Impact of intraoperative intravenous magnesium on spine surgery: A systematic review and meta-analysis of randomized controlled trials

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EClinicalMedicine 2022;43: 101246
Published online xxx
https://doi.org/10.1016/j.eclinm.2021.101246

Summary

Background The effectiveness and safety of intraoperative intravenous magnesium (IIM) on spine surgery remain uncertain, as recent randomized controlled trials (RCTs) yielded conflicting results. The purpose of this study was to determine the impact of IIM on spine surgery.

Methods A literature search was performed on multiple electronic databases, ClinicalTrial.gov and Google Scholar on July 12th 2021, and reference lists were examined. We selected RCTs comparing the effects of IIM with placebo treatment on spine surgery. We calculated pooled standard mean difference (SMD) or risk ratio (RR) with 95% confident interval (CI) under a random-effect model. We assessed risk of bias using Cochrane risk-of-bias tool and Jadad score was applied to assess the quality of each included trial. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to determine the confidence in effect estimates. Sensitivity analysis was conducted by omitting each included study one by one from the pooled analysis. PROSPERO Registration: CRD42021266170.

Findings Fourteen trials of 781 participants were included. Low- to moderate-quality evidence suggested that IIM reduces postoperative morphine consumption at 24 h (SMD: -1·61 mg, 95% CI: -2·63 to -0·58) and intraoperative remifentanil requirement (SMD: -2·09 ug/h, 95% CI: -3·38 to -0·81). High-quality evidence suggested that IIM reduces the risk of postoperative nausea and vomiting compared with placebo (RR: 0·43, 95% CI: 0·26 to 0·71). Besides, moderate-quality evidence suggested that recovery orientation time in the IIM group is longer than control group (SMD: 1·13 min, 95% CI: 0·83 to 1·43).

Interpretation IIM as adjuvant analgesics showed overall benefits on spine surgery in terms of reducing analgesic requirement and postoperative nausea and vomiting; however, potential risks of IIM, such as delayed anesthetic awakening, should not be ignored. Future evidence will inform the optimal strategy of IIM administration for patients undergoing spine surgery.

Funding This study was funded by Beijing Municipal Natural Science Foundation (Grant No :7212117).

Keywords: Spine surgery; Magnesium; Anesthesia; Analgesics

Introduction

N-methyl-D-aspartate (NMDA) receptor is the key to the induction and maintenance of central sensitization during pain states.[1] Magnesium, the fourth most abundant mineral in the body, acts as an important NMDA receptor antagonist, can regulate calcium entry into cells by antagonizing NMDA receptors. The mechanism of analgesic effect of magnesium lies in its prevention of central sensitization and neural hypersensitivity.[2] The first use of magnesium in anesthesia dates back to 1906 for its depressant effect on central nervous system though it was not considered safe for its risk of respiratory and cardiac depression and following cerebral hypoxia.[3,4] It was not until 1996 when researchers started to regain confidence in the perioperative administration of magnesium, as the randomized trial by Tramer et al. reported that magnesium as an adjuvant analgesic significantly reduced pain severity and improved sleep quality after hysterectomy.[5] However,

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previous systematic reviews showed that the overall analgesic benefit of intraoperative intravenous magnesium (IMM) still remained controversial.[6–8]

Spine surgery is often associated with moderate to severe postoperative pain, while adequate pain control after surgery allows for faster recovery, less complications, and improved overall satisfaction.[9] Typically, pain management after spine surgery relies on opioids, which are effective in relieving pain but associated with dose-dependent side effects (e.g., postoperative nausea and vomiting (PONV), respiratory depression and hypotension).[10] In the past two decades, several randomized controlled trials (RCTs) investigating the impact of IIM on spine surgery have emerged. However, it is uncertain whether IIM reduces postoperative morphine requirements, pain intensity, or postsurgical adverse events on patients undergoing spine surgery.[11-13] A synthesis of the literature is therefore in need.

To date, no similar systematic review was found as the International Prospective Registry of Systematic Reviews (PROSPERO) and Cochrane Database of Systematic Reviews. This systematic review and meta-analysis aimed to evaluate the current evidence from randomized controlled trials (RCTs) related to the effectiveness and safety of IIM as adjuvant analgesics in spine surgery. A comprehensive understanding of the current level of evidence in the literature would help clarify the clinical utility of IIM in spine surgery and inspire future research.

Methods

Study design

This systematic review and meta-analysis was developed according to the guidelines for Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) and the Method Guideline for Systematic Reviews in the Cochrane Back and Neck (CBN) Group.[14,15] We prospectively registered this systematic review in the PROSPERO database (Registration number: CRD42021266170).

Criteria for considering studies for this review. We only included published RCTs that administered magnesium intravenously during spine surgery. No language limit was applied. Original trials included were based on PICO structure:[16] (a) population: patients undergoing spine surgery under general anesthesia; (b) intervention: use of IIM, as single bolus injection and/or continuous infusion. Regional approaches (e.g., intramuscular or intraspinal) were not considered as target interventions; (c) comparison: placebo treatment (normal saline) or other comparative treatments of clear contrast for the index intervention; and (d) predefined outcomes: opioids consumption during and after surgery, postsurgical pain intensity, anesthetic recovery time, blood loss, and adverse events (bradycardia, hypotension, PONV, etc.).

Search strategy. A tri-step search strategy was applied.[17] First, a preliminary search was conducted using terms and key words based on knowledge of the field (i.e., "spine" and "magnesium"). Then, search terms were revised according to the results of the first step; and we searched the following electronic databases, registries and websites on July 12th 2021, unrestricted by date: PubMed, Embase, Cochrane library, SCOPUS, Web of Science, Google Scholar and ClinicalTrials.gov. Lastly, the reference lists of retrieved trials and previous systematic reviews were screened for citation of potentially eligible trials. The detailed search strategy is shown in Table 1.

Study selection. Two independent reviewers screened the titles and abstracts of the initially enrolled studies, and duplicates or irrelevant studies were excluded. Trials selected by the first selection were read in full-text articles for a second selection using the eligibility criteria. Any disagreements were resolved by achieving consensus through discussion.

Data extraction and management. All data were independently extracted using the data extraction form (Supplementary Files 2) by two reviewers. When data extraction of interest from a publication was not possible, the corresponding author was contacted via e-mail for obtaining unpublished data. The missing data was then ignored if no response was received. A double check process was undertaken by a senior researcher when the extraction process was finished.

Assessing the methodological quality. The risk of bias for each included RCTs was assessed by two reviewers independently using the bias tool recommended by the Cochrane Back and Neck (CBN) Group,[15] and the overall quality of each included trials was assessed by Jadad score.[18] Disagreements were resolved by consensus of the whole group. The graphical presentation of assessment of risk of bias was generated by RevMan 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

We also applied Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to evaluate the overall quality of the evidence based on five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. GRADE approach evaluates the quality of evidence as *high, moderate, low,* or *very-low* by the outcomes.[19]

Data synthesis and analysis. All pain scales were converted to a ten-point scale, and a negative effect indicates that IIM is more beneficial than control. Dosage of

Source	Search terms	Searched results
PubMed	(magnesium[All Fields] OR "Magnesium"[Mesh]) AND ("spine surgery"[All Fields] OR "spine operation"[All Fields] OR "spine fusion"[All Fields] OR "lumbar fusion"[All Fields] OR "back surgery" OR laminectomy[All Fields] OR discectomy [All Fields] OR "Spine/surgery"[Mesh])	60
Cochrane Library	#1: MeSH descriptor: [Magnesium] explode all trees #2: (magnesium):ti,ab,kw #3: MeSH descriptor: [Spine] explode all trees #4: ("spine surgery" OR "spine operation" OR "spine fusion" OR "lumbar fusion" OR "back surgery" OR laminectomy OR discectomy):ti,ab,kw #5: (#1 OR #2) AND (#3 OR #4)	52
Embase	magnesium:ab,ti AND ('spine surgery':ab,ti OR 'spine operation':ab,ti OR 'spine fusion':ab,ti OR 'laminectomy':ab,ti)	31
SCOPUS	TITLE-ABS-KEY (magnesium) AND TITLE-ABS-KEY ('spine AND surgery' OR 'spine AND operation' OR 'spine AND fusion' OR 'laminectomy')	68
Web of Science	TS=magnesium AND TS=("spine surgery" OR "spine operation" OR "spine fusion" OR "laminectomy")	49
Google Scholar	allintitle: magnesium AND ("spine surgery" OR "spine operation" OR "spine fusion" OR "lumbar fusion" OR "back surgery" OR laminectomy OR discectomy)	12
ClinicalTrials.gov	Status: All studies; Condition or disease: spine surgery; Other terms: magnesium	8
In total		280

