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Systematic Review

Effects of Systemic Magnesium on Post-operative Analgesia: Is the Current Evidence Strong Enough?

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Background: Clinical studies have been previously carried out on the efficacy of systemic magnesium to minimize postoperative pain, however, with controversial results. A quantitative meta-analysis was performed to evaluate the analgesic efficacy and safety of systemic magnesium on post-operative pain.

Study Design: Comprehensive systematic review of all relevant, publsished randomized controlled trials.

Methods: A search was conducted of published literature in MEDLINE, PsycINFO, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to September 2014. Randomized controlled trials (RCTs) that compared magnesium with placebo were identified. Effects were summarized using standardized mean differences (SMDs), weighed mean differences (WMD), or odds ratio (OR) with suitable effect model.

Results: Twenty-seven RCTs involving 1,504 patients were included. In total, peri-operative magnesium significantly reduced the pain score at rest (SMD, -1.43, 95% CI, -2.74 to -0.12, < 0.01). Magnesium significantly reduced analgesic consumption (SMD, -1.72, 95% CI, -3.21 to -0.23) in patients undergoing urogenital, orthopaedic, and cardiovascular surgeries, but was inconclusive for patients receiving gastrointestinal surgeries. The obvious analgesia of systemic magnesium was observed on reducing the pain score during movement at 24 hours after operation (SMD, -0.05, 95% CI, -0.43 to 0.32). Moreover, magnesium administration showed a beneficial effect with regard to intra-operative hemodynamics and reduced extubation time in the cardiovascular surgery patients (WMD, -29.34 min, 95% CI, -35.74 to -22.94, $P < 0.01$).

Limitations: Focused only on the quality of analgesia on postoperative pain with regards to surgery type.

Conclusions: Our study suggests that systemic magnesium during general anesthesia significantly decreases post-operative pain scores without increasing adverse events. It should be noted that since there are 18 ongoing RCTs without published data, it is still premature to draw conclusions on the long-term analgesic effects of magnesium as well as potential gender or age difference.

Key words: Magnesium, post-operative pain, meta-analysis

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The treatment of post-operative pain is an important health care issue. Aggressive pain prevention peri-operatively can yield both short- and long-term benefits. Unrelieved or poorly managed acute pain affects patient recovery, ability to go home, return to normal functioning, and the likelihood of developing chronic pain. The implication of magnesium in pain reduction lies in its ability to serve as a noncompetitive NMDA receptor antagonist by preventing extracellular calcium movement into the cell and by attenuating central sensitization. Specifically, the blockade of glutamate and aspartate at the NMDA receptor by magnesium is the central mechanism (1). In addition to the effects of magnesium on NMDA receptors, it blocks calcium channels, resulting in potentially clinically beneficial peripheral vasodilation, bronchodilation, and uterine relaxation via its effects on smooth muscle, and demonstrated post-operative analgesia (1).

Magnesium has been used to improve post-operative analgesia since the first randomized clinical trial (RCT) in 1996 (2). However, the efficacy of magnesium on post-operative pain from RCTs remains controversial (3-5). Peri-operative magnesium does not confer any significant analgesic benefit according to 2 previous reviews (6,7). This conclusion was based on a small number of trials and these previous reviews provided qualitative instead of quantitative data reporting (6,7). In this regard, a recent quantitative meta-analysis suggested a positive relationship between magnesium and post-operative pain (1) independent of the mode of administration (e.g., bolus or continuous infusion).

