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SYSTEMATIC REVIEW

The effects of magnesium sulfate added to epidurally administered local anesthetic on postoperative pain: a systematic review

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KEYWORDS
Analgesia, epidural;
Magnesium sulfate, therapeutic use;
Pain, postoperative

Abstract
Background: This study evaluated the efficacy of epidurally administered magnesium associated with local anesthetics on postoperative pain control.
Methods: The study protocol was registered in PROSPERO as CRD42021231910. Literature searches were conducted on Medline, Cochrane, EMBASE, CENTRAL, and Web of Science for randomized controlled trials comparing epidural administration of magnesium added to local anesthetics for postoperative pain in elective surgical adult patients. Primary outcomes were the time to the first Postoperative (PO) Analgesic Request (TFAR), 24-hour postoperative opioid consumption, and Visual Analog Scale (VAS) scores at the first six and 24 postoperative hours. Secondary outcomes included Postoperative Nausea and Vomiting (PONV), pruritus, and shivering. Quality of evidence was assessed using GRADE criteria.
Results: Seventeen studies comparing epidural were included. Effect estimates are described as weighted Mean Differences (MD) and 95% Confidence Intervals (95% CI) for the main outcomes: TFAR (MD = 72.4 min; 95% CI = 10.22—134.58 min; $p < 0.001$; $I^2 = 99.8\%$; GRADE: very low); opioid consumption (MD = -7.2 mg (95% CI = -9.30 — -5.09; $p < 0.001$; $I^2 = 98\%$; GRADE: very low). VAS pain scores within the first six PO hours (VAS) (MD = -1.01 cm; 95% CI = -1.40—0.64 cm; $p < 0.001$; $I^2 = 88\%$; GRADE: very low), at 24 hours (MD = -0.56 cm; 95% CI = -1.14—0.01 cm; $p = 0.05$; $I^2 = 97\%$; GRADE: very low).
Conclusions: Magnesium sulfate delayed TFAR and decreased 24-hour opioid consumption and early postoperative pain intensity. However, imprecision and inconsistency pervaded meta-analyses, causing very low certainty of effect estimates.

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Introduction

Postoperative pain control is a critical component of anesthesia planning and management. Inadequate pain control causes patient dissatisfaction and increases perioperative morbidity, mortality, and hospital length of stay.[1,2]

Epidural Anesthesia (EA) has been considered the gold-standard technique for postoperative pain management in patients undergoing major thoracic, abdominal, pelvic, or orthopedic surgery, particularly for patients at increased risk of postoperative cardiac events, pulmonary complications, or prolonged ileus.[3,4] The implementation of Enhanced Recovery After Surgery (ERAS) protocols associated with a global shift from open to laparoscopic surgery have limited the indication of epidural analgesia to major abdominal, gynecological, urological, thoracic, or orthopedic surgeries.[5] For patients undergoing major surgeries, thoracic epidural anesthesia, and postoperative epidural analgesia are recommended to accelerate the recovery from surgery as an element of the ERAS protocol.[6] Epidural analgesia is obtained with local anesthetics, usually associated with adjuvant analgesics such as opioids, alpha-2 adrenergic agonists, ketamine, or magnesium.[7]

Magnesium inhibits calcium entry into dorsal horn neurons through non-competitive blockade of N-Methyl-D-Aspartate (NMDA) receptors, modulating the projection of nociceptive stimuli and preventing central pain sensitization.[8]

The effectiveness of intravenously administered magnesium sulfate in decreasing postoperative pain has been documented in several randomized controlled trials, systematic reviews, and meta-analyses.[9,10] The intravenous administration of magnesium sulfate as a single bolus (30–50 $mg.kg^{-1}$), a continuous infusion, or both has been associated with decreased postoperative opioid consumption, delayed time to the first postoperative analgesic request, and decreased prevalence of postoperative shivering.[11]

Magnesium as an adjuvant to local anesthetics in spinal anesthesia has been associated with increased duration of anesthesia without affecting the time to achieve sensory or motor blockade.[12] Moreover, intravenous magnesium sulfate attenuates opioid-related side effects (e.g., nausea, vomiting, and pruritus).[9–11] To date, a limited number of studies have addressed magnesium as an adjuvant to local anesthetics for postoperative epidural analgesia. A former systematic review of eleven studies found that magnesium sulfate added to bupivacaine was associated with a delayed first analgesic requirement, fewer patients requiring rescue analgesia, and smaller doses of postoperative analgesics.[13] This systematic review with meta-analyses aimed to estimate the pooled effects of randomized controlled trials addressing the effectiveness and safety of magnesium sulfate as an adjuvant to bupivacaine, levobupivacaine, or ropivacaine for postoperative epidural analgesia in adult surgical patients.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[14] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO)[15] under registration number CRD42021231910.

Sources of information and search strategy

Articles, theses, abstracts, and conference reports of Randomized Control Trials (RCT) were searched from databases: MEDLINE (from 1946), Web of Science (from 1945), EMBASE (from 1947), Scholar Google, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no language restrictions. Filters were applied to searches to identify studies in human adults. Searches were conducted from December 2020 through January 2021.

The PubMed search included the following string: *(magnesium AND epidural anesthesia AND (humans [Filter])) AND ("randomized controlled trial" [Publication Type]) Filters: Humans*. Scholar Google search string was *"allintitle: magnesium epidural*. The string *"(('magnesium sulfate'/exp OR 'magnesium sulfate') AND ('epidural anesthesia'/exp OR 'epidural anesthesia') AND ([cochrane review]/lim OR [systematic review]/lim OR [meta-analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)) AND 'article'/it"* was used to search EMBASE. The Web of Science: was searched by using the following terms *"TI = (epidural AND magnesium)"*. The following terms were used to retrieve abstracts from CENTRAL: *"epidural OR intrathecal OR subarachnoid in Title Abstract Keyword AND magnesium sulfate in Title Abstract Keyword AND "postoperative pain" in Title Abstract"*.

