# Intra-articular Magnesium to Alleviate Postoperative Pain After Arthroscopic Knee Surgery: A Meta-analysis of Randomized Controlled Trials

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# Abstract

**Objective:** We evaluated the safety and efficacy of intra-articular (IA) magnesium (Mg) for postoperative pain relief after arthroscopic knee surgery.

**Methods.** We searched PubMed, Embase, Medline, Cochrane library, and Web of Science to identify randomized controlled trials that compared postoperative pain outcomes with or without IA Mg after knee arthroscopy. The primary outcomes were pain intensity at rest and with movement at different postoperative time points and cumulative opioid consumption within 24 hours after surgery. Secondary outcomes included the time to first analgesic request and side effects.

**Results.** In total, 11 randomized controlled trials involving 677 subjects met the eligibility criteria. Pain scores at rest and with movement 2, 4, 12, and 24 h after surgery were significantly lower, doses of supplementary opioid consumption were smaller, and the time to first analgesic requirement was longer in the IA Mg group compared with the control group. No significant difference was detected regarding adverse reactions between the groups.

**Conclusions.** Administering IA Mg following arthroscopic knee surgery is effective for relieving postoperative pain intensity, reducing opioid consumption, and prolonging the time before analgesics are needed without increasing adverse reactions.

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# Introduction

Arthroscopic knee surgery is an established orthopedic procedure that is performed for diagnostic and therapeutic purposes for intra-articular lesions. It has replaced classic arthrotomy in many cases due to its smaller surgical incision, fewer complications, and faster recovery. However, this procedure is sometimes associated with moderate to acute postoperative pain, which may hinder early mobilization and rehabilitation, and prolong hospital stays; all of which affect patient satisfaction. Therefore, it is essential to strengthen postoperative pain management and enhance convalescence after surgery.

Currently, various strategies have been introduced for the early postoperative pain management after arthroscopic knee surgery, including oral opioid analgesics, intravenous patient-controlled analgesia, and peripheral nerve blocks [1]. Neuraxial blocks such as spinal or epidural analgesia are no longer the first choice for fast-track arthroscopic surgery because of their various side effects, including headache, epidural hematoma, urinary retention, and prolonged motor block. Recent studies have recommended intraarticular (IA) drug administration for pain control due to their ability to directly block nociceptive stimuli at the local site, with less systemic absorption [2, 3]. Commonly used IA drugs in clinical practice include opioids (morphine, pethidine, fentanyl, and sufentanil), corticosteroids, clonidine, ketorolac, and local anesthetics (bupivacaine, levobupivacaine, lignocaine, lignocaine, and ketamine) [4–8]. A relatively new approach is the use of IA magnesium (Mg), which recently has been studied extensively.

Mg plays an important role in maintaining organismal homeostasis and it is also a crucial element for cellular signal transduction [9]. Animal studies have demonstrated that Mg can alter the duration and perception of pain as it antagonizes N-methyl-d-aspartate (NMDA) receptors [10]. NMDA receptors not only participate in central sensitization, modulation, and nociceptive transmission of acute pain [11], but also correlate with the peripheral sensory transmission of noxious signals. In addition to their central location, NMDA receptors are also located within peripheral skin [12], muscles [13], and the knee joint [14], where they contribute to human pain after activation [13]. At resting states without stimulus, NMDA receptors are blocked by the presence of Mg ions. Upon receiving afferent activities, nociceptor fibers dislodge Mg ions from the NMDA receptor, activating nociceptors to produce pain.

Clinically, the identified routes of Mg administration for postoperative pain control include intrathecal, epidural, systemic, and topical use, which result in different effects [15–17]. Among these routes, the IA route is likely to be more acceptable for patients due to its intrinsic safety and minimal side effects. Although a large number of clinical studies have been performed to determine the effects of IA Mg administration on postoperative pain outcomes, the findings remain controversial [18–20].

Therefore, the major objective of this quantitative meta-analysis of randomized controlled trials (RCTs) was to investigate the effect of IA Mg on acute pain management outcomes after arthroscopic knee surgery. A secondary aim was to evaluate possible side effects related to the administration of IA Mg.

## Methods

We performed this meta-analysis in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [21].

# Literature Search

Published RCTs that evaluated the effects of IA Mg on postoperative pain management after arthroscopic knee surgeries were searched in the PubMed, Medline, Embase, Web of Science, and Cochrane library electronic databases inclusive until September 30, 2019. The words and MESH terms "Intra-Articular", "Magnesium", "Arthroscopy", "Postoperative", and “Pain” were searched individually and in different combinations. A manual search of references from eligible and relevant studies was performed to find additional trials. No restrictions were imposed regarding language or publication status.

# Inclusion and Exclusion Criteria

Eligible studies were required to meet the following inclusion criteria: (1) RCTs; (2) patients undergoing arthroscopic knee surgery; (3) administration of Mg through the IA route; (4) including an experimental group of IA Mg or IA Mg plus a local anesthetic; and (5) including a control group of saline or local

anesthetic alone. The exclusion criteria were: (1) non-RCTs; (2) reviews, letters, abstracts, case series, or editorials; (3) the administration of Mg not through the IA route; and (4) studies with insufficient data.

# Study Selection

Two authors (Lijun Shi and Jinhui Ma) independently assessed the initial search results to exclude irrelevant trials and identify eligible studies according to the inclusion and exclusion criteria by screening titles and abstracts. Full-texts of any potentially useful studies were reviewed. Any discrepancies were resolved by consulting with a third author (Wei Sun).

# Data Abstraction

Two authors (Lili Shi and Tengqi Li) independently evaluated the included studies and extracted trial details using special data collection forms developed for this investigation. Disagreements were resolved by consensus or consultation with a third author.

