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REVIEW ARTICLE

Intra-Operative Adjunctive Magnesium Sulfate in Pain Management of Total Knee Arthroplasty; a Systematic Review and Meta-analysis

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Abstract: **Introduction:** There has been growing interest in the potential role of adjunctive magnesium sulfate in improving pain management. This systematic review and meta-analysis aimed to assess the effect of intra-operative adjunctive magnesium sulfate on pain management and opioid consumption in total knee arthroplasty (TKA). **Methods:** A comprehensive search was conducted in Medline, Embase, Scopus, Web of Science, and Cochrane Library databases, covering studies up to April 2023. The extracted data included pain management outcomes, opioid consumption, and adverse effects from the selected studies. Standardized mean differences (SMDs) were calculated for continuous outcomes, while risk ratios (RRs) were calculated for dichotomous outcomes. Meta-analysis was conducted employing random-effects models in STATA 17. **Results:** In this meta-analysis of 8 randomized controlled trials involving 536 patients, adjunctive magnesium sulfate in TKA was found to significantly reduce opioid consumption during the first 24 hours after operation (SMD: -1.88, 95% confidence interval (CI): [-3.66 to -0.10]; p = 0.038). It also resulted in lower pain scores at rest 24 hours after surgery (SMD: -1.53, 95% CI: [-2.70 to -0.37]; p = 0.010). There were no significant differences in time to first rescue analgesic and adverse effects between the groups. The included studies were assessed to have low to high levels of risk of bias. **Conclusion:** This study presents evidence at low to moderate levels supporting the use of intra-operative adjunctive magnesium sulfate in TKA for improved pain management and reduced opioid consumption. However, further research is needed to address the heterogeneity and to explore optimal dosing regimens and routes of administration to maximize the benefits of magnesium sulfate in TKA.

Keywords: Arthroplasty, replacement, knee; Magnesium sulfate; Pain management; Analgesics, opioid; Meta-analysis

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1. Introduction

Total knee arthroplasty (TKA) is a common surgical procedure that relieves pain and improves function in patients with end-stage knee osteoarthritis (1). However, effective postoperative pain management remains a challenge, and the excessive use of opioids is often associated with adverse effects, delayed recovery, and increased healthcare costs (2). Therefore, there is a growing interest in identifying adjunctive therapies that can enhance pain control and reduce opioid requirements following TKA (3-5).

Magnesium sulfate, a well-known mineral supplement, has attracted attention for its potential analgesic properties and opioid-sparing effects (6). Magnesium, an essential cofactor in numerous enzymatic reactions, is involved in the modulation of N-methyl-D-aspartate (NMDA) receptors, calcium channels, and inflammatory mediators (7, 8). By modulating these pathways, magnesium sulfate has been hypothesized to possess analgesic properties, reduce central sensitization, and decrease the need for opioid analgesics (9-11). Studies examining the administration of magnesium have reported varying outcomes depending on the route of admin-

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istration. Intravenous (IV) administration of magnesium has been extensively studied and has shown consistent reductions in pain and opioid consumption in various surgical procedures (12, 13). In contrast, the evidence regarding other routes, such as intrathecal injection, periarticular injection, and nerve blocks, is more limited and inconclusive (14-17).

The potential analgesic benefits of intra-operative administration of magnesium sulfate have been investigated in several studies across various surgical procedures. A systematic review conducted in 2018 explored the use of intravenous magnesium sulfate specifically in orthopedic surgery and reported a reduction in postoperative analgesic consumption (18). Similarly, a recent systematic review and meta-analysis examining the effect of intravenous magnesium in noncardiac surgery indicated that magnesium may reduce morphine consumption within the first day after the operation and prolong the time to the first analgesia (12). Another systematic review and meta-analysis focused specifically on knee arthroscopic surgeries and found that adding magnesium sulfate to bupivacaine significantly improved analgesic efficacy (19). However, the specific impact of magnesium sulfate on pain and opioid consumption following TKA has not been comprehensively evaluated. Recent clinical trials investigating the effect of adjuvant magnesium on postoperative pain and opioid consumption following total knee arthroplasty have yielded conflicting findings (20-23).

In this systematic review and meta-analysis, we aim to evaluate the effect of intra-operative administration of magnesium sulfate on postoperative pain, opioid consumption, time to first analgesic in patients undergoing TKA, and its related adverse effects. Secondary outcomes, including knee range of motion, patient satisfaction, and length of hospital stay, will also be assessed. By synthesizing the available evidence, we seek to convey an extensive review of the potential benefits of magnesium sulfate as an adjunctive therapy in TKA.

2. Methods

The present study adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (24), ensuring that the systematic review and meta-analysis were conducted and reported in a rigorous and transparent manner. The study protocol was not registered by the authors prior to its commencement. The PRISMA checklist 2020 can be find in supplementary table 3 and 4.

2.1. Study design

The objective of this review was to evaluate the efficacy of intra-operative magnesium sulfate administration as part of routine analgesic management protocols in TKA. The authors framed their study using the PICO framework as follows:

Population (P): Individuals of any gender and age who underwent TKA.

Intervention (I): Treatment with magnesium sulfate via intravenous, intrathecal, or regional routes, excluding oral administration.

Comparison (C): Patients receiving the same medication as the magnesium group, but without magnesium addition.

Outcome (O): Postoperative pain, opioid consumption, and adverse effects.

2.2. Search strategy

To identify relevant keywords related to TKA and Magnesium Sulfate, a comprehensive approach was employed, including expert recommendations, MeSH and Emtree databases, as well as screening of titles, abstracts, and subject indexing of relevant articles. Distinct search queries were formulated with relevant tags assigned to each specific database, including Medline (via PubMed), Embase, Scopus, Web of Science, and Cochrane Library. Searches were performed from the launch of the databases up until January 2023. The supplementary file provides an inclusive search strategy employed for each individual database utilized in this study. Additionally, a search was conducted on Clinicaltrials.gov and Google Scholar to identify any potentially relevant studies and review grey literature.

Furthermore, a manual search of the bibliographies of all selected articles during the full-text review was performed, along with forward and backward citation tracking, to identify additional relevant articles. The search was updated in April 2023, leading to the identification of one additional article (22), which was subsequently included in the final analysis.

2.3. Eligibility criteria

This study included randomized clinical trials (RCTs) and prospective or retrospective observational studies that assessed the impact of intra-operative magnesium sulfate administration on the management of TKA. There were no restrictions on language or publication date. The following routes of magnesium administration were considered: intravenous (IV), epidural, intra-articular injection, peri-articular injection (PAI), adductor canal block (ACB), and femoral nerve block (FNB). Studies evaluating oral magnesium supplementation or comparing magnesium in combination with another drug in the control group were excluded. Additionally, studies that did not evaluate the main outcomes of interest or compared magnesium to other experimental interventions (instead of a control group) were also excluded. Case-control studies, animal studies, duplicate reports, letters, case reports, case series, and reviews were also excluded.

2.4. Study selection

The initial records retrieved from the search results were exported to Endnote software version 20.0 to remove duplicate records. Two independent authors (AA and FT) conducted a review of titles and abstracts to screen the articles. Subsequently, the full texts of potentially eligible studies were obtained, and final studies were selected based on the predefined eligibility criteria. Any disagreements were resolved through discussion.

2.5. Outcomes of interest and definitions

The primary outcomes of interest in this study were postoperative pain, opioid consumption, and adverse effects during the first two weeks post operation (PO). Postoperative pain refers to the intensity of pain experienced by patients. Opioid consumption refers to the amount of opioid analgesics consumed by patients. The term "time to first analgesic" refers to the duration between the completion of the surgery and the moment when the patient requests the first rescue analgesic for pain relief. Adverse effects encompass any undesired or negative effects resulting from the intra-operative administration of magnesium sulfate, including nausea, vomiting, hypotension, arrhythmias, respiratory depression, renal dysfunction, and allergic reactions. The secondary outcomes of interest included knee range of motion, patient satisfaction, and length of hospital stay.

2.6. Data extraction

The data entry process was carried out by two independent authors (AA and FT) using a pre-designed Excel form. Studies that provided data from a single registry were identified by reviewing the registry title, year, setting, and sample characteristics. In cases where data for meeting the study objectives were missing, we reached out to the corresponding authors of the articles and requested the necessary information or original data. For articles that presented data in the form of figures, PlotDigitizer online software was utilized.