Clinical questions

The clinical questions addressed the following PICOT elements: **Population**: adult patients undergoing general, epidural, or Combined Spinal-Epidural (CSEA) anesthesia scheduled for elective surgical procedures; **Intervention**: epidural administration of magnesium sulfate associated with local anesthetics solutions; **Comparison**: epidurally-administered local anesthetic alone or with placebo; **Primary outcome**: time to first analgesic request, opioid consumption, and visual analog pain scores; **Secondary outcomes**: prevalence of postoperative nausea or vomiting, pruritus, and shivering. **Time:** during the initial 24 postoperative hours.

Eligibility criteria and study selection

The three authors (GNB, AMJ, GROF) conducted independent literature searches and assessed titles, abstracts, and full papers of the selected references. The authors searched for Randomized Controlled Trials (RCT) on the adult (≥ 18 years old) surgical population, comparing the analgesic efficacy of magnesium sulfate added to epidurally administered local anesthetics solutions compared to local anesthetic alone or with a placebo. Studies were required to also provide data on at least one of the primary outcomes: the time to first postoperative request for rescue analgesics or the opioid consumption during the first 24 postoperative hours. No language restrictions were applied. The following were exclusion criteria: magnesium sulfate was administered via a route other than epidural (e.g., intrathecal, intravenous, or intramuscular); epidural magnesium sulfate

was associated with other adjuvants (e.g., opioid, ketamine, alpha-2 adrenergic agonists were added to the local anesthetic solution in the control group), the study was not a randomized controlled trial; the study was conducted in children or did not report any of the primary outcomes. Controversies about study inclusion were resolved by consensus among the authors.

Data extraction process and data items

Two investigators (GNB, AMJ) independently extracted data from the eligible studies on dedicated spreadsheets. Data presented as graphs in the original articles were extracted with the Engauge Digitizer software.[16] The following information was extracted from the studies included in meta-analyses: the number of patients in the intervention and control groups, type of surgery, anesthesia technique, anesthetic agents, epidural local anesthetic and dose, dose and concentration of the magnesium sulfate bolus and infusion, rescue analgesic and administration route, reported outcomes and the respective mean and standard deviation or frequency. The time to the first analgesic request was computed in minutes. Because distinct analgesics and routes of administration were used for rescue analgesia, their doses were transformed into intravenous morphine equivalents (mg) using converting factors provided elsewhere.[17–19] Average standard deviations of studies assessing the same outcome were imputed to studies that did not report the mean's standard deviation or standard error.[20] Outcome data were double-checked, consolidated, and included in the meta-analysis software.

Assessment of the risk of bias within studies

Individual within-study risk of bias was assessed according to the revised Cochrane risk-of-bias tool for Randomized Trials (ROB 2).[21] Studies were classified as "high risk" if a high risk of bias was assigned to any domain, or "some concerns" were assigned to multiple domains of the ROB 2.[21]

Summary measures

Weighted Mean Differences (MD) were used to summarize the effect sizes of outcomes measured on continuous variables: time to the first analgesic request, opioid consumption during the first 24 postoperative hours, and VAS pain scores at the sixth and 24th postoperative hours. The Risk Ratio (RR) was used to summarize results measured on categorical variables: postoperative nausea or vomiting, pruritus, and shivering. Ninety-five percent confidence intervals (95% CI) were estimated for effect size measures.

Synthesis of results

Random effects meta-analyses were used to estimate pooled effect sizes based on the following assumptions: the studies involved different treatment protocols (e.g., varying dose combinations of magnesium with local anesthetics in the intervention groups). Moreover, distinct time points were used to measure postoperative outcomes. Thus, variability among the different effect estimates could be attributed to within-study sampling error, between-study heterogeneity, or both. Cochrane Q tests and I^2 statistics were used to estimate statistical heterogeneity in effect sizes among the studies included in the meta-analyses,

Assessment of risk of bias across studies

The risk of publication bias was assessed by visual inspection of funnel plots based on the primary outcomes and quantified using Egger's test. Missing studies were filled, and the effect size was corrected using Duval & Tweedie's trim-and-fill method.[22,23] The standardized mean difference against its standard error was used to construct contour-enhanced funnel plots for the primary outcome, including filled studies and adjusted effect sizes from the trim-and-fill method.

Sensitivity analyses

Leave-one-out analyses were conducted to discard single-study dominance in effect sizes. Analyses were done by sequentially removing one study and estimating the effect size based on data from the remaining studies. Study dominance was ascribed to the removed study whenever pooled effect size *p*-values changed from significant to non-significant, or vice-versa.[24]

Different doses of magnesium sulfate were added to local anesthetics, intraoperative magnesium infusions followed bolus doses of magnesium sulfate in some studies, and effects were estimated on patients undergoing different types of surgery. These distinct characteristics might have affected the effect size estimates. Subgroup analyses and meta-regression were used to estimate the simultaneous influence of the abovementioned potential effect modifiers on the pooled effect sizes and the between-study heterogeneity. Random effects and Knapp-Hartung variance adjustment were used in meta-regression.[25]

Quality of evidence

The quality of evidence provided by the meta-analyses was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[26]

Software

Review Manager software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for meta-analyses. STATA 14/MP (StataCorp, College Station, TX, USA) was used to conduct Egger's tests (*metabias* module), Duval & Tweedie's trim-and-fill analyses (*metatrim* module), and meta-regression (*metareg* module).[22,25,27] The GRADEpro GDT software was used to construct a Summary of Findings (SoF) table and estimate evidence quality.[28]

Results

Study selection

Seventeen studies were included in the meta-analyses (Fig. 1). The complete list of retrieved references with reasons for rejection or acceptance are provided in e-component 1.

The seventeen studies[29–43] (1150 patients) used only magnesium as an adjuvant to local anesthetic in the intervention group. Only data applicable to the meta-analyses of the current study were extracted from these studies. The main characteristics of the studies are described in Table 1.

