Perioperative Systemic Magnesium to Minimize Postoperative Pain

A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Background: Systemic magnesium has been used to minimize postoperative pain with conflicting results by clinical studies. It remains unknown whether the administration of perioperative systemic magnesium can minimize postoperative pain. The objective of the current investigation was to evaluate the effect of systemic magnesium on postoperative pain outcomes.

Methods: A wide search was performed to identify randomized controlled trials that evaluated the effects of systemic magnesium on postoperative pain outcomes in surgical procedures performed under general anesthesia. Meta-analysis was performed using a random-effect model. Publication bias was evaluated by examining the presence of asymmetric funnel plots using Egger regression.

Results: Twenty randomized clinical trials with 1,257 subjects were included. The weighted mean difference (99% CI) of the combined effects favored magnesium over control for pain at rest (≤4 h, −0.74 [−1.08 to −0.48]; 24 h, −0.36 [−0.63 to −0.09]) and with movement at 24 h, −0.73 (−1.37 to −0.1). Opioid consumption was largely decreased in the systemic magnesium group compared with control, weighted mean difference (99% CI) of −10.52 (−13.50 to −7.54) mg morphine IV equivalents. Publication bias was not present in any of the analysis. Significant heterogeneity was present in some analysis, but it could be partially explained by the sole intraoperative administration of magnesium compared with the intraoperative and postoperative administration. None of the studies reported clinical toxicity related to toxic serum levels of magnesium.

What We Already Know about This Topic

- IV magnesium can be used to treat several conditions in the perioperative period
- One frequently studied use of magnesium is as an analgesic adjunct for postoperative pain relief

What This Article Tells Us That Is New

- In this meta-analysis of data from more than 1,200 patients, systemically administered magnesium decreased postoperative pain a small, statistically significant amount; a reduction in morphine use was clearly evident
- The reduction in both pain and morphine use indicates magnesium has some utility as an analgesic adjunct after surgery

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Conclusion: Systemic administration of perioperative magnesium reduces postoperative pain and opioid consumption. Magnesium administration should be considered as a strategy to mitigate postoperative pain in surgical patients.

MAGNESIUM is the second most common intracellular ion with an important role to maintain organisms' homeostasis. Magnesium is a crucial element for the function of enzymes, neurotransmission, and cell signaling.[1] Animal studies demonstrated that magnesium is an antagonist of *N*-methyl-D-aspartate glutamate receptors, which can alter the perception and duration of pain.[2] Since dietary intake is the main source of magnesium in humans, unpredictable operating room schedules along with dietary restrictions before surgical procedures are common contributors for the occurrence of hypomagnesaemia during the perioperative period.[3] Perioperative administration of fluids without magnesium supplementation can also contribute to the occurrence of hypomagnesaemia.[3]

Magnesium has been used for many years in an attempt to minimize postoperative pain. In 1963, Anstett[4] reported on the effect of magnesium chelates on painful postoperative pulmonary scars. Magnesium has been examined *via* different routes of administration (systemic, topical, intrathecal, and epidural) by several investigators for the prevention of postoperative pain.[5] Among the routes of administration, the systemic route is the most studied and likely to have a greater level of therapeutic adherence by perioperative clinicians.

A large number of clinical studies have examined the effect of systemic perioperative magnesium administration on postoperative pain outcomes with contradictory findings. In addition, a previous systematic review performed in 2007 that examined 14 randomized clinical trials on 778 patients did not detect an effect of systemic magnesium administration on the reduction of postoperative pain outcomes.[6] However, the investigators noted the need for more studies due to the inexpensive and promising biological basis for magnesium antinociceptive effects.[6] Currently, perioperative magnesium is not considered a useful adjunct to minimize postoperative pain.[7]

The major objective of this quantitative systematic review was to evaluate the effect of perioperative systemic magnesium on acute pain management outcomes. A secondary objective was to examine possible side effects and toxicity associated with the administration of perioperative magnesium.

Material and Methods

We performed a quantitative systematic review following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[8]

Systematic Search

Published reports of randomized trials evaluating the effects of systemic magnesium on surgical postoperative pain were searched using the National Library of Medicine's PubMed database, the Cochrane Database of Systematic Reviews, and Google Scholar inclusive till June 1, 2012. Free text and MeSH terms "magnesium", "pain", "postoperative", "preoperative", "analgesia", and "opioid" were used individually and in various combinations. No language restriction was used. The search was limited to randomized controlled clinical trials in human subjects more than 18 yr of age. An attempt to identify additional studies not found by the primary search methods was made by reviewing the reference lists from identified studies. No search was performed for unpublished studies. This initial search yielded 84 randomized clinical trials.

Selection of Included Studies

The study's inclusion and exclusion criteria were determined before the systematic search. Two authors (Drs. De Oliveira and Castro-Alves) independently evaluated the abstract and results of the 84 articles obtained by the initial search. Articles that were clearly not relevant based on our inclusion and exclusion criteria were excluded at this phase. Disagreements on inclusion of the articles were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a third investigator (Khan). The third investigator was blinded regarding evaluation of the first two authors.

Inclusion and Exclusion Criteria

We included randomized controlled trials that compared perioperative IV magnesium administration with an inactive (placebo or "no treatment") control group in patients undergoing surgical procedures under general anesthesia. Trials reporting analgesia after neuraxial or nerve administration of magnesium were excluded. Trials that evaluated the effect of magnesium in patients undergoing procedure with a neuraxial or nerve block were excluded to optimize clinical homogeneity. Trials that did not use magnesium intraoperatively were also excluded in order to improve clinical homogeneity. Studies containing a concurrent use of an alternative multimodal analgesia regimen were excluded if a direct comparison of magnesium and control could not be established. Included studies had to report at least on pain scores or opioid consumption as postoperative pain outcomes. No minimum sample size was required for inclusion in the meta-analysis.