***Table 1*: Search strategy and results.**

opioid analgesics administration other than intravenous morphine were adjusted as parenteral morphine (mg),[20] while the efficacy of remifentanil was considered equal to fentanyl in this study.[21]

The results from finally screened studies were combined to estimate as effective results in standardized mean differences (SMD) and 95% confident interval (CI) for continuous outcomes. For dichotomous outcomes, pooled risk ratio (RR) and 95% CI were estimated. The synthesis was done by generating a forest plot of the study estimates using R package meta. Heterogeneity was reported using the I^2 statistic, and I^2 values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity.[22] The random-effects model was used regardless of heterogeneity. Statistical significance was set at $P < 0{\cdot}05$ in this review.

Reporting bias assessment and sensitivity analysis. Funnel plots and Egger regression asymmetry test were planned, where possible, to explore reporting bias.[23] To confirm the robustness of our findings, a sensitivity analysis was conducted by omitting each included study one by one from each pooled analysis.

Role of funding sources. Data collection, checking, analysis, and manuscript preparation was supported by the Beijing Municipal Natural Science Foundation (Grant No: 7212117).

Results

A total of 280 published citations from September 1965 to April 2021 were captured, of which 185 were screened at title/abstract level according to the eligibility criteria. We retrieved full-text for 30 articles, and 1 study from the reference lists was also included. Finally, 14 randomized trials consisting of 781 participants, representing seven countries, were included in the systematic review and meta-analysis. The study selection process was presented in Figure. 1.

Difference between protocol and review

In the current study, there are differences in methods from those described in the registered protocol. First, the planned eligibility criteria of "operation duration shorter than 300 min" and "American Anesthesiologist Score (ASA) score ≤ 3" were not adopted in this review due to lack of information in many studies. Then, the data of blood loss volume and cumulative dose of intraoperative anesthetics was not combined due to insufficient data.

Study characteristics

The final included studies were published between June 2002 and July 2020. The study sample size ranged from 24 to 102 (median 50). All included trials applied randomization in patient allocation, and most of the trials (13/14) had clear descriptions of blinding. The included population was adolescent to middle-aged patients (14·2–55·9 years of age). Most trials administered magnesium as bolus injection followed by continuous infusion (12/14)—the bolus dosage ranged from 20 to 50 mg/kg and the continuous dosage ranged from 8 to 20 mg/kg/h. Two trials administered the magnesium as standalone continuous infusion and one trial as single bolus injection.[24–26] Noteworthily, only normal saline administration (placebo treatment) was

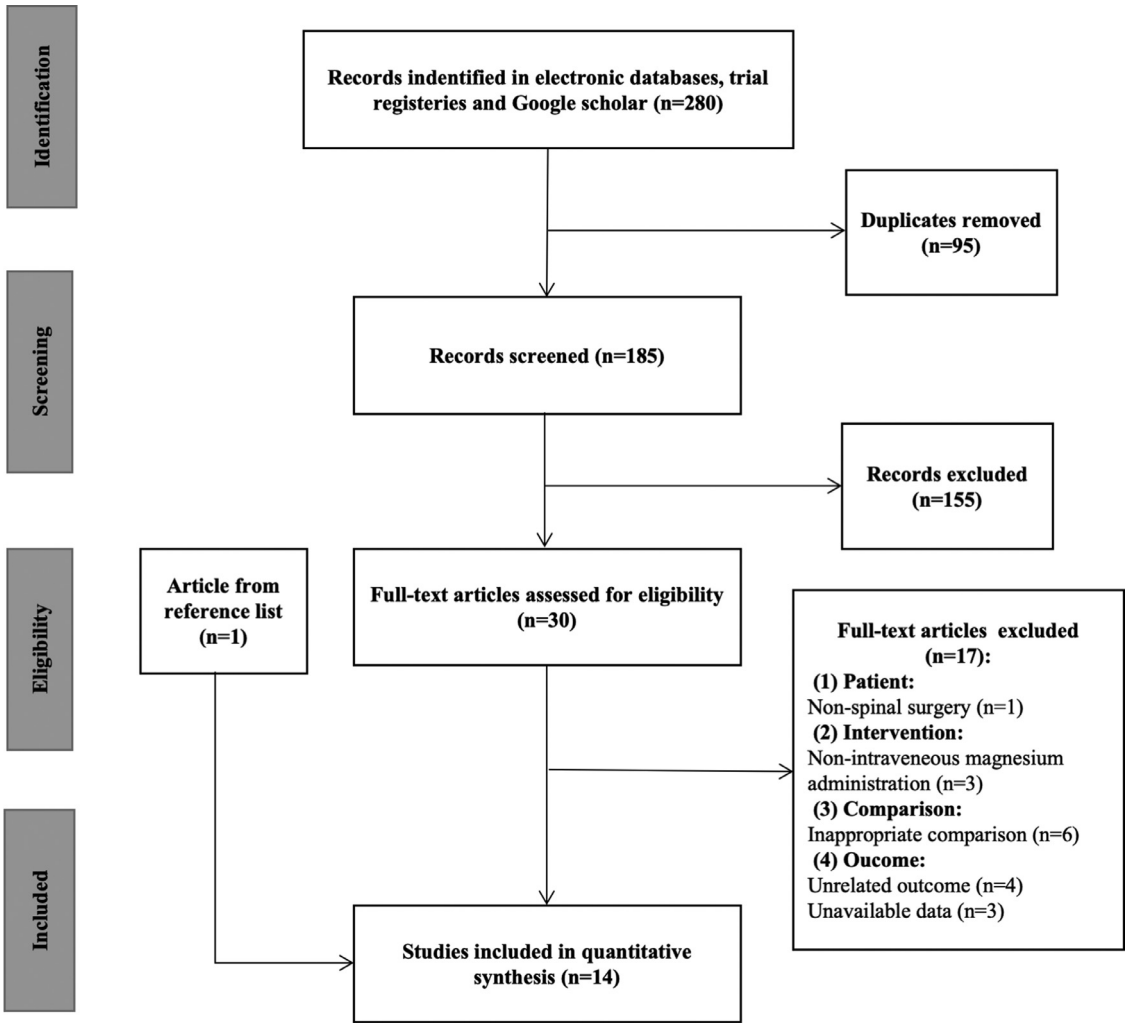

Figure 1. Selection of studies through review.

considered as appropriate comparative in this study. Table 2 provides a summary of the findings and Jadad scores of included trials.

Methodological quality

The CBN risk of bias assessment revealed low risk of bias among the included studies, see Fig. 5. All included studies were at "low" risk of bias as the median Jadad score for included studies were 4, indicating methodologically good-quality trials on average.[18] Publication bias was examined only by funnel plots due to paucity of data (less than ten studies) for all outcomes. Despite the fact that all these funnel plots did not suggest asymmetry, publication bias still cannot be ruled out in the current study (See Supplementary Fig. A-I).