Data extraction involved gathering study characteristics (authors, location, methodology, and anesthesia strategy), patient demographics (population size, age, and gender), intervention details (route, and dosage), and control information (route, and medications used). The recorded outcomes included opioid consumption measured in oral morphine equivalents (OME), postoperative pain assessed using Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), adverse effects documented by frequency or numbers, length of hospital stay measured in days or hours, and knee range of motion (ROM) reported in degrees. The "time to first analgesic" data was collected and recorded in minutes or hours following the surgery. The conversion equivalents employed in this review were as follows: 1 mg of morphine (IV/IM/SC) was considered equivalent to 0.01 mg of fentanyl (IV or Epidural) and 10 mg of pethidine (IV/IM). These conversion factors were utilized to standardize and compare opioid dosages across different administration routes based on the recommendations of UpToDate (25). In staged TKA studies, data pertaining to the first knee operated was collected and analyzed.

2.7. Risk of bias assessment

Due to the limited number of observational studies included, the meta-analysis in this study focused solely on RCTs. To assess the quality of these studies, the second version of the Cochrane risk of bias assessment tool was employed (26). Two independent authors (AA and FT) evaluated all included articles using the criteria outlined in this tool and made decisions based on the available data. The assessment of bias in the included studies was conducted based on several domains, including randomization, deviations from intended interventions, missing data, outcome measurement, and selection of reported outcomes. A classification of "low" was assigned to studies with no risk of bias in any of these domains. On the other hand, if "some concerns" or "high" were identified in more than one domain, the overall rating was categorized as "some concerns" or "high" accordingly.

2.8. Certainty of evidence

The authors employed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guideline to determine the level of evidence for each outcome (27). Publication bias, risk of bias assessments, inconsistency, imprecision, and indirectness, were taken into consideration. Based on these assessments, the level of evidence for each investigated outcome was reported as high, moderate, low, or very low.

2.9. Data synthesis and analysis

The analysis of data was conducted using STATA software (version 17) for the meta-analysis. The outcomes of postoperative pain and opioid consumption were assessed using the Standardized Mean Difference (SMD), while the analysis of adverse effects was performed using the risk ratio (RR). Forest plots were employed to visually present the effect sizes of the evaluated outcomes.

The subgroup analyses in this study were determined based on the specific follow-up time at which the desired outcome was evaluated. However, due to the limited number of included articles, subgroup analyses based on the route of magnesium administration could not be conducted. Considering the variations in outcome measurement and intervention procedures across the included reports, it was expected that high heterogeneity would be present. To address this potential issue, random effects model was employed.

Heterogeneity among the results was assessed using the I2 statistic, following the classification by Higgins (28). Additionally, the Egger's test (29) was performed to examine the presence of publication bias. Visual inspection of the funnel plot by subgroup was also conducted to further evaluate publication bias and assess the symmetry of the data distribution.

3. Results

3.1. Search results

The initial database search yielded a total of 401 articles based on the specified search strategy. An additional 4 studies were identified from the references of included papers. After removing duplicate records using EndNote, the titles and abstracts of the remaining 195 studies were screened. From this screening, 20 specific studies were selected for a full-text review. Following a thorough evaluation based on the eligibility criteria, 11 studies were excluded for various reasons (30-40), as depicted in Figure 1. Ultimately, 9 articles were deemed suitable for inclusion in the current investigation (20-23, 41-45). However only the 8 RCTs were included in the meta-analysis. The process of study selection, as illustrated in the PRISMA flow diagram, can be found in Figure 1.

3.2. Study characteristics

Table 1 presents the baseline characteristics of the studies included in this review. The data used for the meta-analysis were derived from 8 RCTs comprising a total of 536 patients. Among these studies, 267 patients were allocated to the treatment group, and 269 patients to the control group. The other article had a retrospective observational methodology and was not involved in the meta-analysis. Regarding the administration route of magnesium, two studies utilized intravenous administration (23, 41), two studies employed periarticular injection (21, 22), two studies utilized adductor canal block (20, 45), one study used femoral nerve block (43), and one study utilized the epidural catheter (44). Due to the limited number of studies available, it was not possible to conduct subgroup analyses based on the route of magnesium administration. In the studies where magnesium was administered intravenously, the control group received normal saline as the control (23, 41, 42). However, in the other studies, the control group received local anesthetics, and in the intervention group, magnesium was prescribed in addition to these medications (20-22, 43-45).

3.3. Main outcomes

The results of the meta-analysis comparing opioid consumption in subgroups with different timing are presented in Figure 2. The standardized mean difference of opioid consumption was not statistically significant in the first six hours (SMD: -1.36, 95% confidence interval (CI): [-3.72 to 1.00]; p-value = 0.260), 24 to 48 hours after operation (SMD: -0.61, 95% CI: [-1.32 to 0.10]; p-value = 0.095), and 0 to 48 hours PO (SMD: -0.80, 95% CI: [-1.60 to 0.00]; p-value = 0.050). However, a statistically significant SMD in favor of magnesium was observed in the 0 to 24 hours postoperative period (SMD: -1.88, 95% CI: [-3.66 to -0.10]; p-value = 0.038).

The forest plot in Figure 3 illustrates the differences in pain among five subgroups. The pooled analysis revealed a significant decrease in pain for the intervention group 24 hours after the operation (SMD: -1.53, 95% CI: [-2.70 to -0.37]; p-value = 0.010). Although the Magnesium group showed favorable differences in pain compared to the control group in six hours, 12 hours, 48 hours, and 72 hours after the operation, these values were not statistically significant (All P-values > 0.05).

Figure 4 displays a forest plot depicting the difference in time to first rescue analgesic based on a pooled analysis. The results indicate that the Magnesium group did not significantly differ in time to first analgesic compared to the control group (SMD: 6.72, 95% CI: [- 5.72 to 19.15]; p-value = 0.290).

Figure 5 illustrates the meta-analysis results for the adverse effects reported in the studies. The risk ratio analysis did not show a statistically significant increase in nausea (SMD: -0.14, 95% CI: [-0.34 to 0.05], P-value = 0.156) or pruritus (SMD: 0.26, 95% CI: [-0.40 to 0.91]; p-value = 0.446).

3.4. Secondary outcomes

In relation to the secondary outcomes of interest in this review, range of motion (ROM) was assessed in only one study (22), which showed insignificant differences amid the intervention and control groups. Two studies evaluated the length of hospital stay and found that magnesium had no advantage (20, 22). Patient satisfaction with pain control was investigated in three studies (20, 23, 45), revealing no significant superiority in favor of the intervention group. Summary of these outcomes can be found in Supplementary Table S1.

3.5. Heterogeneity

Heterogeneity levels for all analyzed outcomes in each subgroup were reported in Figures 2-5. High levels of heterogeneity were observed for opioid consumption (over 86% in all subgroups), pain (ranging from I2=0% to I2=98%), and time to first analgesic (I2=99%). However, the results indicated relatively low heterogeneity among the studies for the adverse effects (I2=0%).

3.6. Publication bias

The Egger's test was performed to assess small-study effects. The regression-based Egger's test showed a significant association between the effect size and the standard error for opi-

oid consumption (z = -6.25, p-value < 0.001), postoperative pain (z = -4.14, p-value < 0.001), and time to first rescue analgesic (z = 8.37, p-value < 0.001) suggesting the presence of small-study effects. Funnel plots for opioid consumption, postoperative pain, and time to first analgesic are presented in supplementary figures S1, S2, and S3, respectively. Overall, the funnel plots exhibited a symmetrical distribution of studies in each subgroup, suggesting little evidence of publication bias.

3.7. Risk of bias

Figure 6 summarizes the assessment of the risk of bias for individual articles via the revised Cochrane Collaboration tool (RoB 2). Among the included studies, three were determined to have a low risk of bias, four were assessed as having a high risk of bias, and one study was deemed to have some concerns based on the authors' judgment. Despite variations in the risk of bias scores, all studies within each subgroup were included in the analysis due to the limited number of available studies.

3.8. Certainty of the evidence

The certainty of the evidence for each outcome in this study has been evaluated and reported based on the authors' judgment using the GRADE approach. According to the assessment, the evidence for opioid consumption and postoperative pain was determined to be of low certainty. There was moderately certain evidence supporting the findings related to the time to first analgesic and adverse effects. Supplementary Table S2 contains additional information on the certainty of evidence for each outcome.