Primary and secondary outcomes of the included studies

Time to the first analgesic request was reported in 12 studies (790 patients).[29,31,33,34,36–42] Analgesic consumption during the first 24 postoperative hours was reported in six studies (416 patients).[30–32,34,37,44] Postoperative pain intensity was reported as visual analog pain scores during the first six postoperative hours in eight studies[31–34,37,39,41,43] (540 patients), and during the first 24 postoperative hours in five studies[30–32,34,37] (356 patients). Postoperative nausea and vomiting were reported in 12 studies[29–33,35,37,39–42] (818 patients), shivering was reported in ten studies[29,31,33,35,37,38,40–42] (640 patients), and pruritus was reported in five studies[31,32,35,37] (318 patients).

Types of surgery

Included studies were performed on patients undergoing the following surgical procedures: cesarean section (n = 2),[31,45] lower limb surgery (n = 6),[29,30,35,40,42,44] lower abdominal and pelvic surgeries (n = 5),[32,34,36,39,41] mixed lower limb and low abdominal surgery (n = 2),[33,38] spine surgery (n = 1),[43] and thoracotomy (n = 1).[37]

Type of anesthesia

Combined spinal-epidural anesthesia was used in one study,[45] combined epidural-general anesthesia was used in

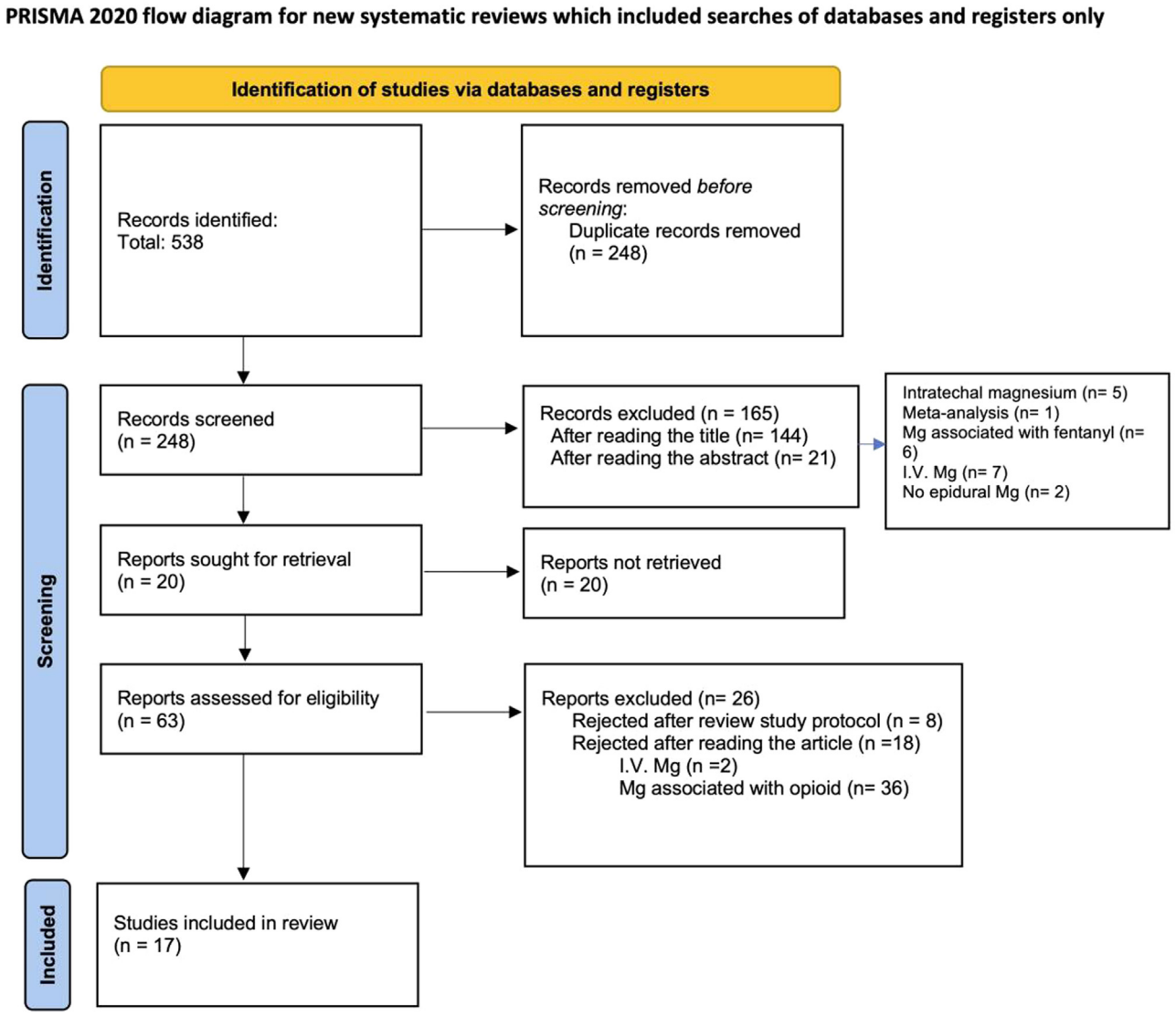

Figure 1 PRISMA study flow diagram.

Table 1 Characteristics of the studies.