Perioperative analgesic consumption and pain intensity

Six trials reporting data on 403 participants were included in the meta-analysis to estimate the effect of IMM on analgesic consumption at 24 h after surgery.[13,25–29] The pooled results provide moderate-quality evidence that IIM reduces postsurgical morphine consumption at 24 h after surgery compared with control (SMD=−1·61 mg, 95% CI −2·63 to −0·58; I^2=95%). Very-low-quality evidence suggested that there is no significant difference in the pain intensity at 24 h after surgery (five trials, 309 patients) between the two groups (SMD=0·04, 95% CI −0·33 to 0·42; I^2=61%). When compared with the placebo group, IIM is associated with a significant reduction of intraoperative remifentanil requirements (four trials, 237 patients) (SMD=−2·09 μg/h, 95% CI −3·38 to −0·81; I^2=94%). The grade of evidence for intraoperative remifentanil requirements is low-quality (See Figure. 2 and Supplement Table A).

Anesthetic recovery time

Moderate-quality evidence suggested that the orientation time after surgery (four trials, 206 patients) is

Author year	Patients (Magnesium vs control) Randomized patients (completed); mean age; gender.	Intervention Magnesium administration	Comparison Control group	Outcomes (Magnesium vs Control) Remifentanil consumption	Extubation time (min)	Recovery time (min)	Analgesics consumption postoperatively	Pain score postoperatively	Blood loss (ml)	Adverse Events	Quality of evidence Jadad score
Altan et al. 2005[46]	N: 20 (20) vs 20 (20) Age: 42·25 (33–51) vs. 40·75 (29–51) Gender (female): 7/20 vs 9/20	Bolus (30 mg/kg) + continuous infusion (10 mg/kg/h)	Same volume of normal saline.	–	8·71 ± 10·6 vs. 6·52 ± 1·26	Follow commands: 9·97 ± 1·04 vs. 7·82 ± 1·27 Orientation: 10·70 ± 1·08 vs. 8·96 ± 1·44	–	–		–	3
Dehkordy et al. 2020[27]	N: 40 (40) vs 40 (40) Age: 49·9 ± 12·1 vs. 45·7 ± 12·7 Gender (female): 23/40 vs. 26/40	Bolus (50 mg/kg) + continuous infusion (15 mg/kg/h)	Same volume of normal saline.	–	–	–	38·00 ± 13·50 vs. 53·00 ± 16·00 (morphine, mg) (24 h) 53·00 ± 16·20 vs 78·00 ± 23·60 (morphine, mg) (48 h)	23·00 ± 21·00 vs. 32·80 ± 22·50 (mm) (24 h) 26·30 ± 23·40 vs. 37·10 ± 27·10 (mm) (48 h)	472·39 ± 287·48 vs. 406·41 ± 267·98	PONV: 4/40 vs 13/40 Hypotension: 8/40 vs. 6/40 Bradycardia: 4/40 vs.7/40	5
Delavari et al. 2019[26]	N: 51 (51) vs. 51 (51) Age: 53·25 ± 13·87 vs. 51·72 ± 13·81 Gender (female): 36/51 vs. 32/51	Bolus (50 mg/kg)	Same volume of normal saline.	–	–	–	23·72 ± 9·78 vs. 22·58 ± 8·10 (pethidine, mg) (24 h)	1·56 ± 0·67 vs. 1·35 ± 0·56 (24 h)	–	–	4
Demiroglu et al. 2016 [25]	N: 25 (25) vs. 25 (25) Age: 43·76 ± 10·55 vs. 46·36 ± 12·43 Gender (female): 11/25 vs. 12/25	Continuous infusion (50 mg/kg)	Same volume of normal saline.	–	–	–	283·68 ± 64·61 vs. 335·72 ± 59·09 (tramadol, mg) (24 h)	0·96 ± 1·51 vs. 0·32 ± 0·69 (24 h)	–	PONV: 5/25 vs. 9/25	2
Ghaffaripour et al. 2016[12]	N: 20 (20) vs. 20 (19) Age: 44·70 vs. 43·50 Gender (female): 8/20 vs 8/19	Bolus (30 mg/kg) + continuous infusion (10 mg/kg/h)	Same volume of normal saline.	–	–	–	–	1·20 ± 0·83 vs. 1·37 ± 0·86 (24 h)		–	5
Göral et al. 2011[41]	N: 20 (20) vs. 20 (20) Age: 48·00 ± 9·00 vs. 49·00 ± 11·00 Gender (female): 10/20 vs 11/20	Bolus (50 mg/kg) + continuous infusion (20 mg/kg/h)	Same volume of normal saline.	–	–	–	–	–	190·00 ± 95·00 vs 362·00 ± 170·00	Bradycardia: 1/20 vs. 0/20	5

Table 2 (Continued)

Author year	Patients (Magnesium vs control) Randomized patients (completed); mean age; gender.	Intervention Magnesium administration	Comparison Control group	Outcomes (Magnesium vs Control) Remifentanil consumption	Extubation time (min)	Recovery time (min)	Analgesics consumption postoperatively	Pain score postoperatively	Blood loss (ml)	Adverse Events	Quality of evidence Jadad score
Jabbour et al. 2014[28]	N: 25 (25) vs 25 (25) Age: 14·56 ± 2·13 vs. 14·48 ± 2·02 Gender (female): 23/25 vs 21/25	Bolus (50 mg/kg) + continuous infusion (8 mg/kg/h)	Same volume of normal saline.	1836·20 ± 694·42 vs. 1952·60 ± 806·68 (ug)	21·40 ± 9·78 vs. 20·79 ± 9·17	–	32·03 ± 14·56 vs. 44·68 ± 19·79 (morphine, mg) (24 h) 51·53 ± 22·44 vs. 73·16 ± 36·37 (morphine, mg) (48 h)	–	–	PONV: 0/25 vs. 4/25	5
Levaux et al. 2003[24]	N: 12 (12) vs. 12 (12) Age: 55·00 ± 16·00 vs.46·00 ± 19·00 Gender (female): 8/12 vs. 5/12	Continuous infusion (50 mg/kg)	Same volume of normal saline.	–	–	–	–	–	–	PONV: 0/12 vs. 1/12 Hypotension: 8/12 vs. 6/12 Shivering: 3/12 vs. 3/12	4
Martin et al. 2018[30]	N: 20 (19) vs. 20 (19) Age: 15·30 ± 1·90 vs. 14·20 ± 1·40 Gender (female): 16/19 vs. 16/19	Bolus (50 mg/kg) + continuous infusion (10 mg/kg/h)	Same volume of normal saline.	0·2 ± 0·03 vs. 0·19±0·03 ug/kg/min	1·70 ± 1·60 vs. 2·50 ± 1·80	Open eye: 1·40 ± 1·10 vs 2·60 ± 1·40 Follow commands: 1·50 ± 1·10 vs. 2·90 ± 1·60	0·33 ± 0·11 vs. 0·29 ± 0·09 (morphine, mg/kg) (24 h)	4·70 ± 1·30 vs. 4·80 ± 3·50 (24 h)	–	–	3
Oguzhan et al. 2008[13]	N: 25 (25) vs. 25 (25) Age: 44·00 ± 1·79 vs. 42·00 ± 2·04 Gender (female): 12/25 vs. 11/25	Bolus (30 mg/kg) + continuous infusion (10 mg/kg/h)	Same volume of normal saline.	0·18 ± 0·02 vs. 0·32 ± 0·03 (mg/h)	5·20 ± 0·36 vs. 5·00 ± 0·41	Open eye: 7·10 ± 0·46 vs 6·90 ± 0·61 Follow commands: 8·00 ± 0·41 vs. 8·00 ± 0·66 Orientation: 10·20±0·59 vs. 9·60±0·69	12·00 ± 1·28 vs. 23·00 ± 2·30 (morphine, mg) (24 h)	–	–	PONV: 4/25 vs. 6/25	5
Reena et al. 2017[47]	N:30 (29) vs. 30 (30) Age: 33·67 ± 10·24 vs. 33·87 ± 9·25 Gender (female): 9/30 vs. 11/30	Bolus (30 mg/kg) + continuous infusion (10 mg/kg/h)	Same volume of normal saline.	35·68 ± 6·88 vs. 41·89 ± 8·35 (Fentanyl, ug/h)	8·74±0·47 vs. 6·05±0·32	Follow commands: 9·79 ± 1·61 vs. 7·78 ± 1·26 Orientation: 10·96 ± 1·30 vs. 8·97 ± 1·49	–	–	–	–	5
							–	–	–		4