Validity Scoring

Two authors (Drs. De Oliveira and Castro-Alves) independently read the included reports and assessed their methodological validity, using a modified Jadad 5-point quality scale.[9] The scale evaluates the study for the following: randomization, double-blind evaluation, concealment of study group to evaluator, valid randomization method, and completeness of data at follow-up. Discrepancies in rating of the trials were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute

was resolved with the help of a third investigator (Khan). As only randomized trials were included in the analysis, the minimum possible score of an included trial was 1 and the maximum was 5. Trials were not excluded or weighted in the analysis based on quality assessment scores.

Data Extraction

Two authors (Drs. De Oliveira and Castro-Alves) independently evaluated the articles of all included trials and performed data extraction using a data collection form specifically developed for this review.

Discrepancies were resolved by discussion between the two investigators (Drs. De Oliveira and Castro-Alves). If an agreement could not be reached between the two investigators, the decision was made by a third investigator (Khan). Data extracted from trials included the mean systemic magnesium dose and duration of administration, sample size, number of subjects in treatment groups, follow-up period, type of surgery, early pain scores (≤4 h) at rest and at movement, late pain scores (24 h) at rest and at movement, cumulative opioid consumption, time to rescue analgesic administration (minutes), and adverse events. Postoperative opioid consumption was converted to the equivalent dosage of IV morphine.[10] Visual analog scale or numeric rating scale of pain were converted to a 0–10 numeric rating scale.

Data were initially extracted from tables or text. For data not available in tables, the data was abstracted from available figures. Dichotomous data on the presence or absence of adverse effects was extracted and converted to incidence, whereas continuous data were recorded using mean and SD. Data presented only as median and range were converted to means and SD, using previously described methodology.[11] In studies that involved more than one dosage group comparison with a single control group, the control group was split according to the number of comparisons. When required, the SD for pain scores was estimated using the most extreme values. The most conservative value was used when the same outcome was reported more than once for a determined period.

Definition of Relevant Outcome Data

Primary Outcomes. Early acute postoperative pain scores (visual analog scale or numeric rating scale) at rest and at movement (0–4 h postoperatively); late acute postoperative pain scores (visual analog scale or numeric rating scale) at rest and at movement (24 h postoperatively); and cumulative opioid consumption (24 h) in the postoperative period.

Secondary Outcomes. The time to first analgesic administration (minutes); adverse events including, postoperative bradycardia, hypotension, nausea and/or vomiting, and shivering.

Meta-analyses

The weighted mean differences with 99% CI were determined and reported for continuous data. For dichotomous data (adverse effects), the Peto odds ratio (OR; to account for the potential of zero counts in the cells for low-frequency outcomes) and 99% CI are reported. For primary outcomes, a significant effect compared with placebo required that the 99% CI for continuous data did not include zero, and for dichotomous secondary data, the 95% CI did not include 1.0. We calculated the number needed to treat, based on the absolute risk reduction, as an estimate of a beneficial effect. Because of the different surgical procedures, we used a random-effect model in an attempt to generalize our findings to studies not included in our meta-analysis.[12] Publication bias was evaluated by examining for asymmetric funnel plots, using Egger regression test.[13,14] A one-sided P value less than 0.05 was considered as an indication of an asymmetric funnel plot. A file drawer analysis described by Rosenthal was performed in the case of an asymmetric funnel plot. The test estimates the lowest number of additional studies required to change the combined effect to nonsignificance assuming the average z-value of the combined P values of these missing studies would be 0.[15] Sensitivity analysis was performed to assess the impact of the elimination of a single trial on the results of the analysis.

Heterogeneity of the included studies was further evaluated if the I^2 statistic was greater than 50%. The I^2 statistic is a test of heterogeneity, which measures the variability between studies included in a quantitative analysis in respect to an evaluated outcome. I^2 values range between 0 and 100%, where 0 represents perfect homogeneity among included studies, and 100% represents the highest degree of heterogeneity. Further analysis was planned *a priori* to explore nontrivial heterogeneity of the treatment effect across the included studies, including duration of magnesium administration (intraoperative only *vs.* intraoperative and postoperative) and quality of included studies evaluated by the Jadad score. Subgroup analysis was performed to investigate the effect of duration of magnesium infusion (intraoperative only *vs.* intraoperative and postoperative) on the pain outcomes. Subgroup analysis was also performed to test whether the overall effect of magnesium on evaluated outcomes changed when lower quality studies (Jadad ≤3) were removed from the analysis. The proportion of the total variance explained by the covariates (R^2) was calculated by dividing the random-effects pooled estimates of variance (τ squared) within studies by the total variance (total τ squared). The value obtained was then subtracted from 1. When values fall outside the range of 0–100%, they were set to the closest value (0 or 100%.). A *post hoc* meta-regression analysis was performed to evaluate a possible association between total magnesium dosage and the effect size on evaluated outcomes. Because we prespecified five primary outcomes (2 pain states at two times each, plus opioids), we utilized a P value less than 0.01 to minimize the chance of type I error.

Analysis was performed using Stata version 11 (College Station, TX) and Comprehensive Meta-analysis software version 2 (Biostat, Englewood, NJ).

Results

Of the 84 initially evaluated abstracts, 34 studies initially met the inclusion criteria (fig. 1). Fourteen studies were subsequently excluded, five did not report on evaluated outcomes,[16–20] one did not used magnesium intraoperatively,[21] two trials did not provide a direct comparison between magnesium and control,[22,23] four did not evaluate the systemic route of magnesium administration,[24–27] and two trials evaluated patients receiving neuraxial anesthesia and/or analgesia.[28,29] The characteristics of included studies are listed in table 1. The evaluated trials included data from 1,257 subjects and were published between 1996 and 2011.[30–49] The median and interquartile range number of patients in the included studies receiving magnesium was 25 (17.5–35). The median and interquartile range modified Jadad scale score was 4 (3–4.5). The trials tested systemic magnesium given either intraoperatively, or intraoperatively/postoperatively in a large variety of surgical procedures. All 20 studies reported on opioid consumption and/or pain scores. Six studies reported pain scores for both rest and activity.[32–34,37,39,45]