4. Discussion

This study was a systematic review and meta-analysis of the randomized clinical trials focusing on the effect of intraoperative magnesium sulfate in total knee arthroplasty. The results showed significant improvements in pain management with the use of adjunctive magnesium sulfate in TKA. The key outcomes included reduced opioid consumption in the first 24 hours after operation and decreased postoperative pain 24 hours after operation. However, the effect size of magnesium sulfate varied among the different studies included in this analysis. There were no significant differences in time to first rescue analgesic and the incidences of postoperative nausea and pruritus.

The use of magnesium in pain management has emerged as a state-of-the-art topic across various medical conditions. Despite its recent surge in attention, a substantial number of studies have already been undertaken to explore its effectiveness. A recent systematic review conducted in 2021 examined the use of magnesium in various conditions, including post-operative pain, migraine, renal pain, chronic/neuropathic pain, and fibromyalgia. The review found a total of 50 randomized controlled trials specifically focusing on the post-operative setting (46). They concluded that although several studies have demonstrated the pain-relieving and opioid-sparing effects of magnesium, it is important to note that not all studies have reported significant effects (47-50).

Studies investigating the effect of magnesium on pain mechanisms have highlighted the potential influence of the route of administration. Specifically, some articles concentrated on a specific route of magnesium administration in the post-operative setting. For instance, a comprehensive meta-analysis conducted in 2020, encompassing 51 RCTs, examined the impact of IV magnesium on postoperative usage in noncardiac operation. The findings indicated that intravenous magnesium, when used as part of a multimodal analgesia approach, may lead to a reduction in morphine consumption within the first 24 hours after surgery and postpone the first rescue analgesia following a noncardiac operation (12). In addition, another meta-analysis on 12 RCTs evaluated the application of intrathecal magnesium as an analgesic addition for spinal anesthesia. The results indicated that the inclusion of intrathecal magnesium in the spinal anesthetic regimen led to a prolongation of opiate analgesia duration (17). Another review of 21 studies on the use of magnesium sulfate in peripheral nerve blocks found that it effectively reduced pain scores 6 and 12 hours after surgery, and decreased postoperative analgesic use within the initial 24 hours after surgery (15).

Furthermore, it is important to consider that the nature of surgeries can vary, and orthopedic surgeries have been a specific focus in some studies. For instance, a systematic review comprising 11 RCTs examined the efficacy of IV magnesium sulfate for postoperative pain control in the orthopedic setting (18). The review concluded that perioperative IV use of magnesium sulfate in orthopedic procedures may lead to a reduction in analgesic usage and mitigate adverse effects. These studies, however, failed to deliver solid proof of favorable effects on the postoperative level of pain or time to first narcotic need (18). Additionally, another systematic review and meta-analysis involving six RCTs evaluated the impact of combining magnesium with bupivacaine for arthroscopy (51). The findings revealed that the addition of magnesium was associated with a significantly prolonged duration of analgesia, delayed time to analgesic administration, reduced pain scores, and decreased analgesic usage (51). A meta-analysis on intra-articular magnesium for pain management following arthroscopic knee procedures showed that patients who received magnesium experienced lower pain scores at rest and with movement two, four, twelve, and 24h after surgery, and had reduced opioid consumption and longer

time to the first analgesic requirement (16).

To our knowledge, the present study is the first to specifically evaluate the effect of intra-operative magnesium sulfate administration on total knee replacement. The results of this study demonstrated that magnesium sulfate administered via various routes, including intravenous, periarticular infiltration, adductor canal block, femoral nerve block, and intrathecal, reduced postoperative pain at rest 24 hours after surgery and opioid consumption within the first 24 hours postoperatively, which is consistent with previous studies (15-17, 46, 51). However, the findings of this study indicated that magnesium administration does not change the time to the first request for analgesics by the patients, which is in contrast with previous studies (16, 51). One possible reason for this controversy is the limited number of included studies in the meta-analysis of time to rescue analgesic in the current study. Also, the effect size of time to first rescue analgesic had a great variation among the included studies ranging from SMD of -0.02 to 26.53, which resulted in the high heterogeneity observed in the results.

Among the findings, the most clinically significant result was the significant reduction in opioid consumption during the first 24 hours, with a standardized mean difference (SMD) of -2.07. This suggests that the use of magnesium has the potential to substantially decrease reliance on opioids for pain management in the early postoperative period.

The observed effects of adjunctive magnesium sulfate in improving pain management in total knee arthroplasty (TKA) may be attributed to several potential mechanisms. Magnesium sulfate possesses pharmacological properties that could interact with pain pathways and opioid receptors, thereby modulating the analgesic response.

One possible mechanism is the NMDA receptor antagonism activity of magnesium sulfate. NMDA receptors serve a crucial role in the formation and maintenance of central sensitization and chronic pain. By blocking NMDA receptors, magnesium sulfate may attenuate the amplification of pain signals, resulting in reduced pain perception (52). This mechanism aligns with the significant reduction in postoperative pain observed in the early follow-up time points of our study. Additionally, magnesium sulfate has been shown to possess calcium channel blocking properties (53). By inhibiting calcium influx, magnesium sulfate may reduce neuronal excitability and subsequent pain transmission (52). This modulation of calcium channels could contribute to the observed decrease in opioid consumption, as calcium signaling is involved in opioid receptor desensitization and tolerance development.

Moreover, magnesium sulfate has been reported to exhibit anti-inflammatory effects. Inflammation is a crucial component of postoperative pain, and the anti-inflammatory properties of magnesium sulfate may help alleviate pain and reduce the need for rescue analgesics (54). These anti-inflammatory effects may contribute to the short-time pain decreasing role of magnesium seen in this study.

5. Strengths and limitations

One of the strengths of this study is the inclusion of a comprehensive search strategy that yielded a substantial number of relevant studies. By employing a systematic approach, we were able to minimize selection bias and ensure a representative sample for our meta-analysis. Another strength is the rigorous assessment of outcomes using standardized measures. The use of standardized protocols for data extraction and analysis increased the reliability and comparability of the results across studies. Furthermore, the inclusion of multiple outcome measures, such as opioid consumption, postoperative pain scores, time to first analgesic, and adverse effects, allowed for a comprehensive evaluation of the effects of magnesium sulfate on various aspects of postoperative pain management.

Despite the strengths of this study, there are several limitations that should be acknowledged. First, the number of included studies was relatively small, particularly when subgroup analysis was attempted. The scarce number of studies in subgroups restricted our ability to conduct subgroup analyses based on factors such as route of administration or dosage of magnesium sulfate. Second, the heterogeneity observed among the included studies may have influenced the overall findings. Although random effects models were used to account for potential heterogeneity, variations in study design, patient populations, and intervention protocols could have contributed to the observed heterogeneity. Furthermore, the risk of bias in the included studies should be considered. While efforts were made to include studies regardless of their risk of bias score, the presence of studies with high risk of bias or some concerns may have affected the overall reliability and validity of the findings. Finally, based on GRADE, the moderate to low certainty of evidence for certain outcomes, such as opioid consumption and postoperative pain, shows that more studies are needed to strengthen the certainty in effect estimates.

6. Future directions

This study provides valuable insights into the role of magnesium sulfate in postoperative pain management following total knee arthroplasty. However, there are several avenues for future research that could further enhance our understanding and optimize the use of magnesium sulfate in clinical practice.

First, given the limited number of studies available in this review, future research should aim to conduct large-scale, multicenter RCTs to provide more robust evidence. Investiga-

tions comparing different routes and dosages of magnesium sulfate administration could help identify the most effective and well-tolerated regimens, specifically in the TKA setting. In addition to its analgesic properties, the potential impact of magnesium sulfate on other outcomes, such as functional recovery, patient satisfaction, and long-term complications, should be investigated. Long-term follow-up studies assessing the durability of pain relief and the effects on joint function and quality of life would provide valuable information for clinical decision-making and patient counseling. Moreover, the cost-effectiveness of magnesium sulfate in comparison to other analgesic modalities should be assessed. Economic evaluations, such as cost-effectiveness or cost-utility analyses, could provide insights into the value of incorporating magnesium sulfate into perioperative pain management protocols. Finally, the identification of potential biomarkers or predictors of response to magnesium sulfate could help personalize pain management strategies. Genetic, proteomic, or phenotypic profiling studies could identify patient characteristics or biomarkers associated with a favorable response to magnesium sulfate, allowing for more targeted and individualized treatment approaches.