Study ID	n $_{MgSO4}$	n control	Control group	Administration of $MgSO_4$	Language	Surgery	Type of anesthesia	Epidural local anesthetic (LA)	Dose (LA)	Epidural $MgSO_4$ Bolus	Epidural $MgSO_4$ infusion	Duration of infusion	Rescue analgesics	Outcomes of interest
Asha 2012[29]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Ropivacaine	16 mL 0.75%	50 mg		Before surgery	Epidural 9 mL of 0.25% ropivacaine bolus	TFAR, adverse effects
Daabis 2013[30]	40	40	Placebo (0.9% saline)	Bolus + infusion	English	Knee replacement	Epidural	Bupivacaine	1 mL 0.5% per segment	50 mg	$MgSO_4$: 10 mg.h^{-1}	During the surgery	Epidural fentanyl 2 μg.mL^{-1} + LA 0.08% bolus	Analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects,
Elsharkawy 2018[31]	30	30	Placebo (0.9% saline)	Bolus	English	Cesarean section	Epidural	Levobupivacaine	20 mL 0.5%	500 mg		Before surgery	diclofenac 75 mg VO or fentanyl 0.5 1 μg.kg^{-1} IV bolus	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Farouk 2008a[32]	29	29	Placebo (0.9% saline infusion before anesthesia induction until the end of the surgery)	Bolus before induction of anesthesia + intraoperative infusion	English	Hysterectomy	General	Bupivacaine	None	50 mg	10 mg.h^{-1}	During surgery	Epidural lidocaine bolus on demand	Analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Farouk 2008b[32]	29	29	Placebo (0.9% saline infusion before anesthesia induction until the end of the surgery)	Bolus at the end of the				surgery + infusion	English				Hysterectomy	General
Bupivacaine	None	50 mg		During surgery	Epidural lidocaine bolus on demand	Analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects								
Ghatak 2010[33]	30	30	Placebo (0.9% saline)	Bolus	English	Lower abdominal and lower limb surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery	Epidural bupivacaine 0.25% 8 mL bolus	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Gupta 2013[34]	30	30	Placebo (0.9% saline)	Bolus	English	Hysterectomy	Epidural	Bupivacaine	9 mL 0.125%	50 mg		End of surgery	Epidural fentanyl 1 μg.kg^{-1} bolus	TFAR, 24h analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Kandil 2012[44]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgery	Epidural	Bupivacaine	0.5% 1 mL per segment	50 mg	10 mg.h^{-1}	During surgery	PCEA fentanyl + LA+ pethidine IM	24h analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Lakra 2015[35]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery		PO adverse effects
Lenin 2012[36]	25	25	Placebo (0.9% saline)	Bolus	English	Lower abdominal surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery		TFAR
Mohamad 2015[37]	20	20	Placebo (0.9% saline)	Bolus	English	Thoracotomy	Epidural + general	Bupivacaine	8 mL 0.25%	50 mg		End of surgery	i.v. tramadol 50 mg	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects

Table 1 (*Continued*)

Study ID	n $_{MgSO4}$	n control	Control group	Administration of $MgSO_4$	Language	Surgery	Type of anesthesia	Epidural local anesthetic (LA)	Dose (LA)	Epidural $MgSO_4$ Bolus	Epidural $MgSO_4$ infusion	Duration of infusion	Rescue analgesics	Outcomes of interest
Munshi 2016[38]	30	30	Placebo (0.9% saline)	Bolus	English	Lower abdominal surgeries and lower limb surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery	Epidural tramadol 50 mg bolus	TFAR, PO adverse effects
Omar 2018[39]	50	50	Placebo (0.9% saline)	Bolus + epidural infusion levobupivacaine + magnesium infusion 5 $mL.h^{-1}$ until the end of the surgery	English	Lower abdominal and pelvic surgeries	Epidural + general	Levobupivacaine	14 mL 0.5%	50 mg	15 $mg.h^{-1}$	during surgery	i.v. pethidine 1 $mg.kg^{-1}$ + paracetamol 1g	TFAR, VAS pain scores, PO adverse effects
Radwan 2017[43]	22	22	Placebo (0.9% saline)	Bolus + infusion	English	Spine surgeries	Epidural + general	Levo-bupivacaine	14 mL 0.5%	50 mg	10 $mg.h^{-1}$ (LA 0.125%+ $MgSO_4$ 2 $mg.mL^{-1}$. 5 $mL.h^{-1}$)	During surgery	Para-cetamol 1g i.v. / 50 mg pethidine i.v.	Analgesic consumption (24 PO hours, VAS pain scores, PO adverse effects
Rekha 2020[40]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Ropivacaine	16 mL 0.75%	50 mg		Before surgery	Epidural ropivacaine bolus	TFAR, analgesic consumption (24 PO hours), PO adverse effects
Roy 2015[41]	30	30	Placebo (0.9% saline)	Bbolus	English	Infra-umbilical surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery	Epidural bupivacaine 0.5% bolus	TFAR, VAS pain scores, PO adverse effects
Shahi 2014[42]	40	40	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Bupivacaine	14 mL 0.5%	50 mg		before surgery	Epidural bupivacaine 12 mL 0.125% bolus	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Sun 2012 [45]	50	50	Placebo (0.9% saline)	Bolus	English	Cesarean section	CSEA	Bupivacaine	10 mL 0.1%	500 mg		During surgery	Epidural 8 mL LA 0.1% bolus + FTN 1 $\mu g.mL^{-1}$ + $MgSO_4$ 1 $mg.mL^{-1}$	TFAR, analgesic consumption (24 PO hours, VAS pain scores, PO adverse effects

CSEA, Combined Spinal-Epidural Anesthesia; i.v., Intravenous; LA, Local Anesthetic; $MgSO_4$, Magnesium Sulfate; PO, Postoperative; TFAR, Time for the First Analgesic Request; VAS, Visual Analog Scale.

two studies.[39,37] Epidural anesthesia alone was used in 14 studies.[29–31,33–36,38,40–42,44]

Magnesium doses and regimens

All studies used epidural magnesium as a single bolus dose. The initial bolus dose of magnesium sulfate was 50 mg in 15 studies,[29,30,32–44] and 500 mg in two studies.[31,45] After the initial bolus, continuous epidural infusion of magnesium sulfate was used in five studies[30,32,39,43,44] at rates varying from 10–15 mg.h^{-1}, limited to the intraoperative period in four studies, and continued for 48 hours postoperatively in one study.[32]