There are a number of reasons why the beneficial effects of magnesium on post-operative pain remain controversial. First, there were only 2 endpoints at one time point (e.g., pain score and analgesic consumption) in the previous studies, resulting in limited conclusions being reached concerning the temporal efficacy of magnesium as well as its adverse events. Second, several lately conducted meta-analyses were published without recently completed relevant investigations. Third, some of the included articles in previous meta-analysis had low Jadad scores, which weakened the conclusions. When we were performing the current meta-analysis, 2 meta-analyses were published (8,9). However, only 20 RCTs were included in one meta-analysis with 7 RCTs published in 2012 not being included (8). Therefore, data from 247 more patients were not involved in the most recently published meta-analysis. Although 25 RCTs were included in another study, the efficacy of magnesium was investigated only at 24 hours post-operatively with the longer analgesic effect of magnesium not being meta-analyzed (9). Thus, we performed this comprehensive systematic review of all relevant, published RCTs with all available outcome measures, time points, and adverse events, in an attempt to more precisely identify the role of magnesium in mediating or modulating post-operative analgesia.

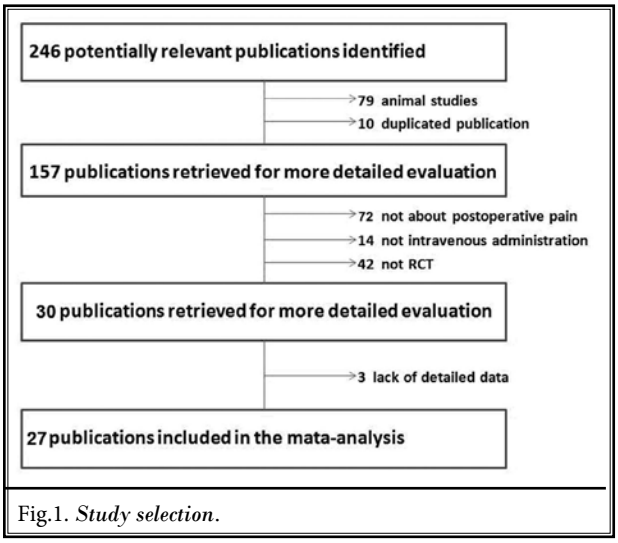

Fig.1. *Study selection.*

Methods

Based on the Quality of Reporting of Meta-analyses (QUORUM) guidelines (10) and the recommendations of the Cochrane Collaboration (11), we performed the current meta-analysis.

Date Sources and Study Selection

The electronic databases screened were MEDLINE (1966 through September 2014), psycNFO (1966 through September 2014), Scopus (1966 through September 2014), Embase (1966 through September 2014), and the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 9 of 12, September 2014). Searches were limited to human and performed for all languages. Studies were searched by using the following key words: magnesium; surgery OR surgical OR postoperative OR post and operative; randomized OR randomised; and human; and pain OR analgesia OR nociception; and RCT OR controlled clinical trial OR open label trial (OLT) design.

The literature search yielded 27 studies (Fig. 1) and a total of 1,504 patients completed the treatment, with 749 receiving systemic magnesium. The characteristics of these studies were presented in Table 1. The potential bias of these publications was also summarized (Fig. 1).

Table 1. Characteristics of studies with Jadad scores over 4.