7. Conclusion

The findings of this study indicate that the addition of magnesium sulfate as adjunctive therapy in total knee arthroplasty improves pain management by reducing opioid consumption and alleviating postoperative pain during the early stages of recovery, without causing an increase in the adverse effects. However, considering the limitations of the included studies and the overall low to moderate certainty of the evidence, these results should be interpreted with caution.

8. Declarations

8.1. Acknowledgments

None to declare.

8.2. Conflict of interest

The authors declare that they have no conflict of interest.

8.3. Funding and support

No funding or grants were obtained for this study.

8.4. Authors' contribution

All authors made substantial contributions to the production of this work:

• Conception and design of the work: Amirali Azimi

• Acquisition, analysis, and data interpretation: Amirali Azimi, Fatemeh-sadat Tabatabaei, Amirfarbod Azimi, Hamid Mazloom

• Drafting and work revision: Amirali Azimi, Amirfarbod Azimi

• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Amirali Azimi, Fatemeh-sadat Tabatabaei, Amirfarbod Azimi, Hamid Mazloom, Mohammad Mehdi Foruzanfar and Nastaran Sadat Mahdavi.

8.5. Patient and Public Involvement

Patients were not involved in this research.

8.6. Data sharing statement

All data relevant to the study are included in this article or available in the supplemental file. The authors ensured that no patient-identifiable data are available.

8.7. Ethical approval

Resulting from the study design (meta-analysis), an ethical approval is not applicable.

8.8. Informed consent

The study was not done on human participants.

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Table 1: Baseline characteristics and method of intervention and control in the included studies

Authors (Year)	Country; Study design	Sample size (n), Mean age (y), Male (%)		General anesthesia	Focal analgesics	Intervention	Intervention route / Magnesium dosage	Control route / Control medication	Postoperative analgesia
		MG	CG						
Zhao et al. (2023) (22)	China; RCT	45 65.9 20	45 64.2 29	GA	PAI	MgSO4 + Control Medications	PAI / 250 mg MgSO4	PAI / Ropivacaine, Epinephrine Dexamethasone,	Subcutaneous morphine; PO Celecoxib
Choi et al. (2022) (45)	United states; RCT	49 66.5 43	53 67.4 38	SA	ACB	MgSO4 + Control Medications	ACB / 150 mg (0.3 mL) MgSO4	ACB / Bupivacaine	Not defined
Zoratto et al. (2021) (20)	Canada; RCT	41 67.5 54	39 66.7 54	SA	PAI	MgSO4 + Control Medications	ACB / 2 g MgSO4	ACB / Ropivacaine	PCA IV morphine; PO acetaminophen; PO Celecoxib
Zhao et al. (2021) (21)	China; RCT	30 69.6 36	30 69.8 40	SA	PAI	MgSO4 + Control Medications	PAI / 250 mg MgSO4	PAI / Levobupivacaine, Triamcinolone	PCA IV Sufentanil and Dezocine
Park et al. (2020) (42)	Sout Korea; ROS	115 72.2 13.9	115 72.2 13	SA	FNB	MgSO4	IV / Bolus 50 mg/kg Infusion 15 mg/kg.h	IV / Normal Saline	PCA IV Fentanyl; PO Acetaminophen, Celecoxib, Pregabalin; Rescue IV opioids
Shin et al. (2016) (41)	Sout Korea; RCT	22 74.3 4.8	22 72.3 0	SA	FNB PAI	MgSO4	IV / Bolus 50 mg/kg Infusion 15 mg/kg.h	IV / Normal Saline	PCA IV Fentanyl; PO Acetaminophen, Celecoxib, Pregabalin; IV Ketoprophen
Frassanito et al. (2015) (23)	Italy; RCT	20 65.6 40	20 67.4 25	SA	-	MgSO4	IV / Bolus 40 mg/kg Infusion 10 mg/kg.h	IV / Normal Saline	PCA IV morphine; IV paracetamol; IV ketorolac
Daabiss et al. (2015) (44)	Saudi Arabia; RCT	40 61.1 50	40 59.5 57	EA	-	MgSO4 + Control Medications	Epidural catheter / Bolus 50 mg MgSO4 Infusion 10 mg/h	Epidural catheter / Bupivacaine	PCA epidural Fentanyl; IM Pethidine
Elmawgoud et al. (2008) (43)	Egypt; RCT	20 55 35	20 55 60	GA	FNB	MgSO4 + Control Medications	FNB / Bolus 1.5 g MgSO4 Infusion 0.3 g/h	FNB / Ropivacaine	PCA IV morphine

RCT: Randomized Clinical Trial; ROS: Retrospective Observational Study; MG: Magnesium Group; CG: Control Group; GA: General Anesthesia; SA: Spinal Anesthesia; PAI: Periarticular infiltration; FNB: Femoral Nerve block; EA: Epidural Anesthesia; IV: Intravenous; ACB: Adductor canal block; PCA: Patient-Controlled Analgesia; MgSO4: Magnesium Sulfate; PO: oral; IM: intramuscular.

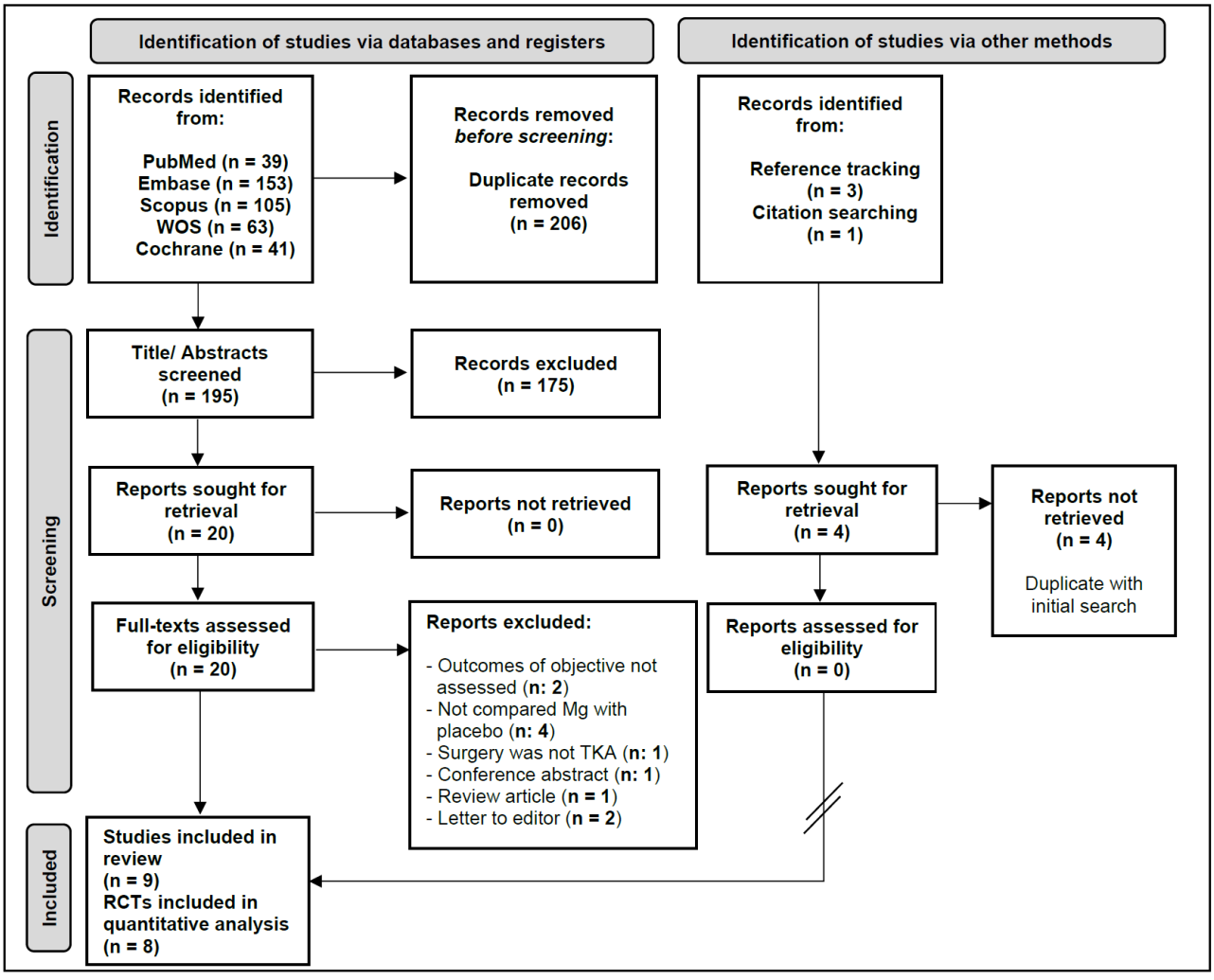


Figure 1: Flowchart depicting the study selection process. WOS: Web of Science; TKA: Total Knee Arthroplasty; RCT: Randomized Clinical Trial.