Rescue medication modalities

In six studies, rescue analgesia was provided by epidural injections of plain Local Anesthetic (LA) solutions;[29,32,33,40–42] fentanyl was added to epidural LA in one study;[30] intramuscular pethidine was used in conjunction with epidural local anesthetic plus fentanyl in one study,[44] and magnesium sulfate was added to the local anesthetic fentanyl solution in one study.[45] Three studies reported only systemic analgesia with IV fentanyl, oral diclofenac, IV paracetamol or IV tramadol.[37,39,43] One study used epidural tramadol as a rescue analgesic.[6] Two studies did not report rescue medication.[7]

Synthesis of results

Primary outcomes

Epidural administration of magnesium sulphate added to local anesthetics delayed the first postoperative analgesic request as compared to placebo by 72.4 minutes (95% CI = 10.22–134.58 min; $p < 0.001$; I^2 = 99.8%; GRADE = very low) (Fig. 2). Postoperative opioid consumption during the first 24 postoperative hours (measured as IV morphine equivalents) was lower among patients who received epidural magnesium in combination with local anesthetics (MD = -7.2 mg; 95% CI = -9.30 – -5.09 mg; $p < 0.001$; I^2 = 98%; GRADE = very low) (Fig. 3). Pain intensity within the first six postoperative hours measured on 10-cm VAS was lower among patients who received epidural magnesium sulfate (MD = -1.01 cm; 95% CI = -1.40–0.64 cm; $p < 0.001$; I^2 = 88%). Comparisons between raw VAS pain scores at the 24 PO hours between magnesium and placebo yielded a borderline p-value (MD = -0.56 cm; 95% CI = -1.14–0.01 cm; $p = 0.05$; I^2 = 97%) (Fig. 4).

Secondary outcomes

Epidural magnesium alone did not differ from placebo regarding the probabilities of PONV (RR = 0.70; 95% CI = 0.34–1.14; $p = 0.15$; I^2 = 0%) or pruritus (RR = 1.23; 95% CI = 0.50–2.98; $p = 0.65$; I^2 = 0%) but reduced the risk of perioperative shivering (RR = 0.39; 95% CI = 0.21–0.71; $p = 0.002$; I^2 = 18%) (Fig. 5).

Sensitivity analyses

Leave-one-out procedures

One study was responsible for the significant p-value found in the meta-analyses of the time to first analgesic request outcome. The elimination of this study's results caused the weighted mean difference between groups move from 72.40 min (95% CI = 10.22, 134.58 min; $p = 0.02$) to 66.10 min (95% CI = -4.49, 136.69 min; $p = 0.07$). There was no study dominance among the postoperative opioid consumption meta-analysis studies.

Distinct doses of magnesium sulfate (50 or 500 mg) added to local anesthetics (t = 1.31; $p = 0.21$), bolus administration versus bolus dose followed by intraoperative magnesium infusions (t = 0.46; $p = 0.65$) or the types of surgery ($F_{(4,7)} = 0.45$; $p = 0.77$) were not identified as effect modifiers or inter-study heterogeneity at meta-regression of the time to first analgesic request outcome. However, magnesium sulfate added to levobupivacaine was associated with longer times to first analgesic request than bupivacaine or ropivacaine (t = 2.81; $p = 0.02$). Forest plots of subgroup analyses are shown in e-component 2. No subgroup analyses or meta-regression were conducted to assess the effect of the potential effect modifiers on the postoperative opioid consumption outcome because of the insufficient number of studies.

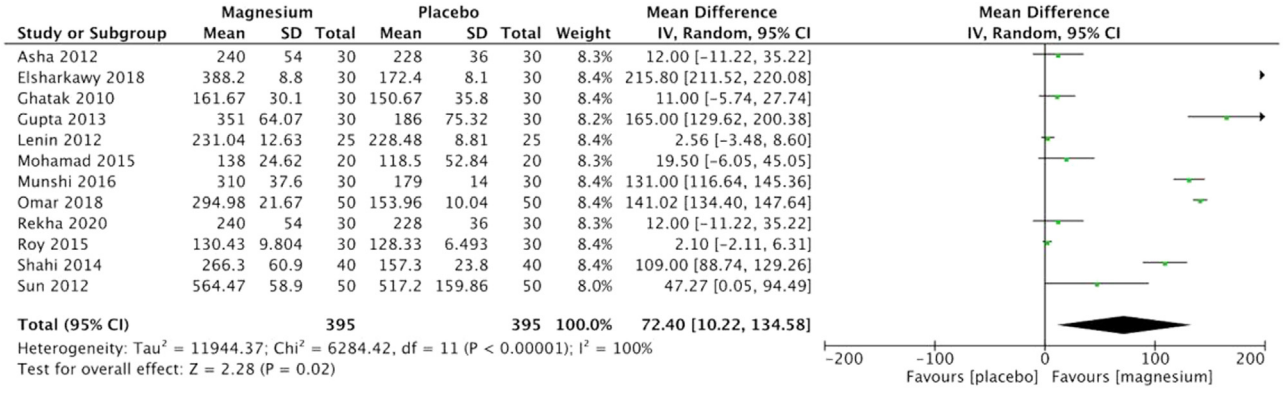

Figure 2 Forest plots of pooled comparisons of time to the first postoperative opioid request. Boxes represent the weighted mean difference between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled averaged mean difference and the lateral extremes, the 95% confidence limits of the mean difference. IV, Inverse Variance Method; Random, Random-effects model; SD, Standard Deviation.