Table 2 (Continued)

Author year	Patients (Magnesium vs control) Randomized patients (completed); mean age; gender.	Intervention Magnesium administration	Comparison Control group	Outcomes (Magnesium vs Control) Remifentanil consumption	Extubation time (min)	Recovery time (min)	Analgesics consumption postoperatively	Pain score postoperatively	Blood loss (ml)	Adverse Events	Quality of evidence Jadad score
Srivastava et al. 2016[48]	N: 30 (28) vs. 30 (29) Age: 48·30 ± 7·70 vs. 46·57 ± 8·73 Gender (female): 13/30 vs. 14/30	Bolus (50 mg/kg) + continuous infusion (15 mg/kg/h)	Same volume of normal saline.	34·93 ± 8·44 vs. 44·38 ± 10·40 (ug/h)	13·39 ± 3·65 vs. 10·78 ± 2·98	Follow commands: 12·68 ± 3·29 vs. 9·82 ± 2·59 Orientation: 14·68 ± 3·19 vs 11·81 ± 2·86				Ventricular ectopic:1/28 vs 0/29	
Telci et al. 2002[49]	N: 40 (40) vs. 41(41) Gender (female): 36/81	Bolus (30 mg/kg) + continuous infusion (10 mg/kg/h)	Same volume of normal saline.	4·74±1·16 vs. 9·35±1·62 (ug/kg/h)	–	–	–	–	–	–	3
Tsaousi et al. 2020[29]	N: 37 (35) and 37 (36) Age: 55·90 ± 10·80 vs. 49·00 ± 15·00 Gender (female): 22/35 vs. 21/36	Bolus (20 mg/kg) + continuous infusion (20 mg/kg/h)	Same volume of normal saline.	44·20 ± 66·80 vs. 196·60 ± 103·30 (ug/h)	6·80 ± 2·90 vs. 8·40 ± 2·90	–	5·33 ± 3·38 vs. 14·68 ± 4·79 (morphine, mg) (24 h)	–	–	Hypotension: 15/35 vs. 8/36 Bradycardia: 2/35 vs. 0/36 PONV: 4/35 vs. 11/36 Shivering: 0/35 vs.9/36	5

***Table 2*: Summary of findings and Jadad scores of included studies.**
Abbreviations: PONV=postoperative nausea and vomiting.

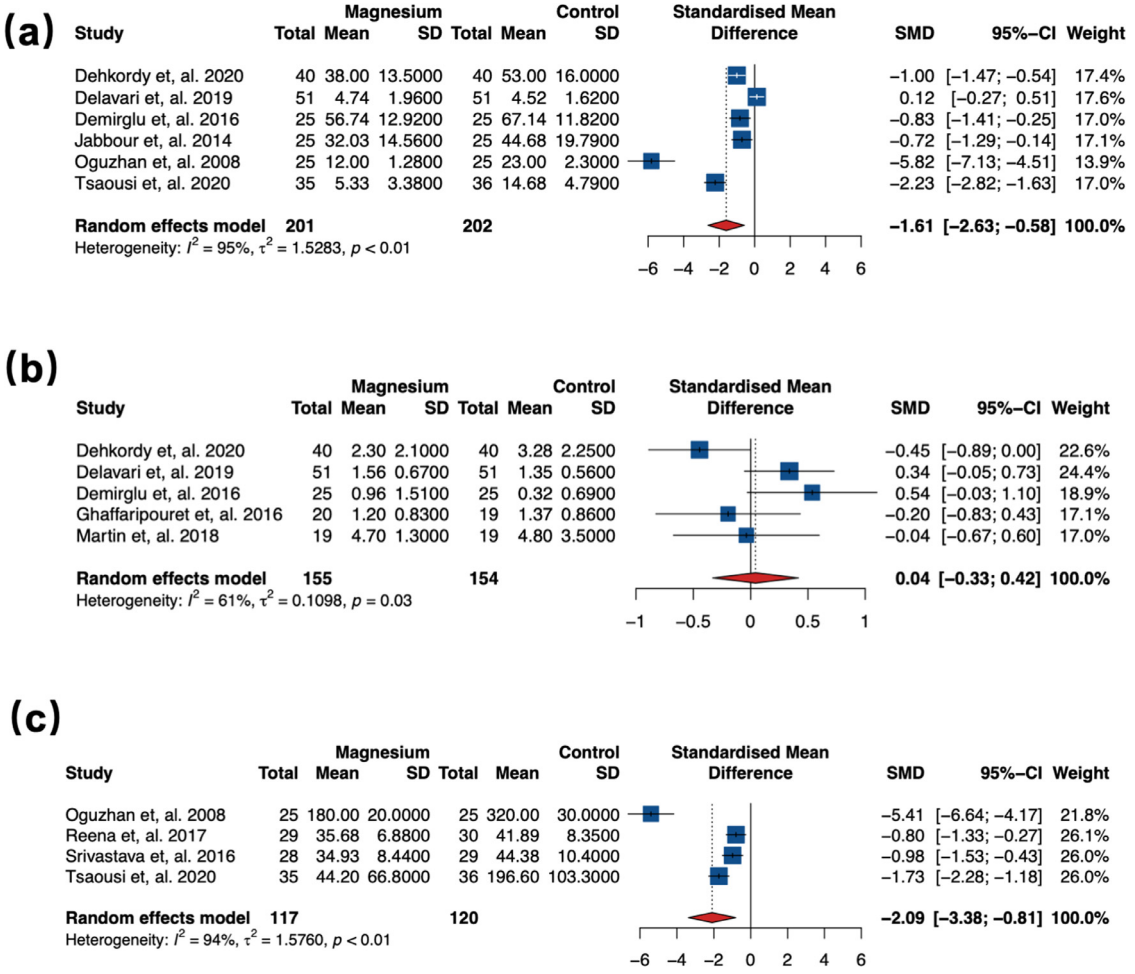

Figure 2. Pooled estimates for postoperative: (a) analgesic consumption at 24 h, (b) pain intensity at 24 h and (c) remifentanil requirements of magnesium vs. control. The blue square shape represents the study weight for each trial (the mid-point of the box represents mean effect estimate), while the red diamond shape represents the pooled effect estimate (the length of the diamond on the x-axis symbolizes the confidence interval of the pooled result).

significantly longer in the IIM group compared with control (SMD=1·13 min, 95% CI 0·83 to 1·43; I^2=0). Very-low-quality evidence suggested that there is no significant difference in extubation time (SMD=0·98 min, 95% CI −0·19 to 2·14; I^2=95%), or time to follow commands (SMD=0·63 min, 95% CI −0·29 to 1·54; I^2=91%), for details see Figure. 3 and Supplement Table A.

Adverse events

Incidence of PONV was investigated in six trials (325 patients). The pooled results provided high-quality evidence that PONV is less likely to occur in the IMM group compared with control (RR=0·43, 95% CI 0·26 to 0·71; I^2=0%). However, low-quality evidence suggested that there is no significant difference in the incidence of intraoperative hypotension (RR=1·53, 95% CI 0·98 to 2·39; I^2=0), or intraoperative bradycardia between IIM and control group (RR=1·10, 95% CI 0·28 to 4·32; I^2=21%), for details see Figure. 4 and Supplement Table A.

Sensitivity analysis

Sensitivity analysis for most outcomes yielded the similar pooled results compared to the original values, indicating the robustness of the results (Supplement Fig. A-I). However, we should note that the only exception is that the sensitivity analysis of *time to follow commands*, in which the pooled difference was highlighted by omitting the value by Martin et al.,[30] which means that the heterogeneity might be largely caused by the single trial.