Author (country)	Jadad scores	Patients				Comparison		Surgery	Treatment group	Placebo group	Outcome measures used for meta-analysis
		Female sex, %	Total number	ASA physical status I&II/ total,%	Age, mean (range)y	Treatment group	Placebo group		Completed, No./ Total (%)	Completed, No. / Total (%)	
Ayoglu (Turkey)	5	62.5	40	100	50.1(44-56)	Magnesium 50mg/h + 8mg/kg/h during surgery(4h)	Saline	Gastrointestinal surgery	100	100	HR, morphine consumption
Bhatia(India)	4	68.4	50	100	50.7(25-60)	Magnesium 50mg/h + 15mg/kg/h during surgery(77min)	Saline	Gastrointestinal surgery	100	100	morphine consumption, PS #
Dabbagh(Iran)	5	70	60	100	34.4(18-65)	Magnesium 8mg/kg/h during surgery(110min)	Saline	Orthopaedic surgery	100	100	morphine consumption, PS
Ferasatkish (Iran)	5	50	218	100	49.3(35-64)	Magneisum 3.84mg/kg/h during surgery(185.3min)	Saline	Cardic surgery	100	100	PS, morphine consumption, extubated time
Oguzhan (France)	5	46	50	100	43(38-48)	Magnesium 30mg/kg(over 10 min)+10mg/kg/h during surgery	Saline	Orthopaedic surgery	100	100	MAP, HR, PS
Seyhan (Turkey)	4	100	40	100	50.7(25-60)	Magnesium 40mg/kg	Saline	Gynaecological surgery	100	100	MAP, HR, morphine consumption, fentanyl consumption
Tauzin-Fin (France)	5	0	30	100	65.5(54-75)	Magnesium 50mg/kg 20min after induction of anesthesia	Saline	Gynaecological surgery	100	100	PS, extubated time
Zarauza (Spain)	4	31.9	47	100	59.6(47-70)	Magnesium 30mg/kg + 10mg/kg/h (20h)	Saline	Gastrointestinal surgery	100	100	PS, morphine consumption
O'Flaherty (USA)	5	?	80	100	?(3-12)*	Magnesium 30mg/kg	Saline	Other operation‡	100	100	
Hwang (South Korea)	5	45	40	100	49.5(27-68)	Magnesium 50mg/kg(15min)+15mg/kg/h during surgery	Saline	Gynaecological surgery	100	100	serum magnesium concentrations, MAP, HR, PS
Mavrommati (Greece)	5	33.3	42	100	40(42-59)	Magnesium 30mg/kg(1h)+6mg/kg/h during surgery(75min)	Saline	Gastrointestinal surgery	100	100	Fentanyl consumption, MAP, HR
Schulz-Stubner (Germany)	5	46	50	100	56.3(33-75)	Magnesium 50mg/kg	Saline	Other surgery	100	100	
Trammer (Switzerland)	5	100	42	100	48(40-55)	20%magnesium sulfate 15ml+2.5ml/h(20h)	Saline	Gastrointestinal surgery	100	100	side effects
Labrada (Cuba)	5	?	60	100	?	Magnesium 4mg/ml (4h)	Saline	Gastrointestinal surgery	100	100	PS

Table 1 (cont.). Characteristics of studies with Jadad scores over 4.

Author (country)	Jadad scores	Patients				Comparison		Surgery	Treatment group	Placebo group	Outcome measures used for meta-analysis
		Female sex, %	Total number	ASA physical status I&II/ total,%	Age, mean (range)y	Treatment group	Placebo group		Completed, No./ Total (%)	Completed, No. / Total (%)	
Koinig (Austria)	5	47.8	46	100	33(19-45)	Magnesium 50mg/kg + 8mg/ kg/h(115min)	Saline	Orthopaedic surgery	100	100	fentanyl consumption
Mentes (Turkey)	4	78.3	83	100	46.9(31-61)	Magnesium 50mg/kg during surgery(72.2min)	Saline	Gastrointestinal surgery	100	100	PS
Steinlechner (Austria)	4	20.5	40	?	60.0(23-79)	Magnesium 86.5mg/kg + 13.8mg/ kg/h (12h)	Saline	Cardic surgery	95	100	Serum magnesium concentrations, PS
Na (South Korea)	5	31.1	62	100	10.5(5-25)*	Magnesium 50mg/kg+15mg/kg/h during	Saline	Orthopaedic surgery	96.8	100	Serum magnesium concentrations, PS
Ko (South Korea)	4	100	60	100	43.6(38-50)	Magnesium 50mg/kg + 8mg/kg/h during surgery (75min)	Saline	Gastrointestinal surgery	100	100	Serum magnesium concentrations, PS
Usmani (India)	5	66.7	60	100	37(18-50)	Magnesium 50mg/kg + 15mg/ kg/h(60min)	Saline	Gastrointestinal surgery	100	100	PS, side effects
Jaoua (Tunisia)	5	62.5	40	100	46.6(33-59)	Magnesium 50mg/kg+10mg/ kg/h(24h)	Saline	Gastrointestinal surgery	100	100	Serum magnesium, PS, fentanyl consumption, morphine consumption, side effects
Saadawy (Egypt)	5	83.75	80	100	40.5(31-51)	Magnesium 50mg/kg+25mg/kg/h	Saline	Gastrointestinal surgery	100	100	Morphine consumption, fentanyl consumption, PS, side effects
Ryu (South Korea)	5	100	50	100	42.4(28-52)	Magnesium 50mg/kg+15mg/kg/h	Saline	Gastrointestinal surgery	100	100	MAP, HR, PS
Kiran (India)	3	100	100	100	?(15-50)	Magnesium 50mg/kg 250ml	Saline	Gynaecological surgery	100	100	PS
Kara (Turkey)	3	100	24	100	?(26-65)	Magnesium 30mg/kg +500mg/h (20h)	Saline	Gastrointestinal surgery	100	100	Morphine consumption
Kaya (Turkey)	3	100	40	100	50(18-65)	Magnesium 30mg/kg + 500mg/h	Saline	Gastrointestinal surgery	100	100	Morphine consumption
Tan (China)	2	56	50	100	43.6(25-57)	Magnesium 40mg/kg + 15mg/kg/h	saline	Gastrointestinal surgery	100	100	PS