Early (0–4 h) Pain at Rest

The aggregate effect of the 18 studies evaluating the effect of systemic magnesium on early pain at rest favored magnesium over control with a weighted mean difference (99% CI) of −0.74 (−1.08 to −0.48; fig. 2).[30–41,43,45–49] One study provided two comparisons and both were included in the analysis.[39] There was no evidence of publication bias as given by the test for an asymmetric funnel plot (P = 0.40; fig. 3). Heterogeneity was high (I^2 = 87). Seventy-seven percent of the total variance was explained by studies which did not use systemic magnesium postoperatively. Heterogeneity was low for studies that used systemic magnesium both intraoperatively and postoperatively (I^2 = 32%) and high for studies that used systemic magnesium intraoperatively only (I^2 = 91%). The aggregated effect for studies that used systemic magnesium both intraoperatively and postoperatively on early pain at rest was greater than studies that used magnesium only intraoperatively, weighted mean difference (99% CI) of −0.74 (−0.85 to −0.64) and −0.34 (−0.62 to −0.05), respectively (P = 0.001). A meta-regression analysis did not identify an association between the total magnesium dosage administered and an effect on early pain at rest (slope [95% CI] = 0.01 [−0.95 to 0.07]; P = 0.73 compared with slope = 0.) Removal of lower quality studies (Jadad ≤3) did not significantly change the effect of magnesium on early pain at rest, weighted mean difference (99% CI) of −0.77 (−1.06 to −0.48) compared with the original analysis (P = 0.93).

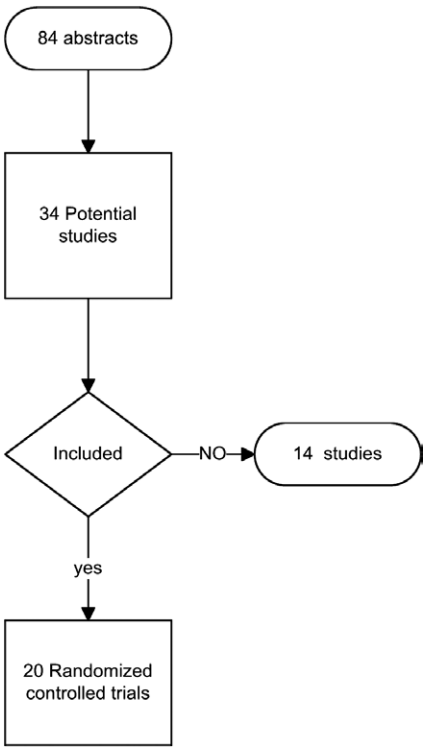

Fig. 1. Flow chart outlining retrieved, excluded, and evaluated randomized controlled trials.

Early (0–4 h) Pain at Movement

The overall effect of six studies[32–34,37,39,45] evaluating systemic magnesium on early pain at movement compared with control, did not show a significant benefit of magnesium, mean difference (99% CI) of −0.52 (−1.15 to 0.10; fig. 4). One study provided two comparisons and both were included in the analysis.[39] The funnel did not demonstrate asymmetry (P = 0.35; fig. 5). Heterogeneity was moderate (I^2 = 57) and it could not be explained by duration of the systemic magnesium infusion. Sensitivity analysis demonstrated that removal of the study of Saadawy *et al.*[32] or Mentes *et al.*[34] would significantly change the results. Removal of lower quality studies (Jadad ≤3) did not significantly change the effect of magnesium on postoperative opioid consumption, weighted mean difference (99% CI) of −0.2 (−0.8 to 0.32) compared with the original analysis.

Late (24 h) Pain at Rest

The overall effect of 13 studies[30–34,36–38,41,43,45,46,48] evaluating systemic magnesium on late pain at rest compared with control favored magnesium with a mean difference (99% CI) of −0.36 (−0.63 to −0.09; fig. 6). The funnel did not demonstrate asymmetry (P = 0.40; fig. 7). Heterogeneity was high (I^2 = 71). Twenty-nine percent of the total variance could be explained by studies which only used systemic magnesium intraoperatively. The aggregated effect for studies that used systemic magnesium both intraoperatively and postoperatively on late pain at rest was significantly different when compared with control, weighted mean difference (99% CI) of −0.40 (−0.47 to −0.33). In contrast, the aggregated effect for studies that used magnesium only during the intraoperative period on late pain at rest was not significantly different than the control group, weighted mean difference (99% CI) of −0.22