We first extracted data from tables or text. For data not reported numerically, we extracted them from available figures using the software GetData (http://getdata-graph-digitizer.com/index.php). Continuous data were reported using means and standard deviations (SD), and data presented in terms of the median and range were converted to means and SD [22]. For trials that involved more than one experimental group in comparison with a single control group, the relevant comparisons to the comparator were split for primary analysis.

The data extracted from trials included the first author, year of publication, sample size, patient baseline characteristics, type of surgery, type of anesthesia, IA Mg dose, pain scores at rest and with movement (postoperative 2, 4, 12 and 24 h), cumulative opioid consumption, time to first rescue analgesic request (min), and adverse events. The pain intensity was measured using the 10-point visual analogue scale (VAS), where 0 means no pain and 10 means the most severe pain. The numerical rating scale (NRS) of pain was converted to a VAS score. Postoperative opioid consumption within 24 h was converted to the equivalent dosage of intravenous (IV) morphine [23].

The primary outcomes of interest were the pain VAS scores at rest and with movement at different postoperative time points and total opioid consumption (IV morphine equivalent, mg) in the first 24-h postoperative period. The secondary outcomes included the time to first analgesic requirement (min) and the incidence of side effects.

# Assessments of the Risk of Bias and Methodological Quality

Two senior authors (Fuqiang Gao and Wei Sun) independently evaluated the methodological quality of the included studies using the Cochrane Collaboration's Risk of bias tool [24], which contains seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias was defined as high, low, and unclear. Disagreements were resolved by discussion.

The quality of evidence for each outcome was judged with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [25], which consists of five items: study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. This methodology categorizes the strength of evidence as high, moderate, low, or very low, and each of these items may be used to define the quality level. This process was conducted using Grade Profiler software (GRADEpro version 3.6).

# Statistical Analysis

All statistical analyses were conducted using Review Manager software (RevMan version 5.3). Continuous variables are reported as mean differences (MD) with 99% confidence intervals (CIs). As the incidence of adverse events was very low, only qualitative analysis and description was performed. Statistical heterogeneity was measured and reported as $I^2$, which describes the percentage of the total variability caused by heterogeneity rather than by chance. The $I^2$ values ranged between 0% and 100%, where values above 50% and 75% represent substantial and considerable heterogeneity, respectively. If the heterogeneity was significant ($p < 0.05$, $I^2 > 50\%$), the random-effects model was used. Otherwise, the fixed effects model was adopted ($p > 0.05$, $I^2 < 50\%$). Sensitivity analysis was further performed by removing one trial at a time to explore possible explanations for heterogeneity and to identify the influence of a single RCT on the overall mean differences.

## Results

# Search Results and Selected Articles

The initial literature search retrieved 72 citations, among which 17 were excluded due to duplication. After screening the titles and abstracts, 36 citations were excluded based on the inclusion criteria, while eight studies were subsequently excluded after reading the full-text. Eventually, 11 RCTs [26-36] met the inclusion criteria and were qualified for this meta-analysis (Fig. 1).

The characteristics of the included trials are presented in Table 1. These 11 studies were published between 2006 and 2018, and a total of 677 patients were included, with individual sample sizes ranging from 18 to 51. Five studies compared IA Mg versus saline or bupivacaine alone [26, 28, 30, 31, 34], five

studies compared IA Mg plus bupivacaine versus bupivacaine [27, 29, 32, 33, 36], while one study contained these two kinds of comparisons [35], and both were included.

Table 1

Characteristics of the included 11 randomized controlled trials

| Author, year | Country | Groups (n) | Interventions | Age (y), %Males | Type of arthroscopy | Anesthesia | Main outcomes |
|---|---|---|---|---|---|---|---|
| Sadoni, 2017 | Iran | Mg: 51 | Mg 1 g + saline to 20 ml | 30.6 ± 7.6, 82.3% | Meniscectomy | General | VAS, AC, AD |
| | | P: 43 | Saline 20 ml | 29.9 ± 9.5, 79.0% | | | |
| Devi, 2018 | India | Mg + B: 18 | Mg 10 mg/kg + 0.25% B to 20 ml | 33.44 ± 10.87, 72.2% | Arthroscopy | Spinal | VAS, AC |
| | | B: 18 | 0.25% B 20 ml | 37.22 ± 13.36, 55.5% | | | |
| Abdulatif, 2015 | Egypt | Mg: 28 | Mg 1 g + saline to 20 ml | 34.6 ± 9.3, 60.7% | ACL reconstruction | FNB + General | VAS, AC, AD, SE |
| | | P: 27 | Saline 20 ml | 35.0 ± 10.4, 74.0% | | | |
| FAROUK, 2009 | Egypt | Mg + B: 20 | Mg 0.15 g + 0.25% B to 20 ml | 36 ± 6, 90% | Meniscectomy | General | VAS, AC, AD |
| | | B: 20 | 0.25% B 20 ml | 35 ± 7, 80% | | | |
| Radwan, 2012 | Egypt | Mg: 20 | Mg 0.8 g + saline to 20 ml | 31.10 ± 7.90, 85% | Meniscectomy | General | VAS, AC, AD, SE |
| | | B: 20 | 0.5% B 20 ml | 32.20 ± 9.62, 90% | | | |
| Koltka, 2011 | Turkey | Mg: 30 | Mg 0.5 g + saline to 20 ml | 48.4 ± 11, 30% | Meniscectomy | General | NRS, AC, AD |
| | | P: 30 | Saline 20 ml | 46.0 ± 15.6, 36.6% | | | |
| Suhrita, 2009 | Kolkata | Mg + B: 30 | Mg 0.5 g+ 0.25% B to 20 ml | 37.9 ± 11.8, 36.6% | Meniscectomy, Ligament repair | General | VAS, AC, AD, SE |
| | | B: 30 | 0.25% B + saline to 20 ml | 36.8 ± 10.6, 70% | | | |
| Kizilcik, 2017 | Turkey | Mg + LB: 32 | Mg 1.5 g + LB 50 mg to 15 ml | 43.06 ± 13.19, 68.7% | Meniscectomy | General | VAS, AC, SE |
| | | LB: 32 | LB 100 mg 10 ml | 40.06 ± 9.24, 75% | | | |
| Bondok, 2006 | Egypt | Mg: 30 | Mg 0.5 g + saline to 10 ml | 27 ± 4, 100% | Meniscectomy | General | VAS, AC, AD |
| | | P: 30 | Saline 10 ml | 25 ± 4, 100% | | | |
| Elsharnouby, 2008 | Egypt | Mg: 27<br>P: 27 | Mg 1 g + saline to 20 ml<br>Saline 20 ml | 39 ± 12, 11.1%<br>41 ± 13, 14.8% | Meniscectomy | General | VAS, AC, AD |
| | | Mg + B: 27<br>B: 27 | Mg 1 g + 0.25% B to 20 ml<br>0.25% B 20 ml | 40 ± 11, 3.7%<br>45 ± 9, 7.4% | | | |
| Venkateshamurthy, 2018 | India | Mg + B: 30 | Mg 1 g + 0.25% B to 30 ml | Un | Arthroscopy | General | VAS, AC, AD |
| | | B: 30 | 0.5% B + saline to 30 ml | | | | |