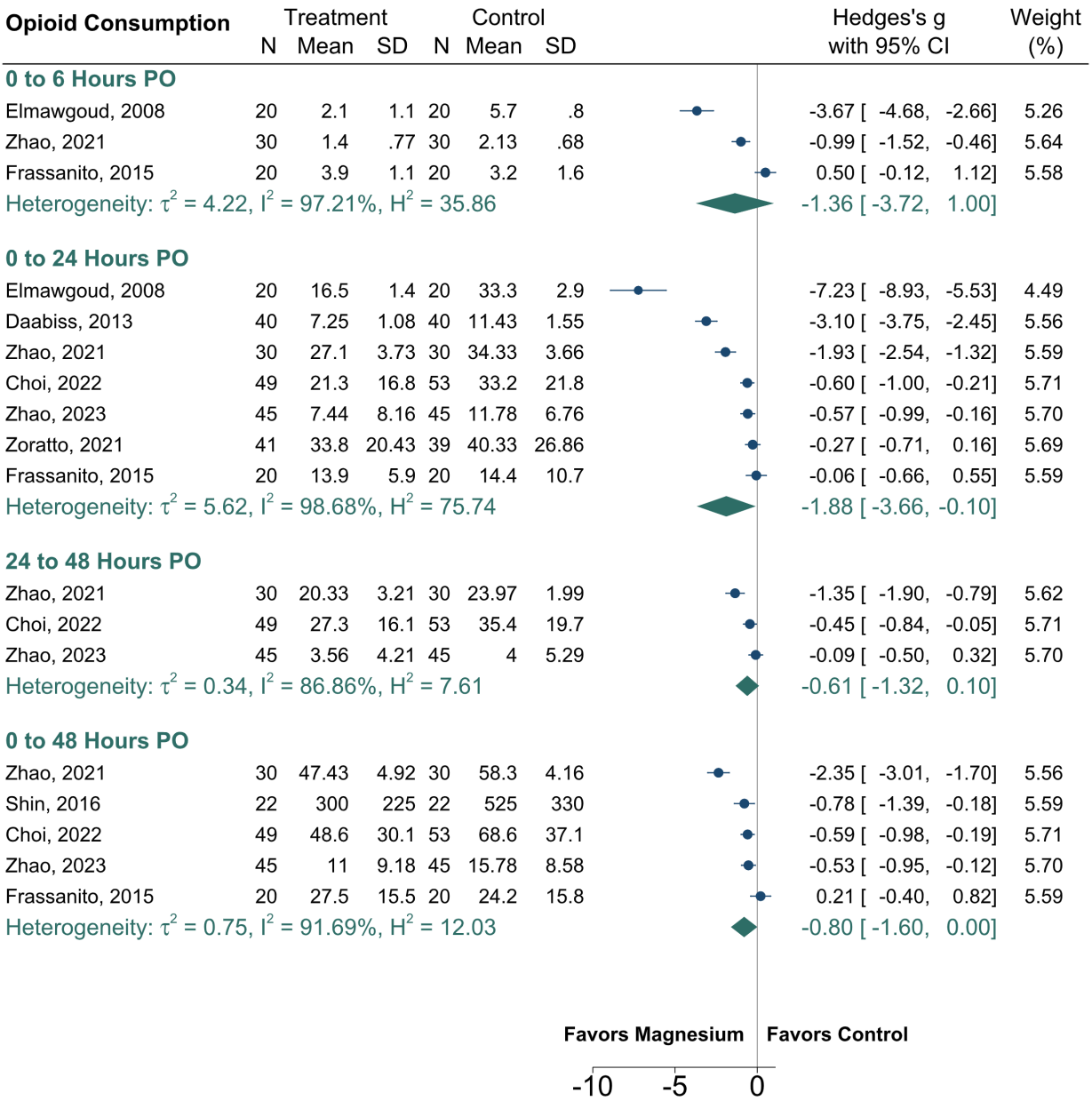


Figure 2: Forest plot presenting the effect of adjunctive magnesium sulfate on opioid consumption in four subgroups by timing. PO: post operation; SD: Standard Deviation; CI: Confidence Interval.

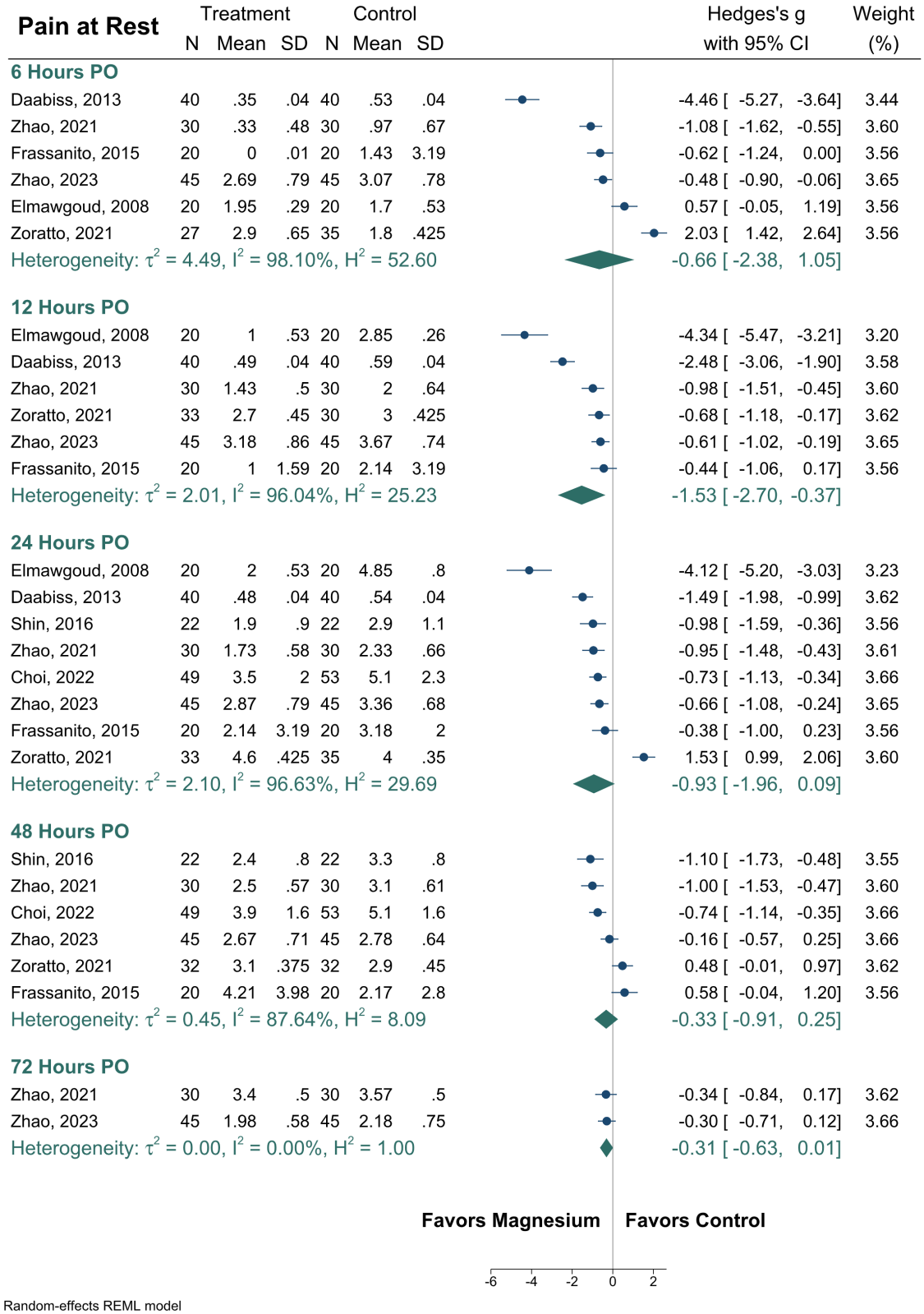


Figure 3: Forest plot presenting the effect of adjunctive magnesium sulfate on postoperative pain in five subgroups by timing. PO: post operation; SD: Standard Deviation; CI: Confidence Interval.