Table 1. Summary of Studies Included in Analysis

Authors	Procedures	Number Treatment/ Control	Intervention
Song *et al.*[30]	Thyroidectomy	28/28	Magnesium sulfate 30-mg/kg bolus followed by 10 mg/kg intraoperative infusion
Jaoua *et al.*[31]	Major abdominal surgery	20/20	Magnesium sulfate 50-mg/kg bolus followed by 10 mg kg^{-1} h^{-1} infusion over 24 h
Saadawy *et al.*[32]	Laparoscopic cholecystectomy	40/40	Magnesium sulfate 50-mg/kg bolus followed by 25 mg kg^{-1} h^{-1} intraoperative infusion
Amor *et al.*[33]	Major abdominal surgery	24/24	Magnesium sulfate 50-mg/kg bolus followed by 0.5 g/h infusion over 6 h
Mentes *et al.*[34]	Laparoscopic hysterectomy	41/42	Magnesium sulfate 50-mg/kg intraoperative infusion
Ferasatkish *et al.*[35]	Coronary artery bypass surgery	109/109	Magnesium sulfate infusion 32 M kg^{-1} h^{-1} (Infusion duration was not specified)
Oguzhan *et al.*[36]	Lumbar disc surgery	25/25	Magnesium sulfate 30-mg/kg bolus followed by 10 mg kg^{-1} h^{-1} intraoperative infusion
Ryu *et al.*[37]	Total abdominal hysterectomy	25/25	Magnesium sulfate 50-mg/kg bolus followed by 15 mg kg^{-1} h^{-1} intraoperative infusion
Ozcan *et al.*[38]	Thoracotomy	12/12	Magnesium sulfate 30-mg/kg bolus followed by 10 mg kg^{-1} h^{-1} infusion over 48 h
Tramèr *et al.*[39]	Inguinal hernia repair and varicose veins	41/39 41/60	Magnesium sulfate 4 g intraoperative infusion
Cizmeci *et al.*[40]	Nasal surgery	30/30	Magnesium sulfate 50-mg/kg bolus followed by 8 mg kg^{-1} h^{-1} intraoperative infusion
Tauzin-Fin *et al.*[41]	Prostatectomy	15/15	Magnesium sulfate 50 mg/kg bolus after induction and before skin closure
Seyhan *et al.*[42]	Total abdominal hysterectomy	60/20	Magnesium sulfate 40-mg/kg bolus followed by no infusion, 10 mg/kg or 20 mg/kg infusion for 4 h
Bhatia *et al.*[43]	Open cholecystectomy	25/25	Magnesium sulfate 50-mg/kg bolus followed by 15 mg kg^{-1} h^{-1} intraoperative infusion
Levaux *et al.*[44]	Spine surgery	12/12	Magnesium sulfate 50-mg/kg bolus
Kara *et al.*[45]	Abdominal hysterectomy	12/12	Magnesium sulfate 30-mg/kg bolus followed by 0.5 g/h infusion over 20 h
Zarauza *et al.*[46]	Colorectal surgery	23/24	Magnesium sulfate 30-mg/kg bolus followed by 10 mg kg^{-1} h^{-1} infusion over 20 h
Koinig *et al.*[47]	Knee arthroscopy	23/23	Magnesium sulfate 50-mg/kg bolus followed by 8 mg kg^{-1} h^{-1} intraoperative infusion
Wilder-Smith *et al.*[48]	Abdominal hysterectomy	12/12	Magnesium laevulinate 8-M bolus followed by 8-M/h infusion over 5 h
Tramer *et al.*[49]	Abdominal hysterectomy	21/21	Magnesium sulfate 3 g-bolus followed by 0.5 mg/kg infusion over 20 h

IV = intravenous; PCA = patient-controlled analgesia; PRN = as needed.

(−0.58 to 0.13). The overall analysis did not significantly change by removing any of the included studies. A meta-regression analysis did not identify an association between the total magnesium dosage administered and an effect on late pain at rest (slope [95% CI] = −0.04 [−0.08 to 0]; P = 0.07 compared with slope = 0). Removal of lower quality studies (Jadad ≤3) did not significantly change the effect of magnesium on late pain at rest, weighted mean difference (99% CI) of −0.5 (−0.74 to −0.26) compared with the original analysis (P = 0.25).

Late Pain at Movement

The overall effect of five studies[32–34,37,45] that examined the effect of systemic magnesium on late pain at movement compared with placebo favored systemic magnesium, mean difference (99% CI) of −0.73 (−1.37 to −0.1; fig. 8). The funnel did not demonstrate asymmetry (P = 0.42; fig. 9). Heterogeneity was high (I^2 = 72) and it could not be explained by the time of systemic magnesium administration (intraoperatively only *vs.* intraoperatively and postoperatively). Sensitivity analysis demonstrated that removal

Table 1. (*Continued*)

Type of Anesthesia	Postoperative Analgesia	Modified Jadad Score (1–5)[9]	Method of Data Extraction
Thiopental/remifentanil/sevoflurane	Fentanyl 1 μg/kg PRN	4	Table/text
Thiopental/fentanyl/isoflurane	Morphine PCA	3	Table/text/figure
Propofol/fentanyl/sevoflurane	Morphine PCA	5	Table/text/figure
Propofol/remifentanil/isoflurane	Morphine PCA	5	Table/figure
Propofol/fentanyl/sevoflurane/nitrous oxide	Tramadol PCA	3	Table/figure
Sulfentanil/isoflurane	0.1 mg/kg IV morphine PRN	4	Table/text
Propofol/remifentanil/sevoflurane/ nitrous oxide	Morphine PCA	5	Table/text/figure
Propofol/remifentanil	Morphine PCA and ketorolac 30 mg PRN	4	Text/figure
Propofol/fentanyl	Morphine PCA and tenoxicam 20 mg IV PRN	3	Table/text/figure
Propofol/fentanyl/isoflurane/nitrous oxide	Dextropropoxyphene hydrochloride 32.5 mg/acetaminophen 325 mg orally PRN	4	Table/text
Propofol/remifentanil	Meperidine 1 mg/kg intramuscular PRN	5	Text/figure
Propofol/sufentanil/sevoflurane	Tramadol PCA and Paracetamol 1 g IV PRN	4	Table/text/figure
Propofol/fentanyl/nitrous oxide	Morphine PCA	4	Table/text
Thiopental/morphine/halothane/ nitrous oxide	Morphine IV PRN	3	Table/text/figure
Propofol/remifentanil/sevoflurane/ nitrous oxide	Piritramide PCA	3	Table/figure
Thiopental/fentanyl/isoflurane/nitrous oxide	Morphine PCA	3	Table/text/figure
Thiopental/fentanyl/isoflurane/nitrous oxide	Morphine PCA	3	Table/text/figure
Propofol/fentanyl	Fentanyl 0.5 μg/kg PRN	4	Table/figure
Propofol/alfentanil/isoflurane	Morphine PCA	3	Table/figure
Thiopental/fentanyl/isoflurane/nitrous oxide	Morphine PCA	5	Text/figure

of the study of Saadawy *et al.*[32] or Mentes *et al.*[34] would significantly change the results. Removal of lower quality studies (Jadad ≤3) did not significantly change the effect of magnesium on late pain at movement, weighted mean difference (99% CI) of −1.03 (−1.57 to −0.49) compared with the original analysis ($P = 0.31$).