Mg = magnesium sulfate; B = bupivacaine; LB = levobupivacaine; ACL = anterior cruciate ligament; Un = unknown; FNB = femoral nerve block; VAS = visual analogue scale score; NRS = numeric rating scale; AC = analgesic consumption; AD = analgesic consumption duration; SE = side effects

# Study Quality and GRADE of Evidence

Figure 2 illustrates the risk of bias assessment. Among the 11 included studies, two [28, 29] did not describe their random sequence generation (high risk of selection bias) and four [26, 29, 32, 33] did not design a clear allocation concealment plan (unclear or high risk of selection bias). All trials adopted the double-blind method, except one [31], which adopted a single-blind method (high risk of performance

bias). The GRADE level of evidence for each RCT is shown in Table 2, and the quality was mostly high or moderate.

Table 2

The GRADE evidence quality for each outcome

| Outcome | Included Studies | Total Participants (Mg/ Control) | MD (95% CI) | Heterogeneity | Quality of Evidence (GRADE) |
|---|---|---|---|---|---|
| VAS at rest | | | | | |
| at 2h | 8 | 212/211 | -0.74 (-0.84, -0.64) | $I^2 = 0\%$, P = 0.51 | LOW |
| at 4h | 6 | 152/151 | -0.24 (-0.37, -0.11) | $I^2 = 45\%$, P = 0.11 | MODERATE [d] |
| at 12h | 6 | 152/152 | -0.53 (-0.64, -0.41) | $I^2 = 47\%$, P = 0.10 | HIGH |
| at 24h | 7 | 186/186 | -0.33 (-0.42, -0.24) | $I^2 = 30\%$, P = 0.20 | HIGH |
| VAS with movement | | | | | |
| at 2h | 7 | 140/139 | -0.46 (-0.64, -0.27) | $I^2 = 39\%$, P = 0.14 | HIGH |
| at 4h | 6 | 150/149 | -0.85 (-1.40, -0.30) | $I^2 = 95\%$, P < 0.00001 | MODERATE [b] |
| at 12h | 6 | 150/149 | -0.83 (-1.17, -0.48) | $I^2 = 71\%$, P = 0.004 | MODERATE [c] |
| at 24h | 7 | 170/169 | -0.58 (-0.79, -0.36) | $I^2 = 45\%$, P = 0.09 | HIGH |
| Anesthetic Consumption | 8 | 229/220 | -4.23 (-4.64, -3.82) | $I^2 = 27\%$, P = 0.21 | HIGH |
| Anesthetic duration | 11 | 311/302 | 329.99 (228.73, 431.24) | $I^2 = 99\%$, P < 0.00001 | LOW [b] |

# (1) GRADE working group grades of evidence:

*High quality:* Further research is very unlikely to change our confidence in the estimate of effect.

*Moderate quality:* Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

*Low quality:* Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

*Very low quality:* Any estimate of effect is very uncertain.

# (2) Explanations:

[a] Study limitation: included trials are quasi design.

[b] Inconsistency of results: large heterogeneity.

[c] Indirectness of evidence: large differences between the interventions in different trials.

[d] Imprecision: small sample size and wide 95%CI.

[e] Reporting bias: positive values showing benefits of the studied intervention.

# Outcomes of the Meta-analysis

# VAS Scores at Rest

Nine studies, including ten trials, evaluated the effects of IA Mg on pain relief at rest. The combined results demonstrated significantly lower pain scores at postoperative 2 h (MD = −0.74, 95% CI: −0.84–−0.64; p = 0.51; $I^2$ = 0%), 4 h (MD = −0.24, 95% CI: −0.37–−0.11; p = 0.11; $I^2$ = 45%), 12 h (MD = −0.53, 95% CI: −0.64–−0.41; p = 0.10; $I^2$ = 47%), and 24 h (MD = −0.33, 95% CI: −0.42–−0.24; p = 0.20; $I^2$ = 30%) in patients who received IA Mg alone or IA Mg plus local bupivacaine compared with placebo or bupivacaine alone after arthroscopic knee surgery (Table 2, Figure 3). The heterogeneity test showed that the heterogeneity was acceptable, hence a fixed-effects model was used, and further sensitivity analysis was not performed.