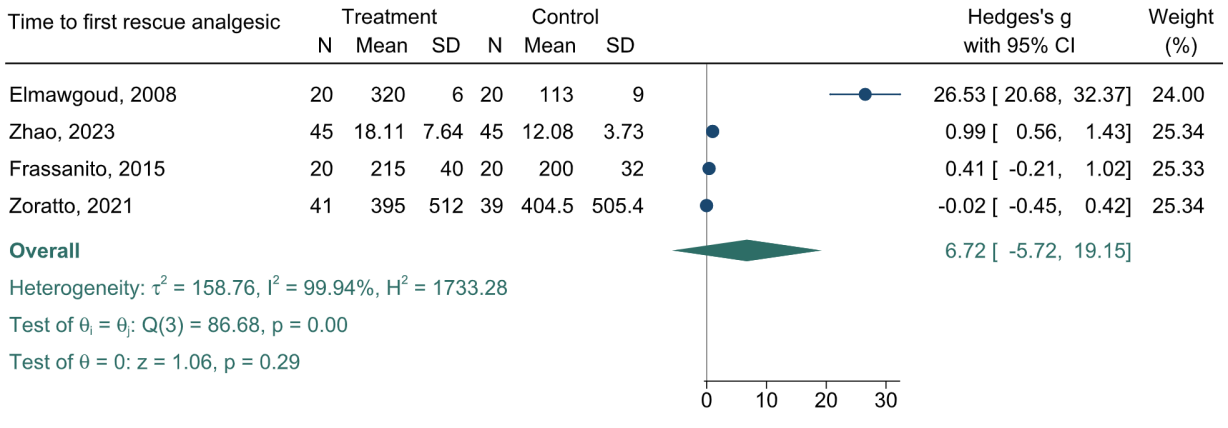


Figure 4: Forest plot illustrating the effect of adjunctive magnesium sulfate on time to first rescue analgesic. SD: Standard Deviation; CI: Confidence Interval.

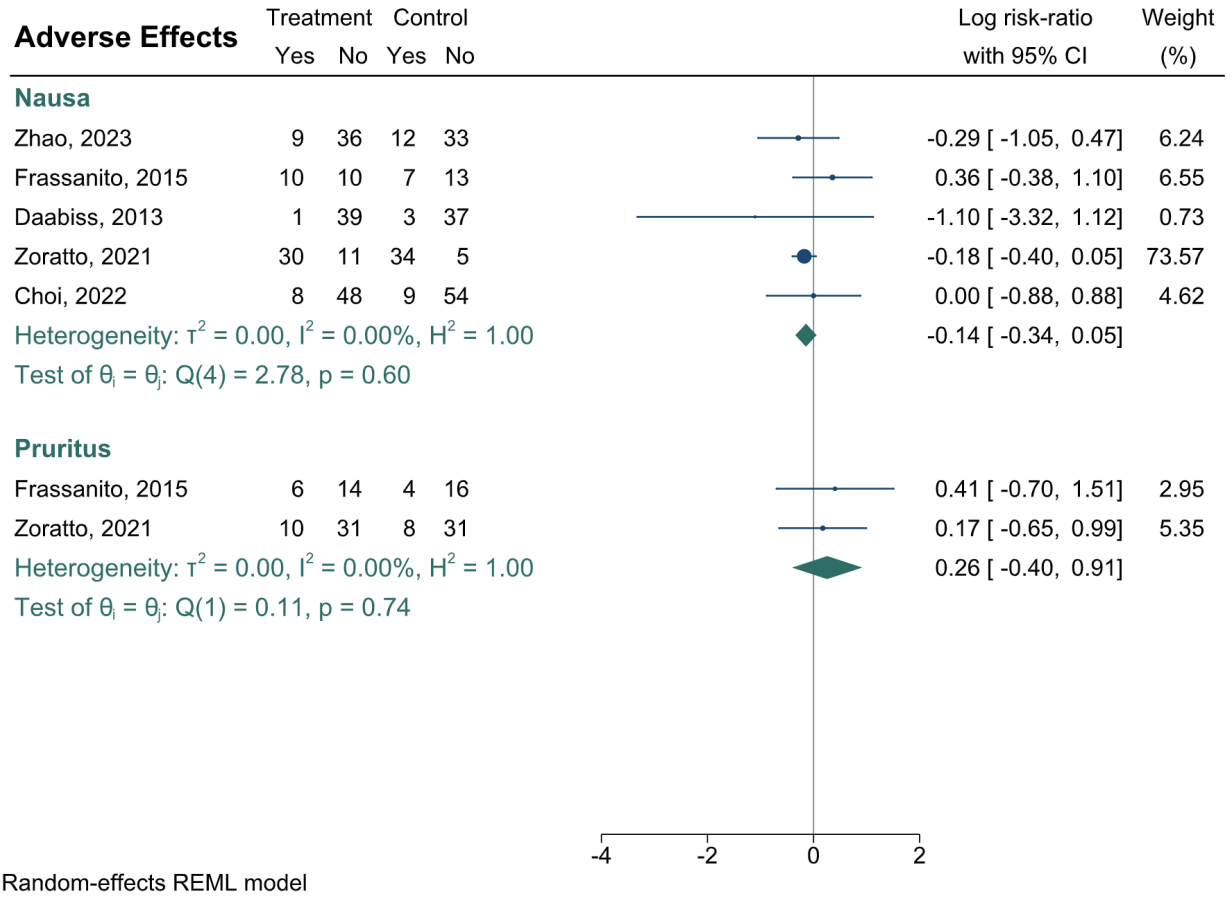


Figure 5: Forest plot for adverse effects reported in the included studies. This figure presents the risk ratio analysis for the occurrence of nausea and pruritus.CI: Confidence Interval.