Postoperative Opioid Consumption

The aggregated effect of 16 studies[32–38,41–49] evaluating the effect of systemic magnesium on postoperative opioid consumption compared with control favored systemic magnesium, weighted mean difference (99% CI) of −10.52 (−13.50 to −7.54) mg morphine IV equivalents (fig. 10). One study provided three comparisons and they were included in the analysis.[42] The funnel plot did not demonstrate asymmetry ($P = 0.11$; fig. 11). Sensitivity analysis did not change the effect when any of the studies were removed from aggregated effect. Heterogeneity was high ($I^2 = 88\%$). Twenty-eight percent of the total variance could be explained by studies that used systemic magnesium during

the intraoperative period but not during the postoperative period. The aggregated effect for studies that used systemic magnesium both intraoperatively and postoperatively on postoperative opioid consumption was greater, than studies that used magnesium only intraoperatively, weighted mean difference (99% CI) of −11.1 (−12.6 to −9.6) and −7.81 (−8.4 to −7.17), respectively ($P < 0.001$). A meta-regression analysis did not identify an association between the total magnesium dosage administered and an effect on postoperative opioid consumption (slope [95% CI] = 0.26 [−0.26 to +0.78]; $P = 0.30$ compared with slope = 0). Removal of lower quality studies (Jadad ≤3) did not significantly change the effect of magnesium on postoperative opioid consumption, weighted mean difference (99% CI) of −13.3 (−16.8 to −9.9) mg IV morphine compared with the original analysis ($P = 0.35$).

Time to First Analgesic Administration (Minutes)

Four studies evaluated the effects of systemic magnesium on time to analgesic administration.[32,33,39,41] One study[39] provided data for two comparisons and both were included in the analysis. There was not a statistically significant prolongation on the time to analgesic requirement when the systemic magnesium group was compared with control, weighted mean difference (99% CI) of 4.4 (−6.9 to 15.9) min (fig. 12). All included studies that reported on time to first analgesic requirement had Jadad score ratings of more than 3.

Safety Analysis

Magnesium Toxicity. None of the included studies reported on clinical manifestations of magnesium toxicity related to high serum levels of magnesium.

Dizziness. Three studies reported on the incidence of postoperative dizziness.[30,39,46] The aggregated effect did not suggest an effect of systemic magnesium on postoperative dizziness compared with placebo, OR (95% CI) of 1.04 (0.53–2.05). Heterogeneity was low ($I^2 = 0$). The sample size included in this analysis had an 87% power to detect a 15% difference in the incidence of dizziness between the placebo and magnesium group using a two-tailed $\alpha = 0.05$.

Headache. Three studies reported on the incidence of postoperative headache.[30,39,46] The pooled effect did not suggest an effect of systemic magnesium on postoperative headache compared with placebo, OR (95% CI) of 0.94 (0.50–1.77). Heterogeneity was low ($I^2 = 9$). The sample size included in this analysis had a 77% power to detect a 15% difference in the incidence of headache between the placebo and magnesium group, using a two-tailed $\alpha = 0.05$. The incidence of headache was 22% in both groups.

Postoperative Nausea and/or Vomiting. Six studies reported on the incidence of postoperative nausea and /or vomiting.[30,31,33,39,44,46] The aggregated effect did not suggest an effect of systemic magnesium on postoperative nausea and/or vomiting, OR (95% CI) of 1.00 (0.64–1.56). Heterogeneity was low ($I^2 = 0$). The sample size included in this analysis had an 87% power to detect a 15% difference in the incidence of postoperative nausea and/or vomiting between the placebo and magnesium group, using a two tailed $\alpha = 0.05$.

Postoperative Shivering. Three studies reported on the incidence of postoperative shivering.[30,39,44] The combined effects showed a reduction on the incidence of postoperative shivering in the magnesium group compared with control, OR (95% CI) of 0.36 (0.14–0.95), number need to treat (95% CI) = 12.0 (6.8–50). Heterogeneity was low ($I^2 = 0$).

Cardiovascular Side Effects. Three studies reported on the incidence of perioperative bradycardia[35] or hypotension.[31,46] None of the studies reported a statistically significant effect of magnesium on perioperative cardiovascular events.

Discussion

The important finding of the current study is the positive effect of systemic magnesium in the reduction of postoperative pain. Systemic magnesium reduced both early and late pain at rest and late pain at movement. In addition, systemic magnesium had a large effect on the reduction of postoperative opioid consumption compared with control. Systemic magnesium is not currently considered an effective intervention to minimize postoperative pain, the findings of this analysis provide evidence that systemic magnesium can be an important adjunct to reduce acute postoperative pain in surgical patients undergoing general anesthesia.

The overall effect of magnesium on the reduction of postoperative opioid consumption was consistently large as represented by even a large effect at the lower limit of the 99% CI, −10.52 (−13.50 to −7.54) mg morphine IV equivalents. The effect on early pain at rest was smaller but clinically significant with a weighted mean difference (99% CI) of −0.74 (−1.08 to −0.48). In contrast, the effect of systemic magnesium on early pain at movement was not significant, weighted mean difference (99% CI) of −0.52 (−1.15 to 0.10).

Another important finding of the current investigation was the detection of greater effects on postoperative pain management outcomes, when magnesium was administered both during the intraoperative and postoperative period as compared with the sole intraoperative administration of the drug. Because of its observational nature, these analyses should only be considered as hypothesis generating for future investigations. Only a large randomized controlled trial can confirm or refute those results.

A previous systematic review performed by Lysakowski *et al.*[6] did not detect a beneficial effect of systemic magnesium on postoperative pain outcomes. There may be several reasons responsible for the lack of observed effect by Lysakowski's analysis compared with the current analysis. First, the previous systematic review included a lower number of