Discussion

Magnesium blocks calcium influx and antagonizes NMDA receptor channels, which prompted the

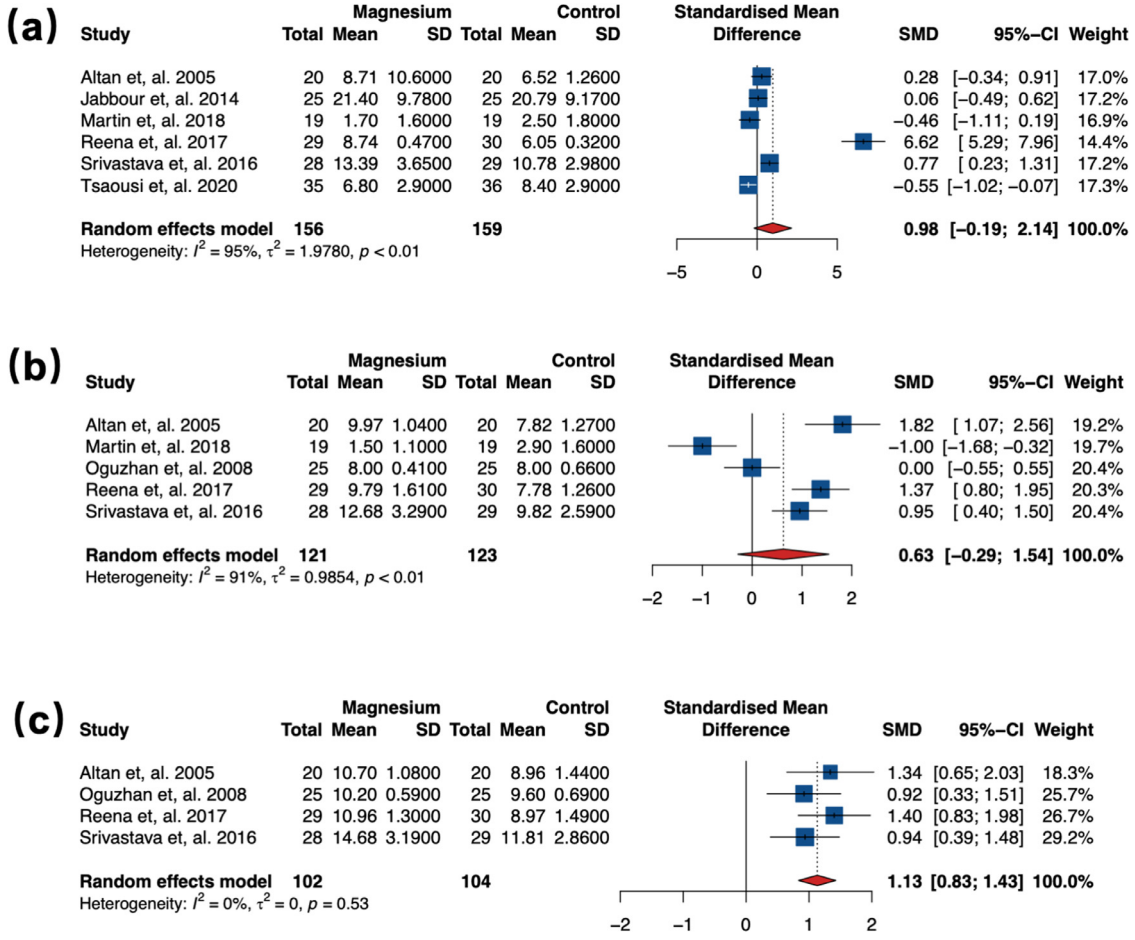

Figure 3. Pooled estimates for anesthetic recovery time in: (a) extubation time; (b) time to follow command; and (c) orientation time of magnesium vs. control. The blue square shape represents the study weight for each trial (the mid-point of the box represents mean effect estimate), while the red diamond shape represents the pooled effect estimate (the length of the diamond on the x-axis symbolizes the confidence interval of the pooled result).

investigation of magnesium as an adjuvant agent for anesthesia-analgesia.[31] The results of the present systematic review and meta-analysis provided low- to moderate-quality evidence that IIM reduces the intraoperative remifentanil requirements and morphine consumption at 24 h. High-quality evidence suggested that IIM is protective of PONV, while moderate-quality evidence suggested that IIM is correlated with longer recovery orientation time. Low-quality evidence showed that no significant difference on perioperative of hypotension or bradycardia was noticed between IIM and placebo. Moreover, the impact of IIM on pain relief at 24 h postoperatively, extubation time, or time to follow commands remains uncertain due to the very-low-quality of evidence. To our knowledge, this is the first systematic review to have invested the impact of IIM on spine surgery and conducted a meta-analysis of RCTs.

Several systematic reviews have examined the effectiveness of IIM on peri-operative analgesia; however, previous reviews included trials of various specialties of surgery, which may lead to considerable heterogeneity (see Table 3). This review provided moderate-quality evidence that, after spine surgery, IIM reduces morphine consumption at 24 h compared with control, which is in line with most previous reviews, and this effect therefore should be considered as robust evidence.[7,8,32–36] Our results also suggested that, similar to pooled outcomes of previous reviews, IIM fails to show clinically better effects for pain relief at 24 h postoperatively.[7,32] However, the effect on pain relief is considered to be of very-low quality and we believe that additional studies are surely necessary. For postsurgical analgesia in even shorter term (< 24 h), most included trials in our study yielded negative results,[12,25,26,30] except for the RCT by Dehkordy et al. in which the pain-reliving effect at both 6 and 12 h favored magnesium group after posterior lumbar fusion.[27] Besides, according to previous studies, intraoperative administration of magnesium as a supplement of anesthetics was found to be helpful in reducing the requirement for other components of