# VAS Scores with Movement

Seven trials evaluated the effects of IA Mg on pain intensity with movement. Similarly, the pain scores with movement were also lower in patients who received IA Mg administration alone or plus local bupivacaine compared with the controls at postoperative 2 h (MD = −0.46, 95% CI: −0.64–−0.27; p = 0.14; $I^2$ = 39%), 4 h (MD = −0.85, 95% CI: −1.40–−0.30; p < 0.0001; $I^2$ = 95%), 12 h (MD = −0.83, 95% CI: −1.17–−0.48; p = 0.004; $I^2$ = 71%), and 24 h (MD = −0.58, 95% CI: −0.79–−0.36; p = 0.05; $I^2$ = 45%) (Table 2, Figure 4). Regarding the pain scores at postoperative 4 h, sensitivity analysis demonstrated that removal of the study Kemalettin *et al.* [31] significantly changed the results (MD = −0.51, 95% CI: −0.62–−0.39; p = 0.45; $I^2$ = 0%). In this RCT, postoperative analgesia was maintained by IV tramadol during the first 4 h after surgery. Meanwhile, sensitivity analyses after excluding one trial at a time still showed a substantial heterogeneity in the pain outcomes at postoperative 12 h.

# Postoperative Opioid Consumption

Eight eligible trials assessed the effect of IA Mg on postoperative opioid consumption (IV morphine equivalent). Within postoperative 24 h, opioid consumption was significantly decreased in patients who received IA Mg alone or in combination with bupivacaine compared with the control group (MD = −4.23, 95% CI: −4.64–−3.82; p = 0.21; $I^2$ = 27%) (Table 2, Figure 5). No statistical heterogeneity was observed, and a fixed-effects model was used.

# Time to First Analgesic Request (Min)

Eleven trials evaluated the effects of IA Mg on the time to first analgesic request after surgery. The administration of IA Mg alone or with bupivacaine resulted in a statistically significant prolonging of the time to analgesic requirement compared with control (MD = 329.99, 95% CI: 228.73–431.24; P < 0.00001; $I^2$ = 99%) (Table 2, Figure 6). The heterogeneity was considerable; however, further sensitivity analysis did not change the heterogeneity when any of the studies were removed.

# Safety Analysis

Only three included RCTs reported adverse reactions. In the study by Abdulatif *et al.* [28], postoperative shivering was observed in 12 and 10 patients in the IA Mg administration (n = 28) and control (n = 27) groups, respectively. In the RCT conducted by Radwan *et al.* [30], one patient in both the IA Mg (n = 20) and placebo (n = 20) groups developed knee effusion. In the study conducted by Suhrita *et al.* [32], two patients developed hypotension and bradycardia in the IA Mg group (n = 30), while no side effects were observed in the placebo group (n = 30). There was no statistically significant difference between the comparable groups in each RCT.

# Discussion

This meta-analysis was performed on a total of 11 RCTs. The chief finding was that IA Mg, whether used alone or with bupivacaine, had a positive effect on pain relief after arthroscopic knee surgery. IA Mg led to reduced pain intensity at rest or with movement within the 24-h postoperative timeframe.

In this meta-analysis, the effects of IA Mg on postoperative VAS pain scores at rest were not so large, but clinically significant with a weighted MD up to − 0.74 (99% CI: −0.84–−0.64) at postoperative 2 h after surgery. The effect of IA Mg on pain relief with movement was also significant, especially at postoperative 12 h, with a weighted MD up to − 0.83 (99% CI: −1.17–−0.48). Additionally, the overall effects of IA Mg on reducing postoperative opioid consumption were consistently large; morphine IV equivalents were 4.23 mg lower in patients who received IA Mg compared with the control group. Currently, IA Mg is not considered a standard strategy for postoperative pain control. However, the findings of this meta-analysis based on 11 clinical RCTs provide evidence that IA Mg is useful for pain relief after arthroscopic knee surgery.

Mg has been used widely for many indications, including headache [37], eclampsia [38], and acute migraine attacks [39]. As to the analgesic effect, Mg does not possess direct analgesic activity, as its function primarily relies on its role as a physiological NMDA receptor antagonists [9]. Nociceptive sensitization of pain stimuli requires calcium for the release of neurotransmitters and other substances. The potential mechanism of the antinociceptive effects of Mg may be that Mg blocks the calcium channel in a voltage-dependent way. Mg can produce a dramatic reduction of NMDA-induced currents. In the knee joint, NMDA receptors not only are located in the peripheral termini of primary afferent fibers, but

also to cellular elements such as immune cells and synoviocytes [40]. Therefore, it is possible that local Mg administration could provide analgesic effects through an IA route.

Furthermore, studies have also shown that adding Mg to a local anesthetic can reduce toxic effect to articular chondrocytes. This may represent a potential approach for IA analgesia [41]. Besides its analgesic effect, a recent *in vitro* study demonstrated that local Mg administration can also be used for *in situ* meniscal repair due to the potential activity of Mg to recruit endogenous stem cells and promote fibrocartilaginous matrix synthesis [42]. Additionally, animal experiments suggest that Mg deficiency in the extracellular matrix of cartilage may lead to typical joint cartilage lesions [43]. In contrast, high concentrations of IA Mg can significantly inhibit extracellular matrix calcification and protect articular cartilage [44, 45]. Similarly, clinical trials have found that subjects with lower levels of serum Mg had a higher prevalence of knee chondrocalcinosis [46]. Low Mg intake is also associated with increased knee pain in subjects with radiographic knee osteoarthritis [47]. Serum Mg concentration may have an inverse relationship with radiographic osteoarthritis of the knee [48].