"pain score" included visual analogue scales (VAS), objective pain score (OPS), and faces pain scale-revised (FPS-R).
*The mean ages of patients in these RCTs were below 16 years old.
*All patients in these RCTs were male.
? The data were not given.
Abbreviations: PS, Pain scores; HR, Heart rate; MAP, mean arterial pressure; ET, extubated time

Data Extraction

Two of the study authors independently screened titles and abstracts of potentially eligible investigations. The full text articles were examined independently by 2 of the study authors to determine whether they met inclusion criteria. Two of the study authors independently extracted information (e.g., study characteristics and results) using data extraction forms. Point estimates for selected variables were extracted and checked by 2 other reviewers. All discrepancies were rechecked and consensus was achieved by discussion.

Based on outcome measurements reported in the RCTs, pain scores, analgesic consumption, and other outcomes which are used to evaluate the safety of systemic magnesium in treating post-operative pain were selected for critical review. Serum magnesium concentration was an additional outcome. When researchers reported more than one scale for the same outcome, the following priority was employed:

1. Pain score: pain intensity measured with visual analogue scales (VAS) or numerical rating scale (NRS), objective pain score (OPS), and faces pain scale-revised (FPS-R).
2. Analgesic consumption: total morphine and/or fentanyl consumption.
3. Other operation indicators: side effects (pruritus and vomiting), intraoperative hemodynamic variables (HR: heart rate, MAP: mean arterial pressure), and extubation time in cardiovascular surgery patients.
4. Serum magnesium concentration.

The Jadad test (5 items) (12) was applied to assess methodological quality as high (score 5), moderate (score 4), or low (scores 1 – 3).

Data Synthesis and Analysis

Because most outcomes were presented as continuous data (e.g., mean value or mean changes), either weighted mean differences (WMDs) or standardized mean difference (SMDs) were used for effect measures. WMDs were calculated for intraoperative hemodynamic variables, side effects, extubation time, and serum magnesium concentration outcomes because they were measured in different trials with the same scale. SMDs were calculated for pain outcomes (including pain score and analgesic consumption) because they were determined in different trials using different scales. Odds ratio (OR) was used to evaluate the incidence of side effects. WMD, SMD, or OR as well as their 95% confidence intervals (CIs) were calculated for each subgroup. Data were analyzed using Review Manager analyses software (RevMan 5.0.25) according to the Cochrane Handbook for Systematic Reviews of Interventions (13). Based on these outputs, summary graphs were made with GraphPad Prism version 5.01 for Windows (Graph Pad Software, San Diego California USA, www.graphpad.com).

A sensitivity analysis was conducted to determine whether type of surgery (orthopedic, cardiovascular, gastrointestinal, or urogenital surgery) affected the meta-analysis conclusion.

Results

Baseline Characteristics

The doses of magnesium, baseline demographic characteristics, exclusion criteria, surgery type, and Jadad score for every study are included in Table 1.