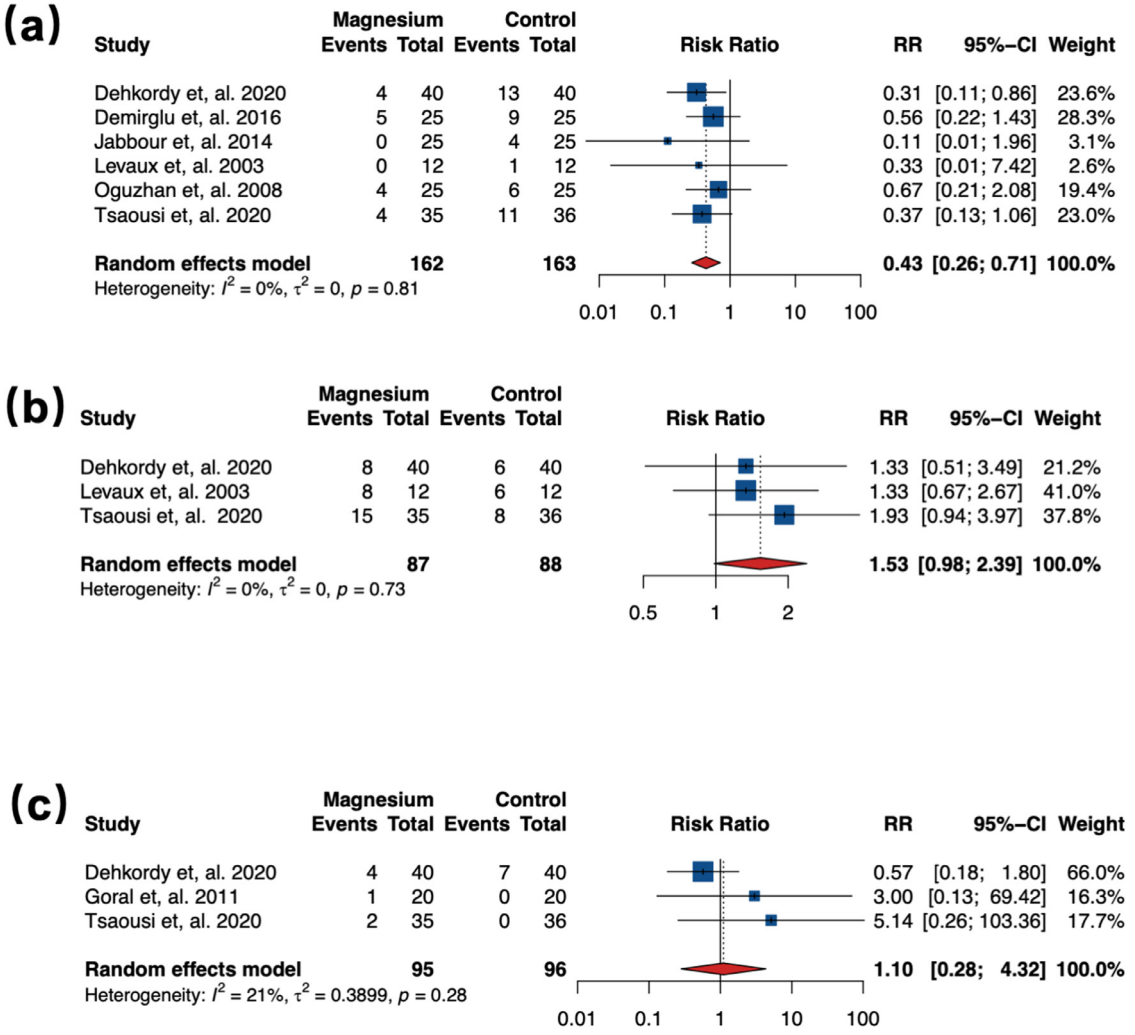

Figure 4. Pooled estimates for adverse events in: (a) postoperative nausea and vomiting; (b) hypotension; and (C) bradycardia of magnesium vs. control. The blue square shape represents the study weight for each trial (the mid-point of the box represents mean effect estimate), while the red diamond shape represents the pooled effect estimate (the length of the diamond on the x-axis symbolizes the confidence interval of the pooled result).

anesthetics (e.g., fentanyl, propofol or vecuronium), and this effect was validated in our study as low-quality evidence suggested that IIM reduced intraoperative remifentanil consumption, compared with placebo treatment.[37,38]

The drug-related adverse events after general anesthesia include PONV, bradycardia, hypotension, shivering, etc.[39,40] Here, qualified evidence highlighted that the proportion of patients who experienced PONV was significantly smaller in the magnesium group compared with placebo. This confirms Peng et al.'s findings that magnesium group had less post-surgical postoperative nausea (RR: 0·32, 95% CI: 0·12 to 0·82) and vomiting (RR: 0·38, 95% CI: 0·15 to 0·92), and therefore the effect of reducing PONV should also be considered as reliable.[6] Contrary to previous systematic reviews, we did not observe the effect of reducing bradycardia on the pooled result,[34] although 2/3 of the included trials indicated such beneficial effect (Figure. 4C).[27,29,41] Besides, previous systematic reviews have reported the protective effect of intravenous administration of magnesium on postoperative shivering,[6,8,33,35,42] which could not be validated in our study due to insufficient data. Furthermore, we should note that the reduced remifentanil dosage may pose protective effects on opioids-related side-effects,[21] which could cause a confounding bias to the results; however, the effect of remifentanil dosage change on opioids-related side-effects could not be determined or ruled out here study due to heterogeneity among included studies (Figure. 5).

Author, year	Number of included trials and participants	Type of surgeries	Analgesic outcomes (Magnesium vs. control)	Other outcomes (Magnesium vs. control)	Quality of evidence of pooled outcomes
Albrecht et al.[34]	25 RCTs, 1461 participants	Urological surgery, thoracic surgery, abdominal surgery, cardiac surgery, spinal surgery, gynecological surgery and lower extremity surgery	(1) analgesic consumption at 24 h postoperatively (WMD: −7·6 mg, 95% CI −9·5 to −5·8); (2) pain intensity (100-point scale): at 24 h postoperatively at rest (WMD: −4·2, 95% CI −6·3 to −2·1); and on movement (WMD: −9·2, 95% CI −6·3 to −2·1)	(1) bradycardia: (RR: 1·76, 95% CI 1·01 to 3·07) (2) hypotension: (RR: 1·49, 95% CI 0·88 to 2·52)	–
Chen et al.[32]	4 RCTs, 263 participants	Laparoscopic cholecystectomy	(1) analgesic consumption postoperatively (SMD: −0·40, 95% CI −0·73 to −0·07); (2) pain intensity: at 2 h postoperatively (SMD: −0·45, 95% CI −0·88 to −0·02); at 8 h postoperatively (SMD: −0·62, 95% CI −0·95 to −0·28); and at 24 h postoperatively (SMD: −0·38, 95% CI −0·79 to 0·02)	–	–
De Oliveira et al.[35]	20 RCTs, 1257 participants	Thyroidectomy, abdominal surgery, cardiac surgery, spinal surgery, thoracic surgery, pelvic surgery, nasal surgery, lower extremity surgery	(1) analgesic consumption at 24 h postoperatively (WMD: −10·52 mg, 99% CI −13·50 to −7·54); (2) pain intensity: at 4 h at rest postoperatively (WMD: −0·74, 99% CI −1·08 to −0·48); at 24 h at rest (WMD: −0·36, 99% CI −0·63 to −0·09); and at 24 h on movement (WMD: −0·73, 99% CI −1·37 to −0·10).	(1) PONV: (OR: 1·00, 95% CI 0·64 to 1·56); (2) postoperative shivering (OR: 0·36, 95% CI 0·14 to 0·95).	–
Guo et al.[36]	27 RCTs, 1504 participants	Gastrointestinal surgery, orthopedic surgery, cardiac surgery, gynecological surgery, other surgeries	(1) analgesic consumption postoperatively (SMD: −1·72, 95% CI −3·21 to −0·23); (2) pain intensity at rest (SMD: −1·43, 95% CI −2·74 to −0·12).	Extubation time (WMD: −29·34 min, 95% CI −35·74 to −22·94).	–
Lysakowski et al.[8]	14 RCTs, 778 participants	Cardiac surgery, abdominal surgery, orthopedic surgery	(1) analgesic consumption postoperatively was significantly reduced in eight (57%) trials, were no different from placebo in five trials (36%), and were increased in one trial (7%) (2) pain intensity was significantly decreased in four (29%) trials, was no different from placebo in seven trials (50%), and was increased in one trial (7%).	(1) postoperative shivering (RR: 0·38, 95% CI 0·17 to 0·88); (2) postoperative nausea: (RR: 1·30, 95% CI 0·88 to 1·93); (3) postoperative vomiting: (RR: 0·82, 95% CI 0·49 to 1·37); (4) hypotension: (RR: 1·43, 95% CI 0·82 to 2·74); (5) bradycardia: (RR: 1·64, 95% CI 0·90 to 2·98).	–
Murphy et al.[7]	22 RCTs, 1177 participants	Abdominal surgery, spinal surgery, thoracic surgery, pelvic surgery, lower extremity surgery, multiple surgery	(1) analgesic consumption postoperatively (WMD: −7·40 mg, 95% CI −9·40 to −5·41); (2) pain intensity: at 4 h postoperatively (WMD: −0·67, 95% CI −1·12 to −0·23); and at 24 h postoperatively (WMD: −0·25, 95% CI −0·62 to 0·71).	PONV: (RR: 0·76, 95% CI 0·52 to 1·09)	–

Table 3 (Continued)

