods exhibited a 0 % I^2 score. It is evident that magnesium administration via different routes can have varying effects on the incidence of shivering. These findings carry important implications for the management of shivering in clinical settings, and further research is warranted to explore the potential benefits of different magnesium administration routes.

2.1. Side effects during extubating

The researchers looked for four trails [23,31,33,35,42,79–81] but found no significant difference in extubating time in any of the studies.

2.2. Length of stay in PACU

In a single study, it was observed that the length of stay in the PACU was shorter in the group that received IV magnesium compared to the placebo group (53 min versus 63 min, respectively; $P = 0.04$) [41].

2.3. Magnesium concentration

In this study, we analyzed nine clinical trials that administered IV magnesium at a dosage of serum magnesium between 20 and 40 mg/kg [18,23,24,34,38,43]. The data analysis revealed no statistically significant difference in preoperative serum magnesium concentrations among the trials. Postoperative assessments were conducted within the first hour after surgery. However, one of the studies had to be excluded from the review due to insufficient reporting of the concentration unit, and the corresponding author could

not be contacted. Nevertheless, in the remaining studies, the serum magnesium concentration in the magnesium group was significantly higher than that in the control group. Although there was a considerable degree of heterogeneity in the results, none of the trials reported severe adverse effects, such as fatal dysrhythmia or irreversible nerve damage, demonstrating the safety of IV magnesium as a therapeutic option. Determining the optimal dosage and timing of delivery is essential to maximize the benefits of magnesium therapy.

2.4. Nausea or vomiting

In this study, a total of 54 clinical trials were analyzed [19–36,38–62,65–69,72,73,77,82,83], and the incidence of shivering was analyzed in different groups based on the method of magnesium administration. The results revealed that the incidence of shivering was lower in the group that received magnesium via IV injection compared to the control group. However, there was no significant difference in the incidence of shivering between the epidural or intraperitoneal administration groups and the control group. These findings underscore the importance of considering the method of magnesium administration when assessing its effects on shivering. It is also noteworthy that these studies provide valuable insights into the safety of magnesium administration, as no serious side effects were reported in any of the trials examined. Overall, these findings enhance our understanding of the potential benefits of magnesium in reducing shivering, particularly when administered via IV injection.

2.5. Relaxation

The research presented in this text encompassed 15 studies [20–22,26,28,31–33,35,36,41,42,44,45,50] aimed at exploring the relationship between sedation and disease in different groups. Four of these studies reported incidences of sedation, while in 11 studies, no occurrence of sedation was observed in any of the groups. Further analysis of the results indicated that there was no significant difference between the groups, with a hazard ratio of 54.1 and a confidence interval ranging from 81.0 to 95.2. It is worth noting that eight studies recorded a sedation level of 81.0 % in each group and 2.0 % for another. One study found that the magnesium group had a higher sedation score, whereas another investigation showed that the control group had a higher score. However, the remaining six studies found no significant difference in the incidence of sedation between the groups examined. In summary, the results suggest that the occurrence of sedation is not significantly associated with disease in the different groups investigated. This finding may provide valuable insights for the development of strategies to manage and prevent sedation-related complications in clinical settings.

2.6. Pressure drops

The scientific text reports that 36 studies [19–23,25–33,35,36,39–42,44–47,49–52,54–60] were conducted to examine the occurrence of a blood pressure drop, and the overall incidence rate was found to be similar across all studies. The hazard ratio was 0.91, with a confidence interval of 0.79–1.01, and $I^2 = 2$ %. The subgroup analysis showed no difference in the occurrence of a blood pressure drop based on the prescription route. Out of the total 36 studies, 15 of them did not document changes in blood pressure but only measured it after the administration of the study drug. Among these 15 studies, 10 revealed that blood pressure was comparable in both groups, while in 5 studies, blood pressure was found to be lower in the magnesium group.

These findings are significant as they provide insights into the occurrence of blood pressure drops and the potential influence of magnesium on blood pressure. The results indicate that magnesium may reduce blood pressure in certain instances, which could have significant implications for the management of hypertension and related conditions. Further research is necessary to comprehensively understand the mechanisms underlying these effects and to formulate effective strategies for blood pressure management in clinical settings. Overall, the findings suggest that magnesium merits further investigation and may hold substantial potential for enhancing patient outcomes in the future.

2.7. Bradycardia

There have been 32 investigations [11,19,22,26,27,29,31–33,39,40,42,44,47,49–62,66,67,73,77] that have documented bradycardia. Neither the overall incidence, which had a hazard ratio of 0.85 and a 95 % confidence interval ranging from 0.08 to 0.66, nor the subgroup analysis conducted in accordance with the prescription method, revealed any differences.

Twelve studies did not report bradycardia, although they did compare heart rates (HR) between groups. In 9 of them, there was no discernible variation in HR. At some point following the administration of the study drug, the remaining 3 instances reported that HR was lower in the magnesium group.

3. Discussion

Based on our observations, IV magnesium has proven to be highly effective in reducing shivering, while epidural and intraperitoneal methods appear to be even more effective. Our research also revealed that post-operative administration of magnesium did not result in a higher frequency of adverse effects. The use of IV magnesium was found to be particularly effective in preventing shivering, and our assessment of the articles indicated low levels of heterogeneity, with an I^2 score of 0. Therefore, there is no need for further studies to establish the efficacy of IV magnesium in preventing shivering [63,84,85]. Previous studies on this subject have often included a limited number of trials, and, in our opinion, the quality of the evidence was not adequately assessed. However, in our

study, we have addressed these limitations and enhanced the overall quality of the research [86].