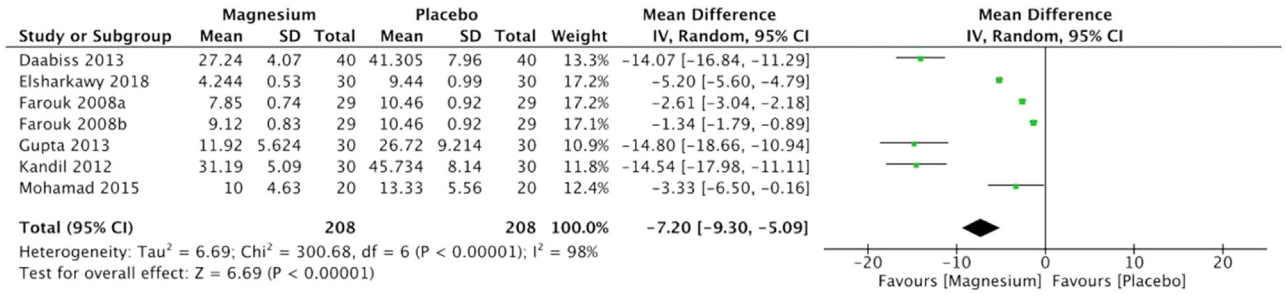

Figure 3 Forest plots of pooled comparisons of postoperative opioid consumption. Boxes represent the weighted mean difference between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled averaged mean difference and the lateral extremes, the 95% confidence limits of the mean difference. IV, Inverse Variance method; Random, Random-effects model; SD, Standard Deviation.

Assessment of risk of bias within studies

Of the 17 studies included in meta-analyses, 15 raised some concerns about bias in at least one ROB 2 assessment tool domain, while 2 were classified as having a low risk of bias in all domains. No study was classified as having a high risk of bias (Fig. 6, e-component 3)

Assessment of risk of publication bias across studies

Eggers's test did not detect publication bias or small-study effects in meta-analyses of time to first analgesic request among studies that compared epidural magnesium to placebo (p = 0.75). Contour-enhanced funnel plots, including filled studies, are shown in e-component 3. Publication bias estimation based on the opioid consumption outcome was impossible given the insufficient number of studies available.

Quality of evidence

Very low confidence was assigned to the meta-analyses of the primary outcomes of the GRADE assessment, suggesting that the actual effect may be different from the estimated effect, driven by the within-study severe risk of bias, inconsistency, and imprecision issues that might have biased meta-analyses.[46] A GRADE summary of findings table is provided in e-component 4. A completed PRISMA checklist is provided in e-component 5.

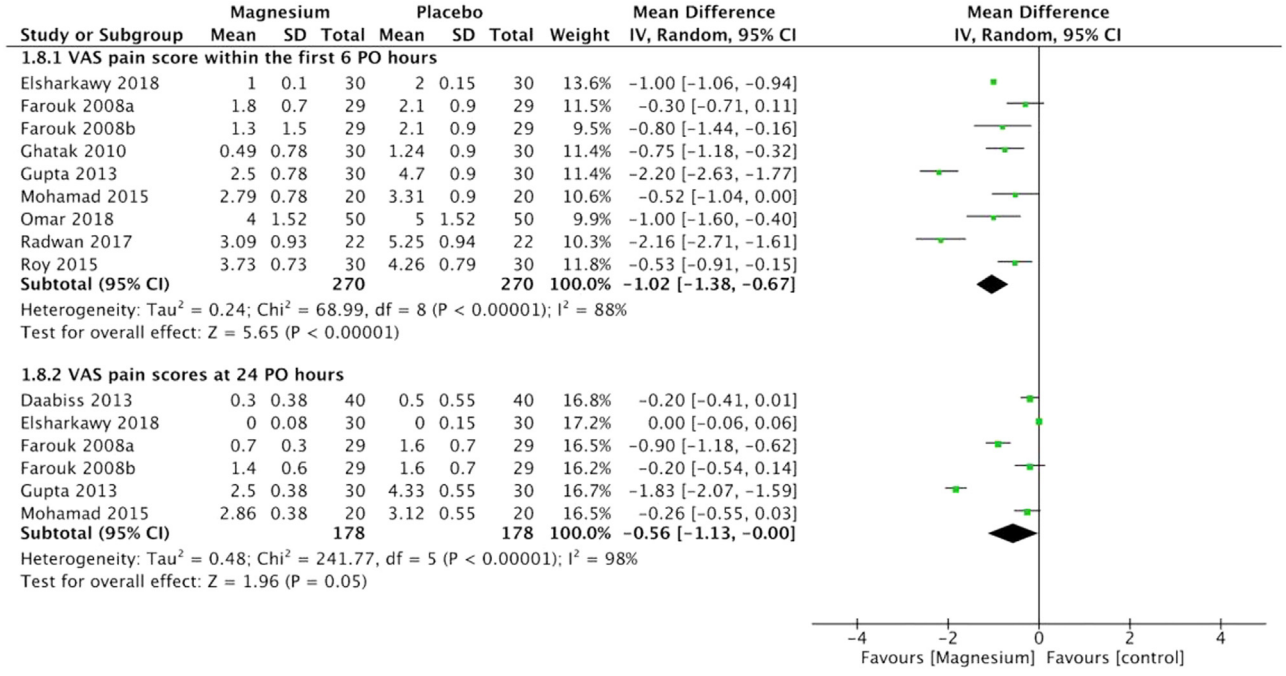

Figure 4 Forest plots of pooled comparisons of VAS pain scores within the first 6 and 24 postoperative hours. Boxes represent the weighted mean difference between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled averaged mean difference and the lateral extremes, the 95% confidence limits of the mean difference. IV, Inverse Variance method; Random, Random-effects model; SD, Standard Deviation.