Although three trials reported adverse reactions in this meta-analysis, including postoperative shivering, knee effusion, hypotension, and bradycardia, there were no statistically significant differences between comparable groups in each RCT. Postoperative shivering is a common manifestation after anesthesia, which can lead to perioperative ischemia [49]. However, Gildasio *et al.* reported that perioperative systemic Mg can reduce the incidence rates of postoperative shivering [50]. Another concern is the increased risk of infection, as previous studies have shown that preoperative IA injections increase the risk of infection after total knee arthroplasty [51], especially corticosteroid or hyaluronic acid injection within 3 months of total knee arthroplasty [52]. The potential etiologies include directed inoculation and immunosuppression caused by the medications themselves, of which corticosteroids are well-known immunosuppressants, and hyaluronic acid may reduce immunity *via* changing the production of immunomodulating factors, which leads to decreased immune responses following total knee arthroplasty [52]. However, different from IA injection prior to total knee arthroplasty, IA Mg injection during knee arthroscopy is much safer due to its simplicity, short operative time, and rigid aseptic technique. More importantly, IA injections of Mg can attenuate osteoarthritis progression and suppress synovial inflammation [53]. Moreover, no relevant joint infections have been reported in clinical trials.

The limitations of this study should also be acknowledged. First, only 11 studies containing 12 trials met the inclusion criteria, and the sample size was relatively small in each trial. Second, the heterogeneity was high for some outcomes, which could affect the results. After careful analysis, we found that the different types of surgery, anesthesia, IA drugs, and data recording methods may all account for the heterogeneity. Finally, the dosages of IA Mg were different with a large range in each group. It is difficult to determine the optimal dosage to truly evaluate the safety of IA Mg administration.

# Conclusions

Our results suggested that IA Mg can reduce the postoperative pain intensity after arthroscopic knee surgery without increasing adverse reactions. Additionally, administration of IA Mg can reduce postoperative analgesic consumption and prolong the time to first analgesic request. Thus, IA Mg administration should be considered as a strategy for minimizing postoperative pain intensity in patients undergoing arthroscopic knee procedures.

## Abbreviations

IA: Intra-Articular; Mg: Magnesium; NMDA: N-methyl-d-aspartate; VAS: Visual Analogue Scale; NRS: Numerical Rating Scale; IV: Intravenous; RCT: Randomized Controlled Trial; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; GRADE: Grading of Recommendations Assessment, Development and Evaluation; SD: Standard Deviation; MD: Mean Differences; CI: Confidence Interval; $I^2$: Statistical Heterogeneity; N: Sample Size.

## Declarations

# Ethics approval and consent to participate

Not applicable.

# Consent for publication

Not applicable.

# Availability of data and materials

The datasets generated/analyzed during the current study are available.

# Competing interests

The authors declare that they have no competing interests.

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# Authors' contributions

All authors contributed to the study conception and design. The literature search was performed by Lijun Shi, Haiyun Zhu, and Jinhui Ma. Article selection and data extraction were performed by Lijun Shi and Lili Shi. Assessments of risk of bias and methodological quality were performed by Fuqiang Gao and Wei Sun. The first draft of the manuscript was written by Lijun Shi, Haiyun Zhu and Jinhui Ma assisted with the preparation of the manuscript. All authors read and approved the final manuscript.