Author, year	Number of included trials and participants	Type of surgeries	Analgesic outcomes (Magnesium vs. control)	Other outcomes (Magnesium vs. control)	Quality of evidence of pooled outcomes
Ng et al.[33]	51RCTs, 3311 participants	Mastectomy, thyroidectomy, abdominal surgery, spinal surgery, thoracic surgery, pelvic surgery, lower extremity surgery, multiple surgery	(1) analgesic consumption postoperatively (WMD: −5·60 mg, 95% CI −7·54 to −3·36); (2) pain intensity at 24 h postoperatively (MD: −0·30, 95% CI −0·69 to 0·09).	(1) postoperative shivering (OR: 0·26, 95% CI 0·15 to 0·44); (2) bradycardia: (OR: 1·13, 95% CI 0·43 to 2·98); (3) PONV: (OR: 0·90, 95% CI 0·67 to 1·22).	Analgesic consumption: *low-quality*; Pain scores at 24 h postoperatively: *low-quality*; Postoperative shivering: *very-low-quality*; Bradycardia: *very-low-quality*; PONV: *moderate-quality*.
Peng et al.[6]	11RCTs, 535 participants	Spinal surgery, lower extremity surgery, arthroplasty, arthroscopic surgery	(1) reduced analgesic consumption postoperatively in 8 trials (73%), and without significant difference in 2 trials (18%); (2) reduced postoperative pain intensity compared with control in 6 trials (55%), but without significant difference in 5 trials (45%)	(1) postoperative nausea: (RR: 0·32, 95% CI 0·12 to 0·82); (2) postoperative vomiting: (RR: 0·38, 95% CI 0·15 to 0·92); (3) shivering: (RR: 0·31, 95% CI 0·11 to 0·88)	–

***Table 3*: Summary of previous systematic reviews and meta-analysis of intraoperative intravenous magnesium.**
Abbreviations: CI=confidence interval, MD=median difference, OR=odds ratio, PONV=postoperative nausea and vomiting, RCT=randomized controlled trial, RR=risk ratio, SMD=standard mean difference, WMD=weighted mean difference.

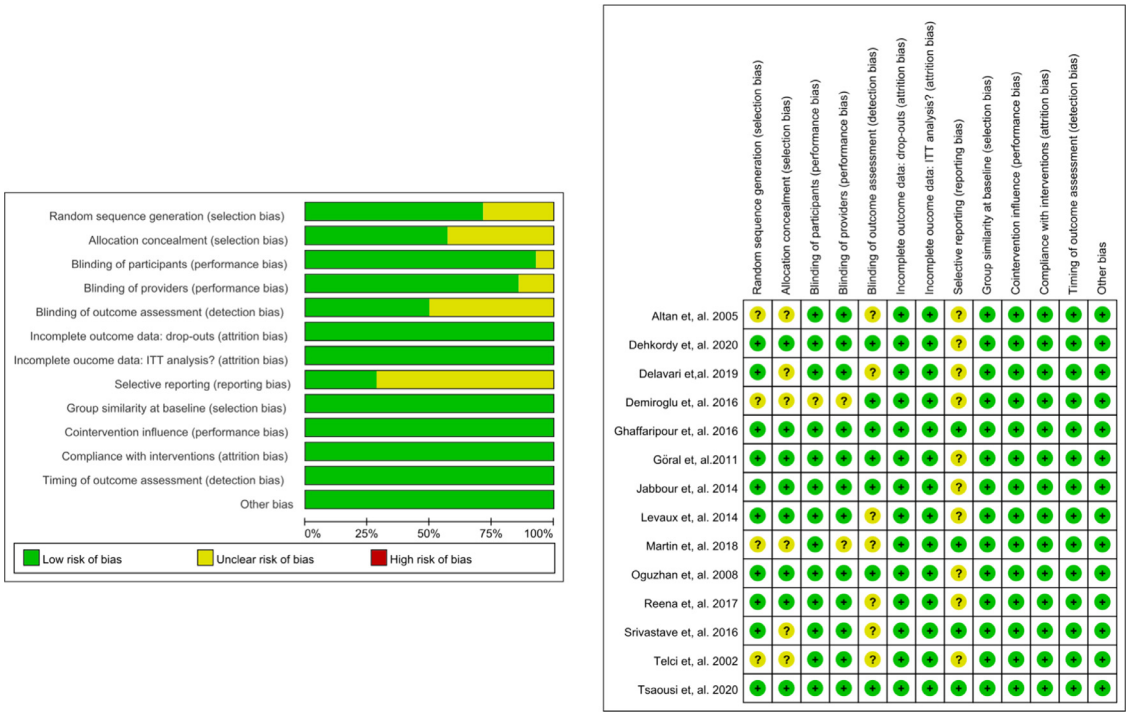

Figure 5. Risk of bias assessment of included studies using the Cochrane Back and Neck (CBN) Group risk of bias tools.[15]

Noteworthily, despite its merits, clinician should keep in mind that administration of magnesium may result in depression of central nervous system.[43] Our study provided moderate-quality evidence that IIM significantly prolongs the early anesthetic orientation time, which is consistent of Rodríguez-Rubio et al.'s systematic review in which the recovery index was higher the placebo group comparing with magnesium group (SMD: 1·42, 95% CI: 0·41 to 2·43).[44] However, differences in dose and onset of magnesium administration made it hard to determine the safety threshold for IIM administration, and we suggest clinicians being conservative about the administration as well as dosage of IIM on spine surgery until optimal strategy has been proved, especially for patients with renal insufficiency. Common countermeasures of magnesium toxicity include intravenous administration of calcium gluconate and, if required, hemodialysis, ventilatory and/or circulatory support.[45]

There are several limitations in the current study. Firstly, the pooled outcomes of our study were based on limited studies, which hampered the planned subgroup analysis, meta-regression and assessment of publication bias, and consequently reduced the reliability of the results. Then, differences in dose and onset of magnesium administration, as well as choice of surgical population caused heterogeneity in effect estimates and limited generalizability of the evidence. Furthermore, we could not extract the long-term follow-up data as most included studies only investigated the peri-operative impact of magnesium.

On a final note, based on the current evidence, IIM as adjuvant analgesics showed overall beneficial effects on spine surgery in terms of reducing analgesics and PONV. Despite these merits, clinicians should keep in mind that IIM may cause delayed anesthetic recovery. Future studies should be composed of large sample size, well-defined subgroups and long follow-up to validate our results.

Contributors

LY concepted the research questions, designed the search strategy and prepared the manuscript draft. GM designed search strategy, edited the manuscript. LY and GM independently screened the potential studies, extract data and assess the risk of bias from included studies. LY and GM revised the search strategy and the manuscript. ZL and HS revised the manuscript and approved the final version and arbitrated potential disagreements. All authors took the decision to submit the manuscript for publication.

Data sharing statement

All the data are available within the manuscript and supplementary material. Supplementary material associated with this article are publicly available via third party platform: (Supplementary file 1: https://doi.org/10.6084/m9.figshare.15016731.v2; Supplementary file 2: https://doi.org/10.6084/m9.figshare.15016749.v2).

Funding

This study was funded by Beijing Municipal Natural Science Foundation (Grant number:7212117).

Declaration of interests

The authors declare no conflict interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101246.