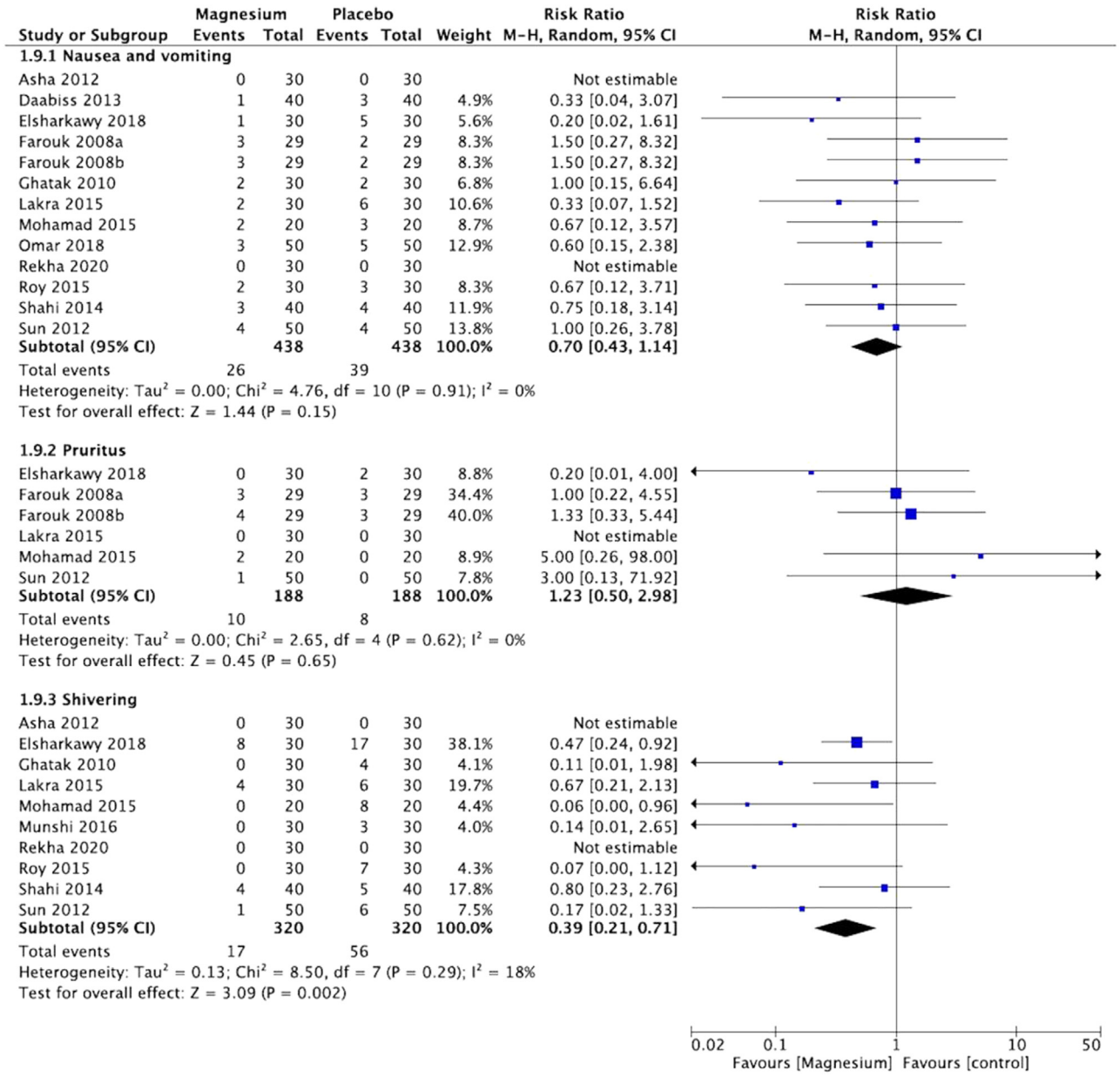

Figure 5 Forest plots of pooled comparisons of postoperative side-effects: PONV, pruritus, and shivering. Boxes represent the Risk Ratio (RR) between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled risk ratio and the lateral extremes, the 95% confidence limits of the mean difference. IV, inverse variance method; Random, Random-effects model; SD, standard deviation.

Discussion

Mathematically, magnesium delayed the first postoperative analgesic request and decreased 24-hour postoperative opioid consumption compared to placebo. However, serious issues pervaded these meta-analyses. First, high statistical heterogeneity was found among studies' effect sizes. According to meta-regression, statistical heterogeneity was not due to between-studies methodological aspects, like the type of surgery, the use or not of an intraoperative magnesium infusion following the bolus dose, or even the doses (50 mg or 500 mg) used in the studies included in the meta-analyses. Consequently, systematic sampling errors may have contributed to differences among studies' effect sizes. Second, part of the data was extracted from graphs using a vector graph software, which may have introduced some imprecision in the extracted data. Moreover, because different analgesic and routes of administration were used, postoperative analgesic consumption was based on published equivalence ratios, which are not exact measures. Third, some concerns were raised about the critical aspects of randomized controlled trial methodology, mainly because most articles provided little information about randomization methods, allocation concealment, and participants' and investigators' blinding. Most studies did not report a clear *a priori* statistical plan or protocol registration, raising concerns about selective reporting bias.