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# Figures

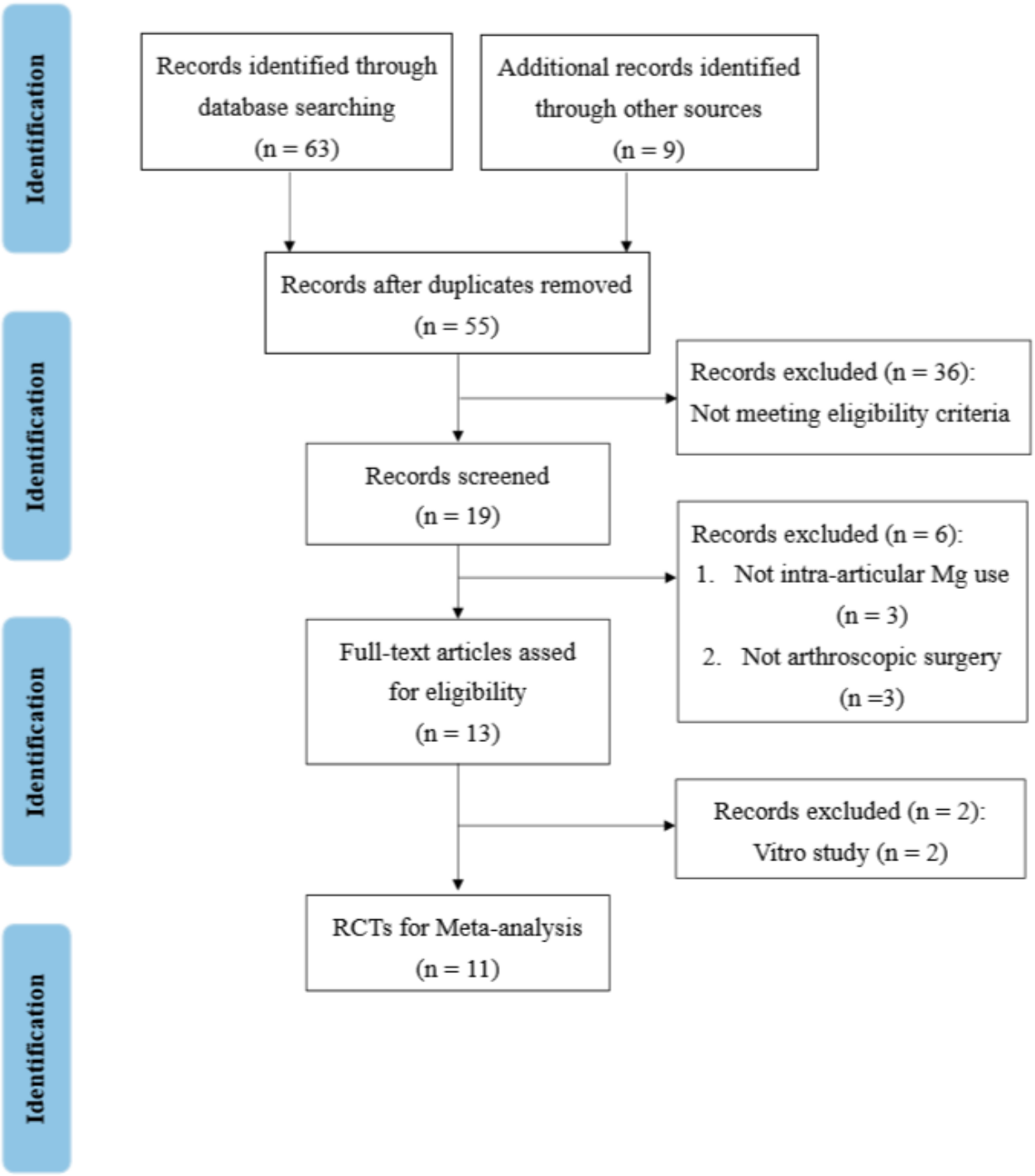
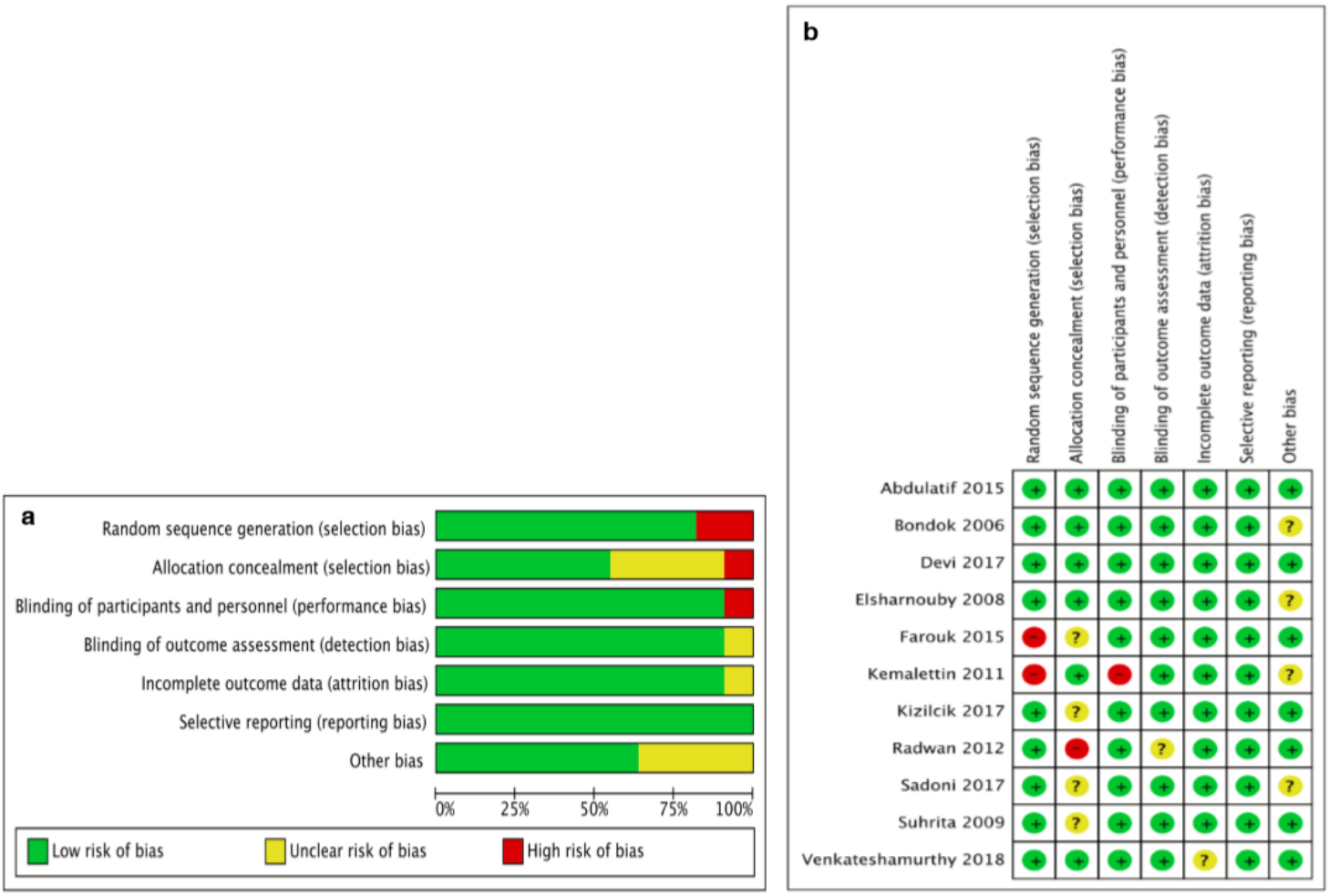