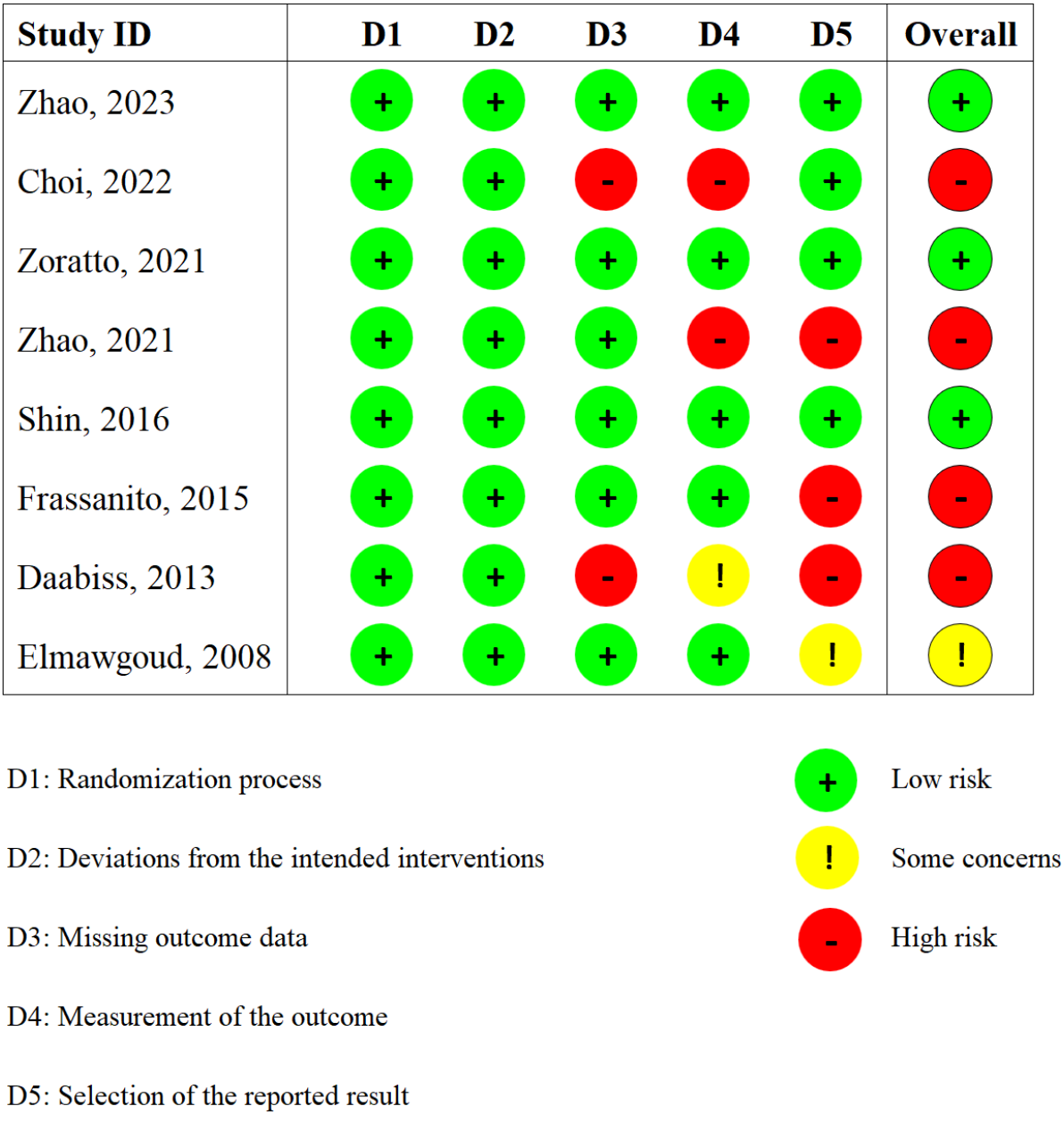
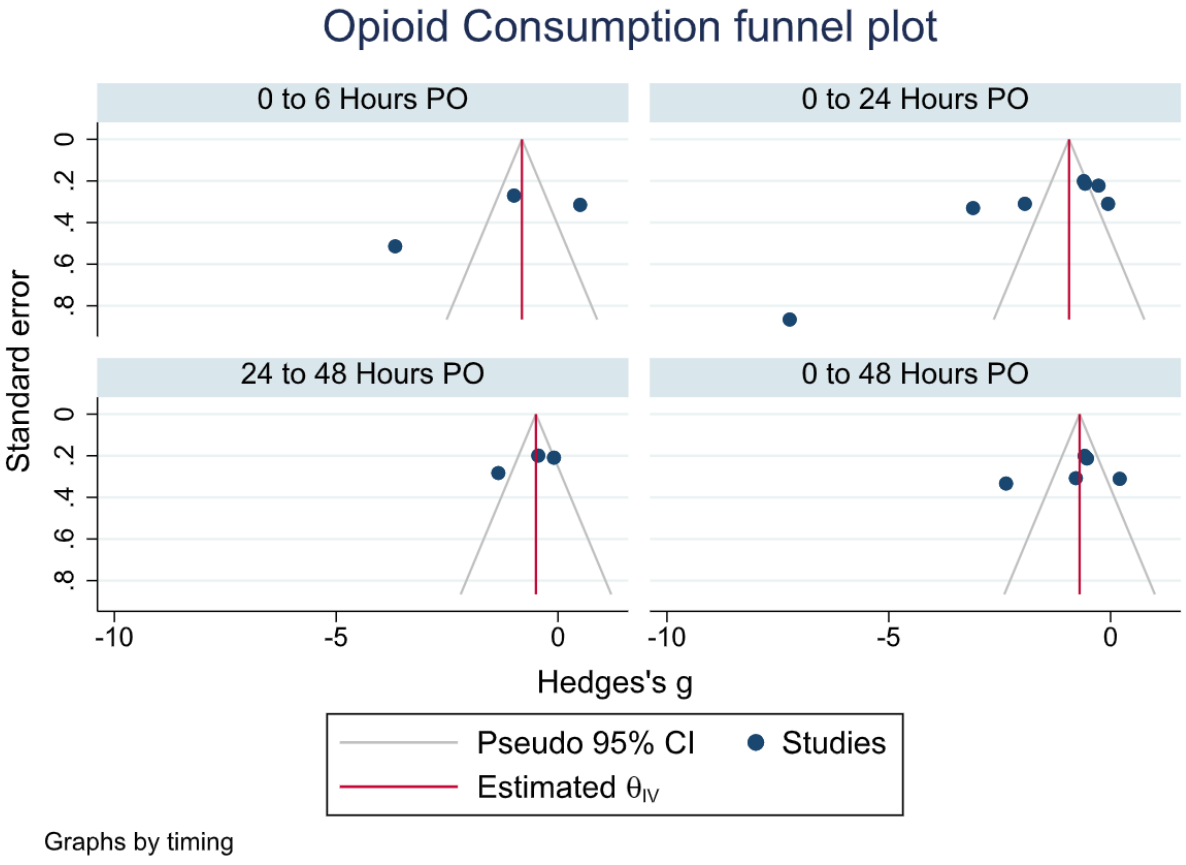


Figure 6: Risk of bias assessment summary using the revised Cochrane Collaboration tool (RoB 2).

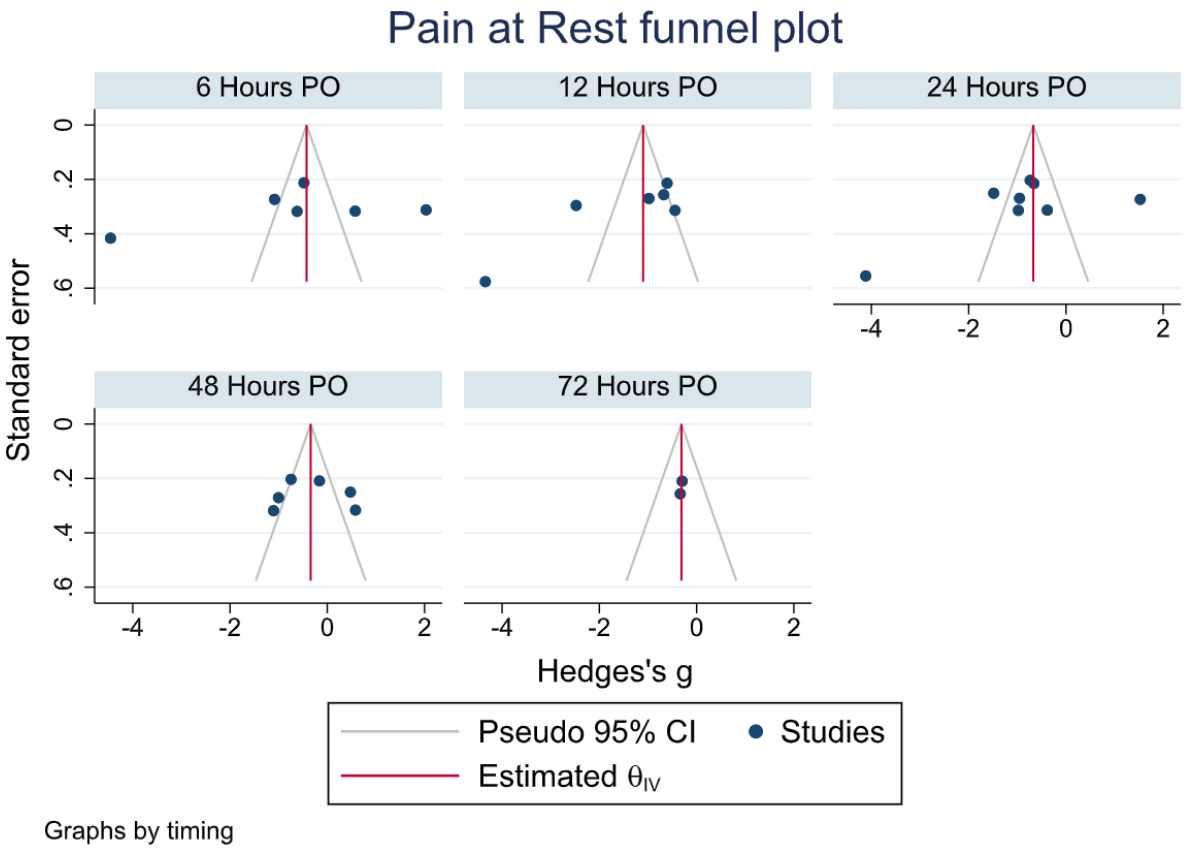


Supplementary figure S 1: Funnel plot for opioid consumption by subgroups. PO: post operation; CI: Confidence Interval.