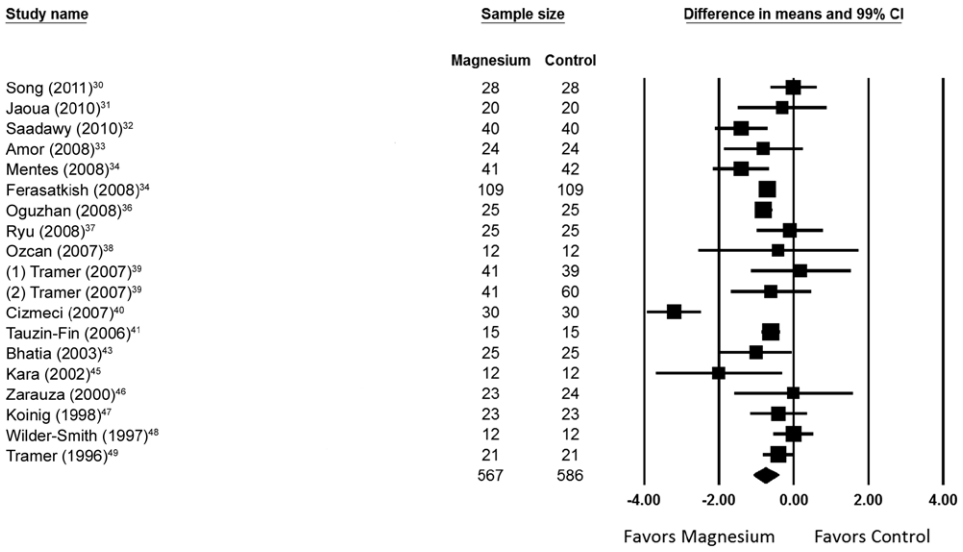

Fig. 2. Meta-analysis evaluating the effect of systemic magnesium on early pain scores (≤4 h) at rest compared with control. The overall effect of magnesium *versus* placebo was estimated with study as a random effect. Point estimate (99% CI) for overall effect was –0.74 (–1.08 to –0.48). Weighted mean difference for individual study represented by *square* on Forrest plot with 99% CI of the difference shown as *solid line*. *Larger sized square* and *thicker 99% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of systemic magnesium compared with control.

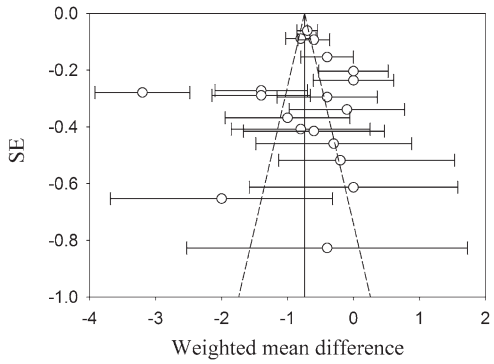

Fig. 3. Early pain at rest funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* weighted difference in mean (Effect). *Vertical line* is the combined effect for early pain with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry (P = 0.40, one-sided).

clinical trials and a lower number of subjects (n = 778) when compared with the current one (n = 1,257). In addition, the aforementioned analysis evaluated patients undergoing different types of anesthesia, including neuraxial blocks, whereas we limited our study to patients undergoing general anesthesia. We also limited our analysis to subjects older than 18 yr of age, whereas in the earlier analysis pediatric patients were included in the assessment of postoperative pain outcomes.[6]

Despite the very large effect of systemic magnesium on opioid sparing, it was somewhat surprising that magnesium did not decrease opioid-related side effects such as nausea and vomiting, despite an 87% power to detect a clinically significant 15% difference on the incidence of postoperative nausea and/or vomiting. Marret *et al.*[50] have also shown that most opioid-related side effects are not reduced by opioid sparing effects of nonsteroidal antiinflammatory medications. In contrast, our group has demonstrated an inverse relationship between opioid consumption and postoperative quality of recovery in patients undergoing ambulatory surgery.[51,52] Only one study included in the analysis examined the effect of magnesium on subjects undergoing ambulatory surgery.[39] Because more than 60% of surgical procedures performed in the United States are done in an ambulatory setting,[53] more studies examining the effect of magnesium on postoperative pain in ambulatory patients are needed.

Besides the effect of magnesium on postoperative pain, we also detected an effect of systemic magnesium in reducing postoperative shivering. Postoperative shivering is a common outcome after anesthesia, which can result in significant morbidity to patients, including perioperative ischemia.[54] A previous systematic review, which had postoperative shivering as a primary outcome, did not detect a significant effect of magnesium sulfate in the reduction of postoperative shivering.[55] Because postoperative shivering was not the primary objective of our analysis, our findings need to be interpreted with caution and can only be considered as hypothesis generating observations.

We did not detect a significant effect of systemic magnesium on important adverse perioperative outcomes such as hypotension and/or bradycardia. The analysis was limited by the low number of studies reporting on these side effects. Our group has examined the effect of systemic magnesium on arrhythmias in higher risk patients undergoing coronary artery bypass grafting.[56] We have not detected an increase in adverse outcomes

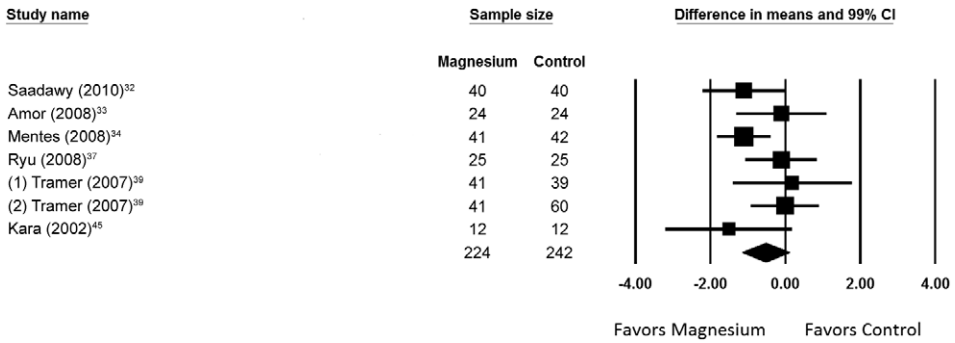

Fig. 4. Meta-analysis evaluating the effect of systemic magnesium on early pain scores (≤4 h) at movement compared with control. The overall effect of magnesium *versus* placebo was estimated with study as a random effect. Point estimate (99% CI) for overall effect was −0.52 (−1.15 to 0.10). Weighted mean difference for individual study represented by *square* on Forrest plot with 99% CI of the difference shown as *solid line*. *Larger sized square* and *thicker 99% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of systemic magnesium compared to control.