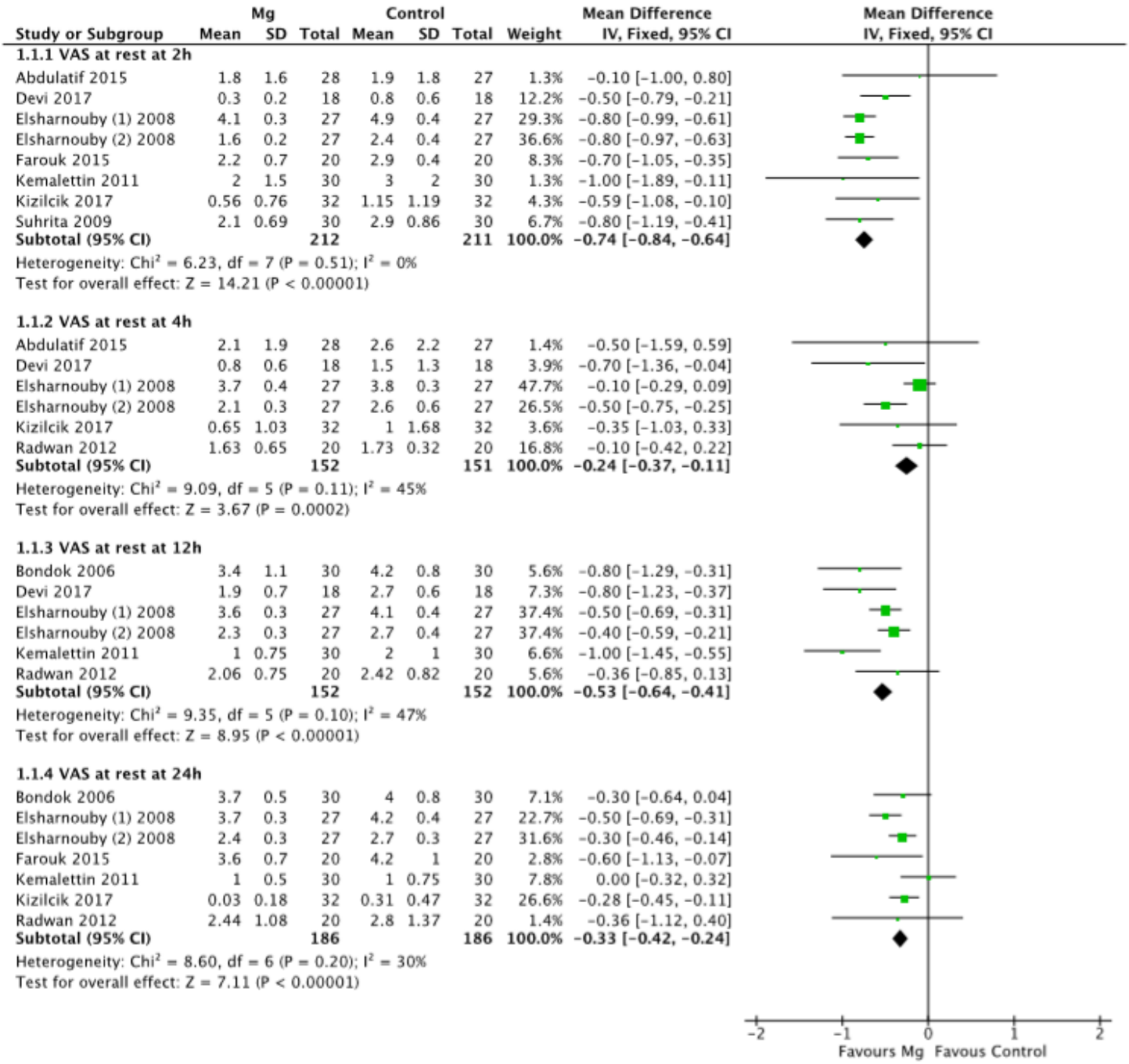

**Figure 1**

Flow chart of the randomized controlled trials selection process.