Supplementary table S 1: Secondary outcomes not included in the quantitative analysis

Outcome	Study ID	Magnesium group	Control group	Reported statistical significance	Magnesium compared to control
Knee ROM					
Degree POD 1	Zhao et al. (2023)	89.0 ± 6.3	87.0 ± 9.0	P-value = 0.465	Not superior
Degree POD 2	Zhao et al. (2023)	95.8 ± 5.1	95.3 ± 7.3	P-value = 0.834	Not superior
Degree POD 3	Zhao et al. (2023)	106.1 ± 5.0	104.7 ± 7.2	P-value = 0.258	Not superior
Degree 3 months	Zhao et al. (2023)	117.9 ± 4.8	115.7 ± 6.2	P-value = 0.099	Not superior
Length of hospital stay					
Hours	Zhao et al. (2023)	68.4 ± 3.2	69.4 ± 3.0	P-value = 0.160	Not superior
Days	Zoratto et al. (2021)	2.2 [2.0–3.1]	2.1 [1.9–3.9]	P-value = 0.550	Not superior
Satisfaction with pain control					
Categorical (Excellent)	Zoratto et al. (2021)	13 (38)	12 (38)	P-value = 0.320	Not superior
Likert scale	Choi et al. (2022)	8.8 ±2.0	8.7 ±1.8	P-value = 0.837	Not superior
Likert scale	Frassanito et al. (2015)	8.9±0.1	8.8±0.2	P-value = 0.060	Not superior

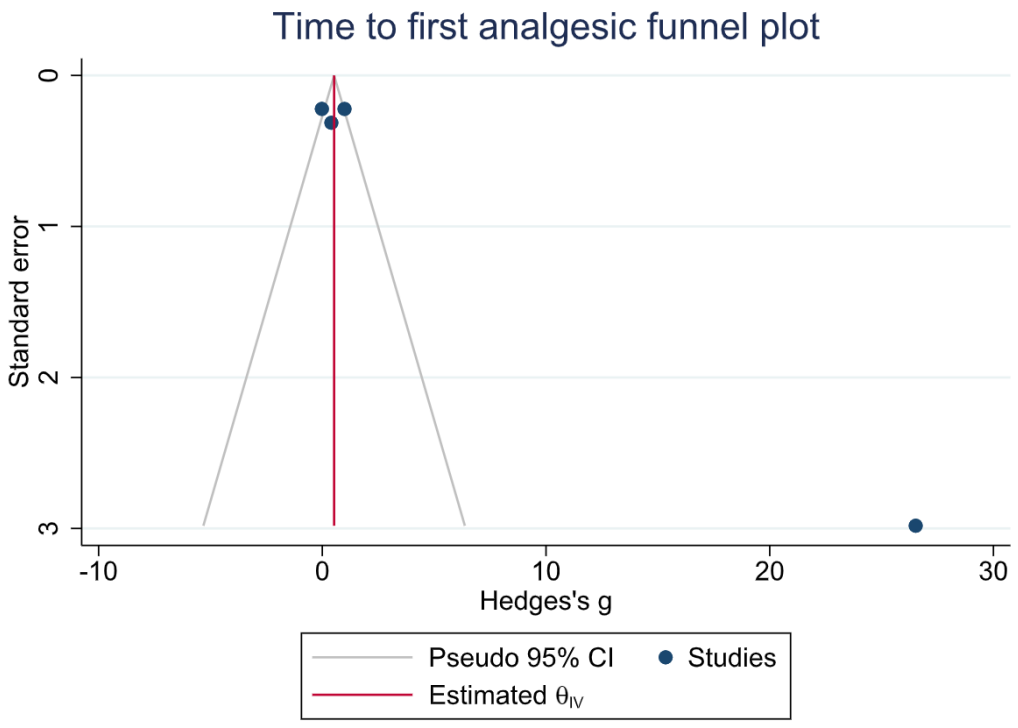
POD: post-operative day; ROM: range of motion.



Supplementary figure S 2: Funnel plot for postoperative pain by subgroups. PO: post operation; CI: Confidence Interval.

Supplementary table S 2: Quality of the evidence assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) scoring system

Outcome of interest	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	Quality of the evidence (GRADE)
Opioid Consumption	Serious limitations	No serious limitations	Serious limitations	No serious limitations	No serious limitations	• • ○ ○ low
Postoperative Pain	Serious limitations	No serious limitations	Serious limitations	No serious limitations	No serious limitations	• • ○ ○ low
Time to first analgesic	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	• • • ○ Moderate
Adverse Effects	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	• • • ○ Moderate



Supplementary figure S 3: Funnel plot for time to first rescue analgesic. CI: Confidence Interval.

Supplements 1: Search strategy

Medline (via PubMed)
1. "Arthroplasty, Replacement, Knee"[mh] OR "Hemiarthroplasty"[mh] OR "knee arthroplasties"[tiab] OR "knee arthroplasty"[tiab] OR "knee reconstruction"[tiab] OR "knee joint replacement"[tiab] OR "knee surgery"[tiab] OR "knee surgeries"[tiab] OR "knee replacement"[tiab] OR "knee replacements"[tiab] OR "total knee arthroplasty"[tiab]
2. "Magnesium"[mh] OR "Magnesium Sulfate"[mh] OR "Magnesium Compounds"[mh] OR "Magnesium Chloride"[mh] OR "Magnesium Hydroxide"[mh] OR "Magnesium"[tiab] OR "Magnesium Sulfate"[tiab] OR "MgSO4"[tiab] OR "Magnesium Compounds"[tiab] OR "Magnesium Chloride"[tiab] OR "MgCl2"[tiab] OR "Magnesium Hydroxide"[tiab] OR "Mg(OH)4"[tiab]
3. #1 AND #2

Embase:
1. 'knee surgery'/exp OR 'knee arthroplasty'/exp OR 'knee replacement'/exp OR 'total knee arthroplasty'/exp OR 'knee arthroplasty':ab,ti OR 'knee reconstruction':ab,ti OR 'knee joint replacement':ab,ti OR 'knee surgery':ab,ti OR 'knee surgeries':ab,ti OR 'knee replacement':ab,ti OR 'knee replacements':ab,ti OR 'total knee arthroplasty':ab,ti
2. 'Magnesium'/exp OR 'Magnesium Sulfate'/exp OR 'Magnesium Chloride'/exp OR 'Magnesium':ab,ti OR 'Magnesium Sulfate':ab,ti OR 'MgSO4':ab,ti OR 'Magnesium Compounds':ab,ti OR 'Magnesium Chloride':ab,ti OR 'MgCl2':ab,ti OR 'Magnesium Hydroxide':ab,ti OR 'Mg(OH)4':ab,ti
3. #1 AND #2

Scopus:
1. TITLE-ABS-KEY("knee arthroplasties" OR "knee arthroplasty" OR "knee reconstruction" OR "knee joint replacement" OR "knee surgery" OR "knee surgeries" OR "knee replacement" OR "knee replacements" OR "total knee arthroplasty")
2. TITLE-ABS-KEY("Magnesium" OR "Magnesium Sulfate" OR "MgSO4" OR "Magnesium Compounds" OR "Magnesium Chloride" OR "MgCl2" OR "Magnesium Hydroxide" OR "Mg(OH)4")
3. #1 AND #2

Web of Science (WOS):
1. TS=("knee arthroplasties" OR "knee arthroplasty" OR "knee reconstruction" OR "knee joint replacement" OR "knee surgery" OR "knee surgeries" OR "knee replacement" OR "knee replacements" OR "total knee arthroplasty")
2. TS=("Magnesium" OR "Magnesium Sulfate" OR "MgSO4" OR "Magnesium Compounds" OR "Magnesium Chloride" OR "MgCl2" OR "Magnesium Hydroxide" OR "Mg(OH)4")
3. #1 AND #2