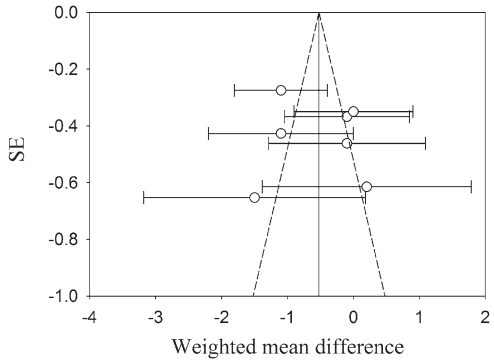

Fig. 5. Early pain at movement funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* weighted difference in mean (Effect). *Vertical line* is the combined effect for early pain with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry (P = 0.35, one-sided).

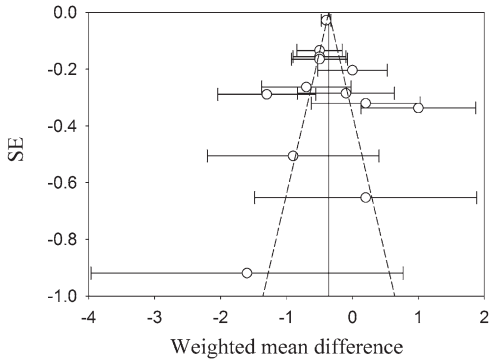

Fig. 7. Late pain at rest funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* weighted difference in mean (Effect). *Vertical line* is the combined effect for early pain with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry (P = 0.40, one-sided).

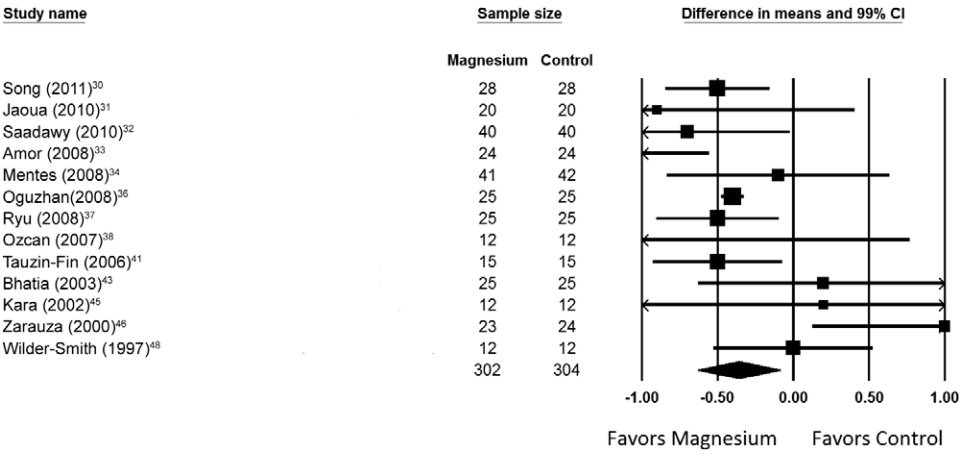

Fig. 6. Meta-analysis evaluating the effect of systemic magnesium on late pain scores (24 h) at rest compared with control. The overall effect of magnesium *versus* placebo was estimated with study as a random effect. Point estimate (99% CI) for overall effect was −0.36 (−0.63 to −0.09). Weighted mean difference for individual study represented by *square* on Forrest plot with 99% CI of the difference shown as *solid line*. *Larger sized square* and *thicker 99% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of systemic magnesium compared to control.

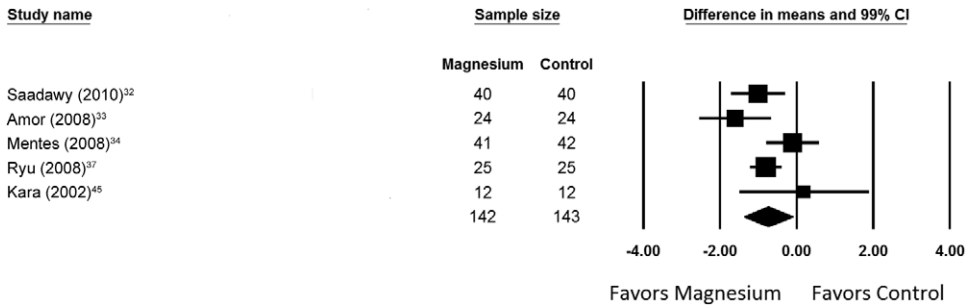

Fig. 8. Meta-analysis evaluating the effect of systemic magnesium on late pain scores (24 h) at movement compared with control. The overall effect of magnesium *versus* placebo was estimated with study as a random effect. Point estimate (99% CI) for overall effect was −0.73 (−1.37 to −0.1). Weighted mean difference for individual study represented by *square* on Forrest plot with 99% CI of the difference shown as *solid line*. *Larger sized square* and *thicker 99% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of systemic magnesium compared with control.

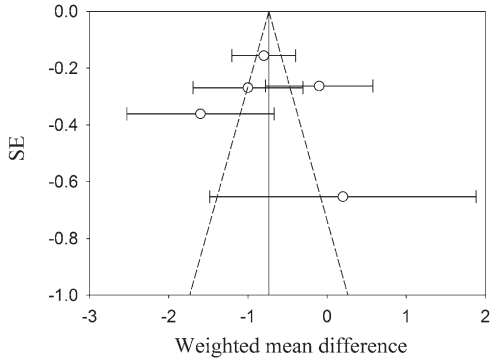

Fig. 9. Late pain at movement funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* weighted difference in mean (Effect). *Vertical line* is the combined effect for early pain with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry (P = 0.42, one-sided).

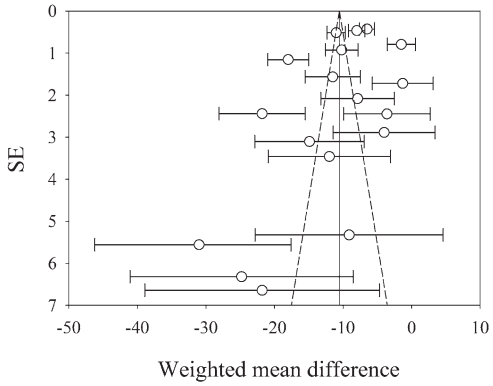

Fig. 11. Opioid consumption funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* weighted difference in mean (Effect). *Vertical line* is the combined effect for early pain with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry (P = 0.11, one-sided).