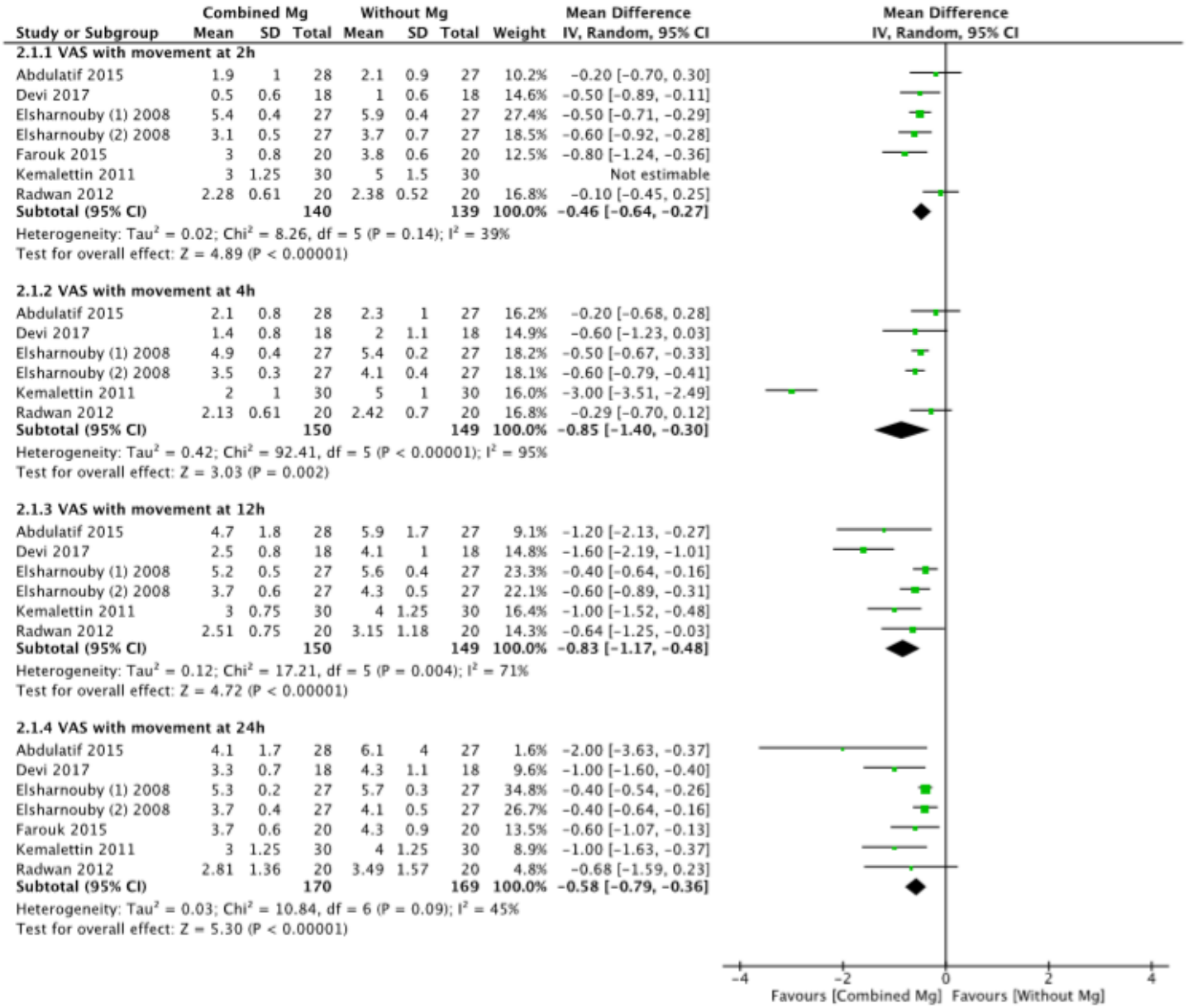

## Figure 2

Risk of bias assessment for the included randomized controlled trials.



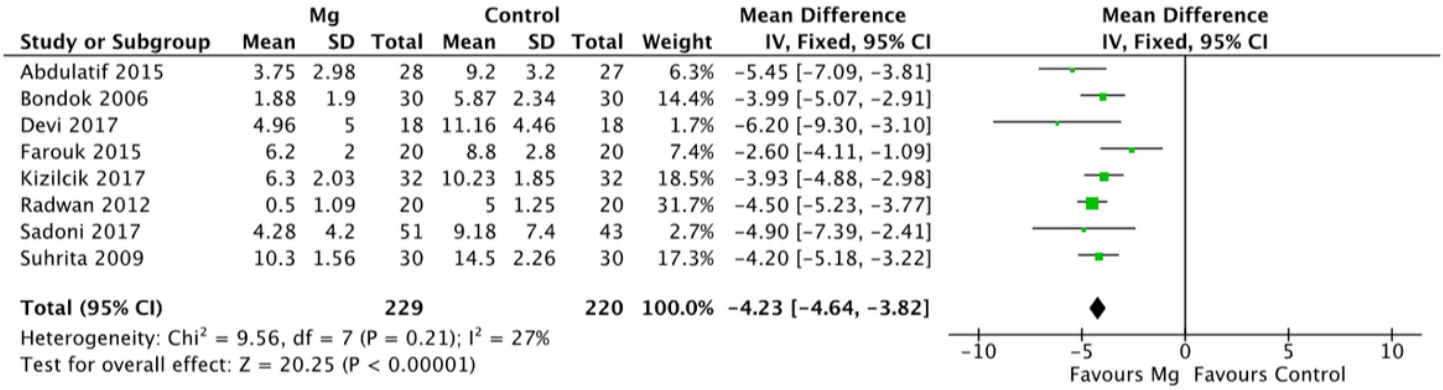

## Figure 3

Forest plots of the meta-analysis that compared VAS scores at rest at postoperative 2, 4, 12, and 24 h.



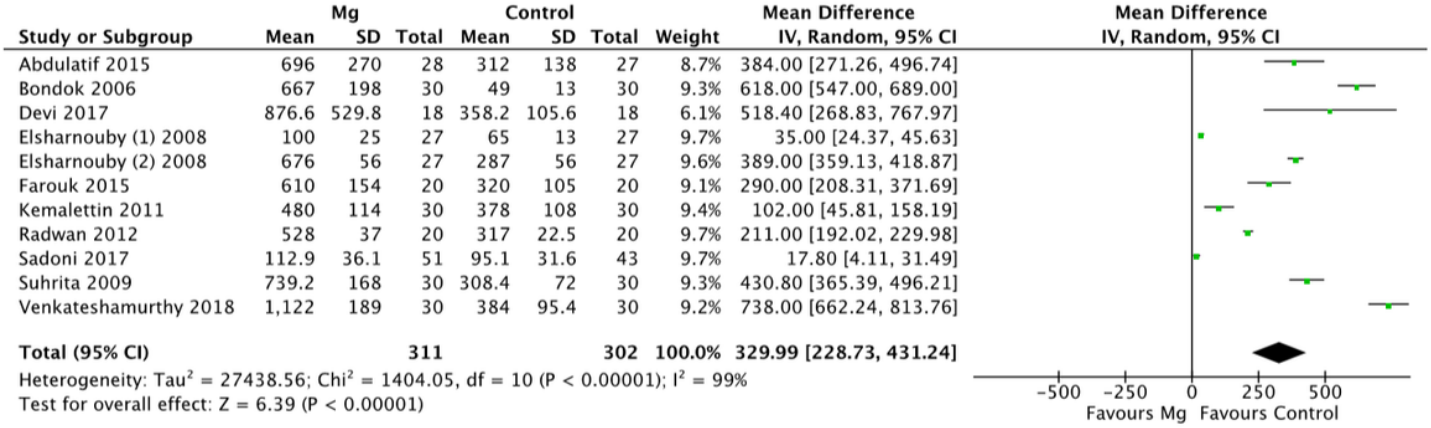

## Figure 4

Forest plots of the meta-analysis that compared VAS scores with movement at postoperative 2, 4, 12, and 24 h.




## Figure 5

Forest plots of the meta-analysis that compared morphine consumption within the 24-h postoperative timeframe.




## Figure 6

Forest plots of the meta-analysis that compared the time to first analgesic request within the 24-h postoperative timeframe.