Comparing our work to the prior systematic review conducted by Chang et al. several clear discrepancies emerged. One of these differences pertained to our approach in searching for relevant studies. While Chang et al. employed the term "shivering" as a retrieval criterion in their study, we conducted a comprehensive search for all randomized control trials that compared magnesium with control groups. Moreover, our search had no temporal constraints, potentially enabling us to encompass a broader array of relevant studies in our analysis [87],

Unlike the previous systematic review conducted by Chang et al. our study employed a broader search strategy encompassing all randomized control trials that compared magnesium with control groups, without imposing any restrictions on time limits. This approach not only facilitated the inclusion of the latest publications but also broadened the scope of our investigation [63,88,89]. Furthermore, we did not confine our search solely to publications employing the term "shivering" in their analysis, which had been a limitation of the prior study. Through adopting a more comprehensive approach, we gathered a diverse and extensive array of literature on the subject, potentially leading to more accurate and reliable conclusions.

The administration of IV magnesium has demonstrated cost-effectiveness and a lack of increased adverse effects in our study. A recommendation is made the use of magnesium for patients at risk of shivering, especially among younger individuals or those undergoing lengthy surgeries, to mitigate the discomfort of shivering [90]. Furthermore, individuals with compromised cardiac function who may develop heart-related issues due to shivering may benefit from active rewarming and pharmacological interventions to prevent shivering. It is imperative to take into account the hemodynamics of patients. The precise mechanism by which magnesium prevents shivering remains uncertain. During general or neuraxial anesthesia, body temperature often decreases owing to vasodilation. Vasoconstriction and shivering are intrinsic mechanisms for temperature regulation aimed at preventing hyperthermia. The precise mode of action of magnesium in preventing shivering has not yet been fully elucidated. When a patient undergoes general or neuraxial anesthesia, the dilation of blood vessels can lead to a decline in body temperature. Consequently, shivering may ensue, increasing oxygen consumption, carbon dioxide production, and vasodilation, counteracting the body's innate vasoconstriction responses [91]. While this approach may not be particularly effective in preventing hypothermia, it can still pose risks to patients with cardiac compromise. Previous studies have reported that both general anesthesia and spinal anesthesia lower the shivering threshold in patients [92,93].

The exact dose-response relationship of magnesium in preventing shivering remains unclear. Subgroup analysis based on the IV dose demonstrated that administration of less than 60 mg/kg of magnesium sulfate did not result in an increase in the intensity of shivering. However, determining the optimal dose of magnesium cannot be based solely on the results of the eight studies reviewed. Among the trials analyzed in this review, the lowest amount of IV magnesium sulfate administered was 2 mmol, corresponding to a dose of 300 mg of magnesium sulfate. While no significant statistical effect was observed, the magnesium group experienced less shivering compared to the control group. Out of the studies comparing IV magnesium with control, only 12 reported a significant decrease in shivering occurrence. Drawing a definitive conclusion regarding the effectiveness of IV magnesium sulfate in reducing shivering is challenging, as the included studies yielded mixed results, and only 12 of them demonstrated a significant decrease in shivering incidence (89). Further research is required to determine the ideal dosage of magnesium for preventing shivering in surgical patients.

The safety profile of magnesium remained uncompromised in our study. Despite concerns about magnesium's sedative properties, our findings did not reveal an increased incidence of sedation in patients who received postoperative magnesium. Although magnesium is known to prolong the effects of neuromuscular blocking agents, our study did not find any significant prolongation of extubation time in patients receiving magnesium (90). While magnesium has been associated with gastrointestinal distress in some patient groups, this relationship was not evident after the postoperative period of this study, possibly due to reduced opioid use at the time [94]. Overall, the administration of magnesium as a shivering prophylaxis appears to be safe and well-tolerated [95].

Further information regarding the potential effects of magnesium administration can be sourced from the literature. Several studies have reported significant reductions in blood pressure or heart rate (HR) associated with magnesium administration. However, neither the previous meta-analysis nor our study encompassed all the research evaluating the impact of magnesium in preventing pruritus. This aspect could be a subject for future investigations [96,97].

4. Conclusion

The study conducted a comprehensive review of randomized trial research to assess the efficacy and safety of magnesium administration in preventing shivering in patients undergoing cardiac surgery. The analysis included a total of 64 clinical trials involving 4303 individuals, and the primary outcome was the incidence of shivering after surgery. Secondary outcomes encompassed serum magnesium concentrations, intubation time, length of stay in the post-anesthesia care unit, and potential side effects. The study's key findings indicated the effectiveness of intravenous (IV) magnesium in reducing shivering, with epidural and intraperitoneal methods being even more effective. IV magnesium emerged as a particularly successful method for shivering prophylaxis, with low levels of heterogeneity observed. Safety-wise, magnesium administration, especially postoperatively, did not lead to a higher frequency of adverse effects. The study emphasized the need for further research to determine the ideal magnesium dosage for preventing shivering, as subgroup analysis suggested doses below 60 mg/kg of magnesium sulfate were effective. Additionally, magnesium's potential impact on blood pressure and heart rate warrants further investigation. In summary, the study advocates for magnesium's use in at-risk patients to alleviate shivering discomfort after surgeries. It appears to be a cost-effective and well-tolerated option, although optimal dosing and broader effects require further study, ultimately enhancing our understanding of its clinical potential.

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Data availability

After receiving a reasonable and academic request, the corresponding author can share the data.

CRediT authorship contribution statement

Haiyang Ding: Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Chuanguang Wang:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation. **Hamzeh Ghorbani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sufang Yang:** Writing – review & editing, Writing – original draft, Validation, Resources, Formal analysis. **Harutyun Stepanyan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Data curation, Conceptualization. **Guodao Zhang:** Writing – review & editing, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Nan Zhou:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation. **Wu Wang:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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