References

1 Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003;**97**(4):1108–16.
2 Shin HJ, Na HS, Do SH. Magnesium and pain. *Nutrients* 2020;**12**(8):2184.
3 Meltzer SJ, Auer J. Physiological and pharmacological studies of magnesium salts.-II. The toxicity of intravenous injections; in particular the effects upon the Centres of the medulla oblongata. *Am J Physiol Leg Content* 1906;**15**(4):387–405.
4 Peck CH, Meltzer SJ. Anesthesia in human beings by intravenous injection of magnesium sulphate. *J Am Med Assoc* 1916;**67**(16):1131–3.
5 Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. *Anesthesiology* 1996;**84**(2):340–7.
6 Peng YN, Sung FC, Huang ML, Lin CL, Kao CH. The use of intravenous magnesium sulfate on postoperative analgesia in orthopedic surgery: a systematic review of randomized controlled trials. *Med. (Balt.)* 2018;**97**(50):e13583.
7 Murphy JD, Paskaradevan J, Eisler LL, et al. Analgesic efficacy of continuous intravenous magnesium infusion as an adjuvant to morphine for postoperative analgesia: a systematic review and meta-analysis. *Middle East J Anaesthesiol* 2013;**22**(1):11–20.
8 Lysakowski C, Dumont L, Czarnetzki C, Tramèr MR. Magnesium as an adjuvant to postoperative analgesia: a systematic review of randomized trials. *Anesth Analg* 2007;**104**(6):1532–9. table of contents.
9 Kurd MF, Kreitz T, Schroeder G, Vaccaro AR. The role of multimodal analgesia in spine surgery. *J Am Acad Orthop Surg* 2017;**25**(4):260–8.
10 Jirarattanaphochai K, Thienthong S, Sriraj W, et al. Effect of parecoxib on postoperative pain after lumbar spine surgery: a bicenter, randomized, double-blinded, placebo-controlled trial. *Spine (Phila Pa 1976)* 2008;**33**(2):132–9.
11 Park JH, Shim JK, Song JW, Jang J, Kim JH, Kwak YL. A randomized, double-blind, non-inferiority trial of magnesium sulphate versus dexamethasone for prevention of postoperative sore throat after lumbar spinal surgery in the prone position. *Int J Med Sci* 2015;**12**(10):797–804.
12 Ghaffaripour S, Mahmoudi H, Eghbal H, Rahimi A. The effect of intravenous magnesium sulfate on post-operative analgesia during laminectomy. *Cureus* 2016;**8**(6):e626.
13 Oguzhan N, Gunday I, Turan A. Effect of magnesium sulfate infusion on sevoflurane consumption, hemodynamics, and perioperative opioid consumption in lumbar disc surgery. *J Opioid Manag* 2008;**4**(2):105–10.
14 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**350**:g7647.
15 Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated method guideline for systematic reviews in the Cochrane back and neck group. *Spine (Phila Pa 1976)* 2015;**40**(21):1660–73.
16 Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995;**123**(3):A12–3.
17 Strom J, Bjerrum MB, Nielsen CV, et al. Anxiety and depression in spine surgery-a systematic integrative review. *Spine J* 2018;**18**(7):1272–85.
18 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**(1):1–12.
19 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**(4):383–94.
20 *Opioid Equivalence Chart*. (2011, July). Gloucestershire Hospitals NHS Foundation Trust. Retrieved July 8, 2021, from https://www.gloshospitals.nhs.uk/gps/treatment-guidelines/opioid-equivalence-chart/.
21 Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005;**65**(13):1793–823.
22 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.
23 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.
24 Levaux C, Bonhomme V, Dewandre PY, Brichant JF, Hans P. Effect of intra-operative magnesium sulphate on pain relief and patient comfort after major lumbar orthopaedic surgery. *Anaesthesia* 2003;**58**(2):131–5.
25 Demiroglu M, Ün C, Ornek DH, et al. The effect of systemic and regional use of magnesium sulfate on postoperative tramadol consumption in lumbar disc surgery. *Biomed Res Int* 2016;**2016**:3216246.
26 Delavari A, Lak M, Arragizade H, Salatini B. Preemptive analgesic effect of magnesium sulfate on postoperative pain in patients undergoing lumbar fusion surgery. *Univ Med* 2019;**38**(3):156–63.
27 Dehkordy ME, Tavanaei R, Younesi E, Khorasanizade S, Farsani HA, Oraee-Yazdani S. Effects of perioperative magnesium sulfate infusion on intraoperative blood loss and postoperative analgesia in patients undergoing posterior lumbar spinal fusion surgery: A randomized controlled trial. *Clin Neurol Neurosurg* 2020;**196**:105983.
28 Jabbour HJ, Naccache NM, Jawish RJ, et al. Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. *Acta Anaesthesiol Scand* 2014;**58**(5):572–9.
29 Tsaousi G, Nikopoulou A, Pezikoglou I, Birba V, Grosomanidis V. Implementation of magnesium sulphate as an adjunct to multimodal analgesic approach for perioperative pain control in lumbar laminectomy surgery: a randomized placebo-controlled clinical trial. *Clin Neurol Neurosurg* 2020;**197**.
30 Martin DP, Samora WP, Beebe AC, et al. Analgesic effects of methadone and magnesium following posterior spinal fusion for idiopathic scoliosis in adolescents: a randomized controlled trial. *J Anesth* 2018;**32**(5):702–8.
31 Kara H, Sahin N, Ulusan V, Aydogdu T. Magnesium infusion reduces perioperative pain. *Eur J Anaesthesiol* 2002;**19**(1):52–6.
32 Chen C, Tao R. The impact of magnesium sulfate on pain control after laparoscopic cholecystectomy: a meta-analysis of randomized controlled studies. *Surg Laparosc Endosc Percutan Tech* 2018;**28**(6):349–53.
33 Ng KT, Yap JLL, Izham IN, Teoh WY, Kwok PE, Koh WJ. The effect of intravenous magnesium on postoperative morphine consumption in noncardiac surgery: a systematic review and meta-analysis with trial sequential analysis. *Eur J Anaesthesiol* 2020;**37**(3):212–23.
34 Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia* 2013;**68**(1):79–90.
35 De Oliveira GS, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2013;**119**(1):178–90.
36 Guo BL, Lin Y, Hu W, et al. Effects of Systemic magnesium on postoperative analgesia: is the current evidence strong enough? *Pain Physician* 2015;**18**(5):405–18.
37 Schulz-Stübner S, Wettmann G, Reyle-Hahn SM, Rossaint R. Magnesium as part of balanced general anaesthesia with propofol, remifentanil and mivacurium: a double-blind, randomized prospective study in 50 patients. *Eur J Anaesthesiol* 2001;**18**(11):723–9.
38 Rodríguez-Rubio L, Nava E, Del Pozo JSG, Jordán J. Influence of the perioperative administration of magnesium sulfate on the total dose of anesthetics during general anesthesia. A systematic review and meta-analysis. *J Clin Anesth* 2017;**39**:129–38.

39 Wildes TS, Mickle AM, Ben Abdallah A, et al. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial. *JAMA* 2019;**321**(5):473–83.

40 Alansary AM, Badawy A, Elbeialy MAK. Dexmedetomidine added to bupivacaine versus bupivacaine in transincisional ultrasound-guided quadratus lumborum block in open renal surgeries: a randomized trial. *Pain Physician* 2020;**23**(3):271–82.

41 Goral N, Ergil J, Alptekin A, et al. Effect of magnesium sulphate on bleeding during lumbar discectomy. *Anaesthesia* 2011;**66**(12):1140–5.

42 Kawakami H, Nakajima D, Mihara T, Sato H, Goto T. Effectiveness of magnesium in preventing shivering in surgical patients: a systematic review and meta-analysis. *Anesth Analg* 2019;**129**(3):689–700.

43 Campbell CE. Delayed awakening or delirium. Decision making in anesthesiology. Elsevier Inc.; 2007. p. 582–5.

44 Rodríguez-Rubio L, Solis Garcia Del Pozo J, Nava E, Jordán J. Interaction between magnesium sulfate and neuromuscular blockers during the perioperative period. A systematic review and meta-analysis. *J Clin Anesth* 2016;**34**:524–34.

45 Herroeder S, Schönherr ME, De Hert SG, Hollmann MW. Magnesium—essentials for anesthesiologists. *Anesthesiology* 2011;**114**(4):971–93.

46 Altan A, Turgut N, Yildiz F, Türkmen A, Ustün H. Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and postoperative recovery. *Br J Anaesth* 2005;**94**(4):438–41.

47 Reena VA. Comparative evaluation of Clonidine and magnesium sulfate infusions upon intraoperative hemodynamics and anesthetic consumption, and postoperative recovery profile in lumbar spine surgery: a prospective, randomized, placebo controlled, double-blind study. *Acta Anaesthesiol Belg* 2017;**68**(1):31–8.

48 Srivastava VK, Mishra A, Agrawal S, Kumar S, Sharma S, Kumar R. Comparative evaluation of dexmedetomidine and magnesium sulphate on propofol consumption, haemodynamics and postoperative recovery in spine surgery: a prospective, randomized, placebo controlled, double-blind study. *Adv Pharm Bull* 2016;**6**(1):75–81.

49 Telci L, Esen F, Akcora D, Erden T, Canbolat A, Akpir K. Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements. *Br J Anaesth* 2002;**89**(4):594–8.