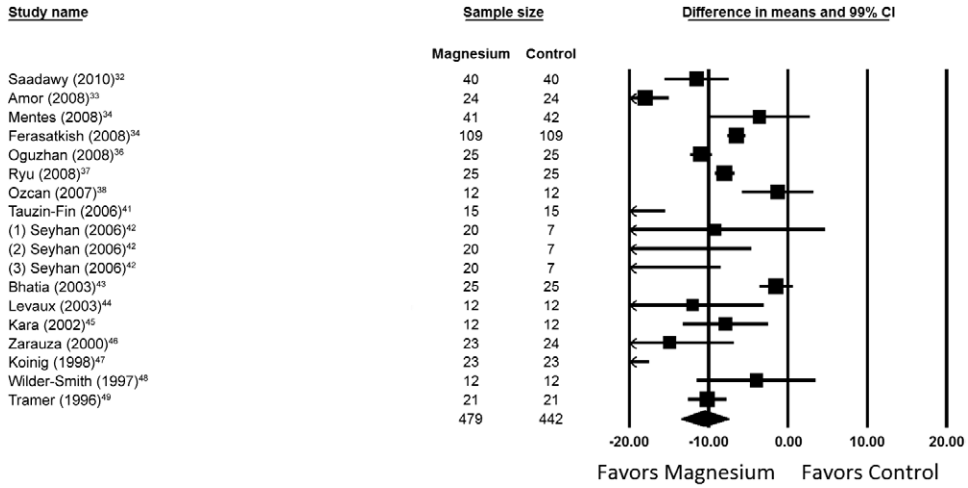

Fig. 10. Meta-analysis evaluating the effect of systemic magnesium on postoperative opioid consumption compared with control. The overall effect of magnesium *versus* placebo was estimated with study as a random effect. Point estimate (99% CI) for overall effect was −10.52 (−13.50 to −7.54) mg morphine intravenous equivalents in favor of magnesium compared with control. Weighted mean difference for individual study represented by *square* on Forrest plot with 99% CI of the difference shown as *solid line*. *Larger sized square* and *thicker 99% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of systemic magnesium compared with control.

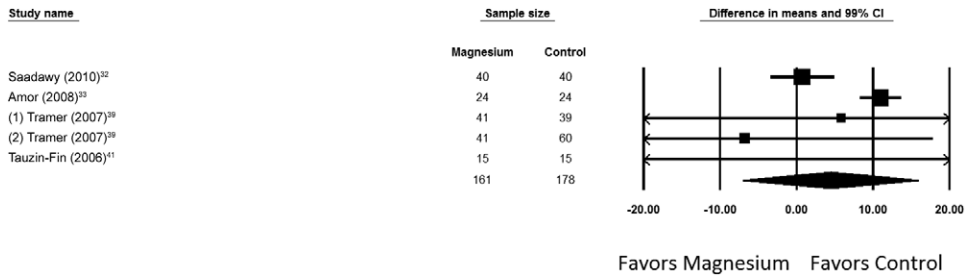

Fig. 12. Meta-analysis evaluating the effect of systemic magnesium on time to analgesic consumption compared with control. The overall effect of magnesium *versus* placebo was estimated with study as a random-effect. Point estimate (99% CI) for overall effect was 4.4 min (–6.9 to 15.9). Weighted mean difference for individual study represented by *square* on Forrest plot with 99% CI of the difference shown as *solid line*. *Larger sized square* and *thicker 99% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of systemic magnesium compared with control.

such as arrhythmias, myocardial infarction, and stroke in patients receiving systemic magnesium compared with placebo in that higher risk population. In addition, none of the studies included in the current analysis had reported clinical toxicity associated with toxic serum levels of magnesium.[57]

Our investigation should be interpreted within the context of its limitations. In order to increase the number of available comparisons, we included studies that evaluated the effect of magnesium in subjects undergoing different surgical procedures. Although this is a common practice in quantitative systematic reviews of interventions addressing perioperative pain,[58–60] this fact might have contributed to some of the heterogeneity observed in certain analyses. We attempted to minimize clinical heterogeneity by only including surgical procedures performed under general anesthesia, and we were able to explain part of the heterogeneity by the duration of magnesium infusion administration. Nevertheless, our findings can only be confirmed by a large randomized controlled trial.

Because few studies reported on magnesium levels, we were not able to evaluate the relationship between magnesium levels and the reported outcomes. It is important to note that several studies included in the current meta-analysis reported postoperative levels of serum magnesium above the normal range of 1.5–2.5 mg/dl.[31,32,37] In addition, the impact of hypomagnesaemia on perioperative pain is unknown. Although not tested, perioperative correction of magnesium to normal systemic levels may not likely be sufficient to affect perioperative pain. Factors leading to perioperative hypomagnesaemia include bowel preparation and electrolyte losses.[61] These factors may influence the dosage needed to observe a beneficial effect on postoperative pain outcomes.

Another limitation of our study is that we did not register the review' protocol on a registry database of systematic reviews. Registration of systematic reviews may prevent reporting bias. Nevertheless, our primary outcomes were identical to previous systematic reviews reported by our group on postoperative pain.[58,62] Because the comparison that examined late pain on movement involved only five studies, it is possible that the Egger regression analysis for that comparison could have been underpowered to detect the presence of publication bias.

In summary, systemic magnesium reduces postoperative pain after surgical procedures following general anesthesia. In addition, the administration of systemic magnesium also reduced the postoperative consumption of opioids. Systemic levels associated with clinical toxicity were not reported in any of the examined studies. Perioperative magnesium administration should be considered as a strategy to reduce postoperative pain outcomes in patients undergoing surgical procedures.

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