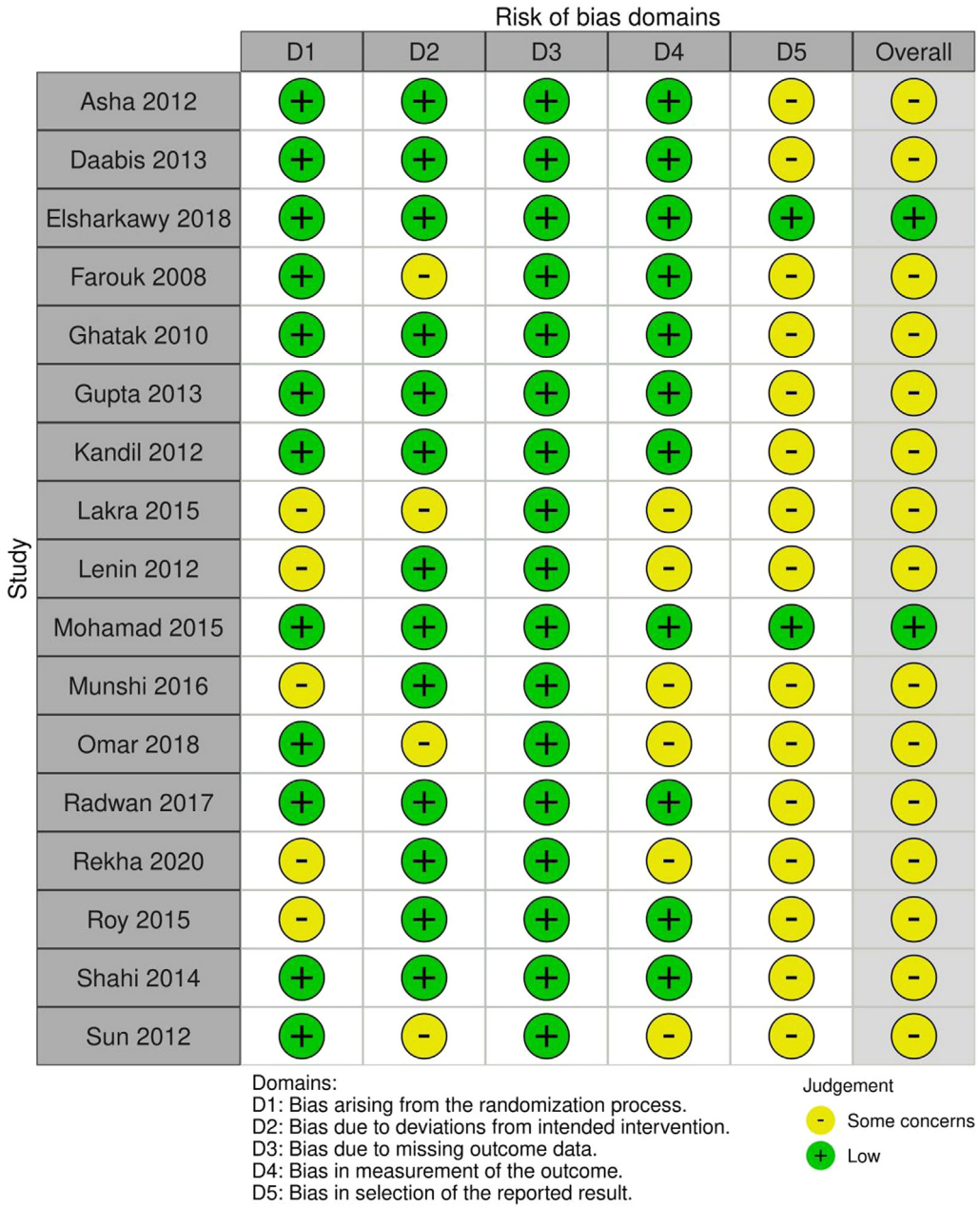

Figure 6 Rob 2 traffic-light plot showing results of within-studies risk of bias assessment. Although some concerns were raised on multiple aspects of most studies, no study showed reasons for assigning a high risk of bias in any domain of the RoB 2 tool.

Visual analog pain scores within the first six postoperative hours were lower among patients who received epidural magnesium. Still, they did not differ from the VAS scores of the placebo group at the 24-hour postoperative measurement occasion. Some studies did not report standard deviations for the mean VAS pain scores. Standard deviations were imputed to those studies to perform the meta-analyses according to the prognostic method proposed by Ma and colleagues.[20] Missing standard deviation imputation methods are acceptable alternatives to study data deletion during data extraction for meta-analyses and have been demonstrated to produce safe and informative estimates.[47]

Epidurally administered magnesium sulfate did not affect the incidence of postoperative nausea, vomiting, and pruritus but decreased the incidence of perioperative shivering. As suggested by the low statistical heterogeneity found in the separate meta-analyses, these findings were consistent across the available studies. Magnesium may affect hemodynamic stability, prolong neuromuscular block, and delay the awakening from anesthesia.[48,49] Insufficient data were present in the available studies. Furthermore, magnesium serum levels were not measured in any of the studies. The absence of such information prevents an appreciation of the safety profile of magnesium administered epidurally. Significant neurodegeneration has been reported after single or repeated intrathecal magnesium sulfate injections in rats.[50] However, data on the postoperative neurological status of patients were not present in the studies

included in this systematic review, further hindering conclusions about the neurological safety of epidurally administered magnesium sulfate.

According to GRADE criteria, this systematic review provided a very low quality of evidence for using epidural magnesium sulfate added to local anesthetics, suggesting that the actual effects may differ substantially from the estimated effects, that is very low certainty.

Besides the issues raised in the preceding paragraphs, additional methodological limitations of this study must be acknowledged. First, time to the first analgesic request, postoperative opioid consumption, and pain scores are imperfect surrogates for postoperative pain intensity because they are affected by factors dependent on the patients (e.g., culture, level of education, altruism, expectation, beliefs),[51] and on the mode of administration (e.g., patient- versus nurse-controlled analgesia or criteria for postoperative analgesia administration),[52] or the evaluator.[53] Second, readers must also consider that the small number of patients included in the limited number of available studies may have caused type II statistical error in meta-analyses and meta-regression. Combined spinal-epidural anesthesia was used in one study included in the time to first analgesic request meta-analysis.[45] Residual effect of spinal anesthetic might have affected the effect size estimator, but the elimination of this study during leave-one-out procedures did not affect the estimate, heterogeneity, or the meta-analysis' *p*-value.

This systematic review highlights caveats of mistrusting the mathematical results of small, low-quality studies and meta-analyses based on such studies. A meta-analysis by itself cannot fix the methodological issues of the included studies. However, systematic review methodology includes a critical appraisal of the data sources for the meta-analyses, helping readers to discern about relying or not on the numbers brought about by statistical calculations.[54]

Conclusion

Adding magnesium sulfate to local anesthetics is associated with a delayed first postoperative analgesic request and decreased opioid consumption during the first 24 postoperative hours. However, because of severe methodological issues in the available studies, the pooled effects found in the meta-analyses may have been seriously biased. Consequently, a very weak level of recommendation supports the use of magnesium sulfate as an adjuvant to epidural analgesia based on local anesthetics. In other words, the clinical use of magnesium sulfate as an adjuvant to epidural anesthetics lacks solid evidence and should be discouraged until large, well-designed clinical trials provide definitive evidence.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2022.08.005.

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