Systemic Magnesium Delivery and Post-operative Pain

Because the surgeries reported in the included RCTs were orthopedic, cardiovascular, gastrointestinal, or urogenital, we focused on the quality of analgesia on post-operative pain with regard to surgery type as well as at different time points, by assessing the mean differences and 95% CI between systemic magnesium and placebo groups.

Orthopaedic surgery

In this patient population, systemic magnesium induced a significantly increased post-operative analgesia indicated by both decrease in post-operative pain score (Fig. 2, -1.07, 95% CI, -1.28 to -0.87; $P < 0.01$) and analgesic consumption (Fig. 3, morphine, -3.00, 95% CI, -3.75 to -2.25; $P < 0.01$; fentanyl, -1.93, 95% CI, -2.64 to -1.22; $P < 0.01$). The decrease in pain score was significant at 6 (-1.51, 95% CI, -1.92 to -1.10; $P < 0.01$, from 2 RCTs) or 24 hours (-0.92, 95% CI, -1.25 to -0.58; $P < 0.01$, from 3 RCTs) after surgery. However, the decrease in pain score at 2, 12, or 48 hours after surgery was observed in only one single RCT, therefore, a concrete conclusion on these 2 time-points cannot be drawn.

Cardiovascular surgery: According to the statistical result in Fig. 2, systemic magnesium induced a significantly increased post-operative analgesia indicated by both decrease in post-operative pain score (Fig. 2, -1.45, 95% CI, -1.59 to -1.32; $P < 0.01$) and analgesic consumption (Fig. 3, morphine, -0.09, 95% CI, -0.10 to -0.08; $P < 0.01$; fentanyl, -0.09, 95% CI, -0.10 to -0.08; $P < 0.01$).

The decrease in pain score was significant at 2 (-0.84, 95% CI, -1.30 to -0.38; *P* < 0.01, from 2 RCTs), 6 (-1.64, 95% CI, -1.84 to -1.44; *P* < 0.01, from 2 RCTs), and 12 hours (-1.25, 95% CI, -1.52 to -0.98; *P* < 0.01, from 2 RCTs) after surgery. However, the decrease in pain score at 24 hours after surgery was observed in only one single RCT, therefore, a concrete conclusion on this time-point cannot be drawn.

Gastrointestinal surgery

According to the statistical result in Fig. 2, systemic magnesium did not increase post-operative analgesia indicated by the post-operative pain score alteration (Fig. 2, -0.20, 95% CI, -0.48 to -0.08; *P* = 0.07). This zero effect was also confirmed in that systemic magnesium did increase the morphine (Fig. 3, 0.26, 95% CI, -0.11 to 0.63; *P* < 0.01) but not fentanyl (-0.16, 95% CI, -0.19 to -0.13; *P* = 0.08) consumption. However, systemic magnesium did decrease the pain score at 2 (-0.55, 95% CI, -0.86 to -0.24; *P* < 0.01, from 3 RCTs) or 6 (-0.13, 95% CI, -0.44 to -0.17; *P* < 0.01, from 3 RCTs) hours, but not 24 (0.22, 95% CI, -0.38 to 0.83; *P* = 0.35, from 3 RCTs), 48 (-0.10, 95% CI, -0.48 to 0.28; *P* = 0.61, from 2 RCTs) or 72 hours (-0.07, 95% CI, -0.43 to 0.29; *P* = 0.69, from 2 RCTs) after surgery.

Urogenital surgery

According to the statistical result in Fig. 2, systemic magnesium induced a significantly increased post-operative analgesia indicated by both decrease in post-operative pain score (Fig. 2, -1.94, 95% CI, -2.64 to -1.24; *P* < 0.01) and analgesic consumption (Fig. 3, morphine, -2.19, 95% CI, -2.63 to -1.74; *P* < 0.01; fentanyl, -5.19, 95% CI, -6.54 to -3.84; *P* < 0.01). The decrease in pain

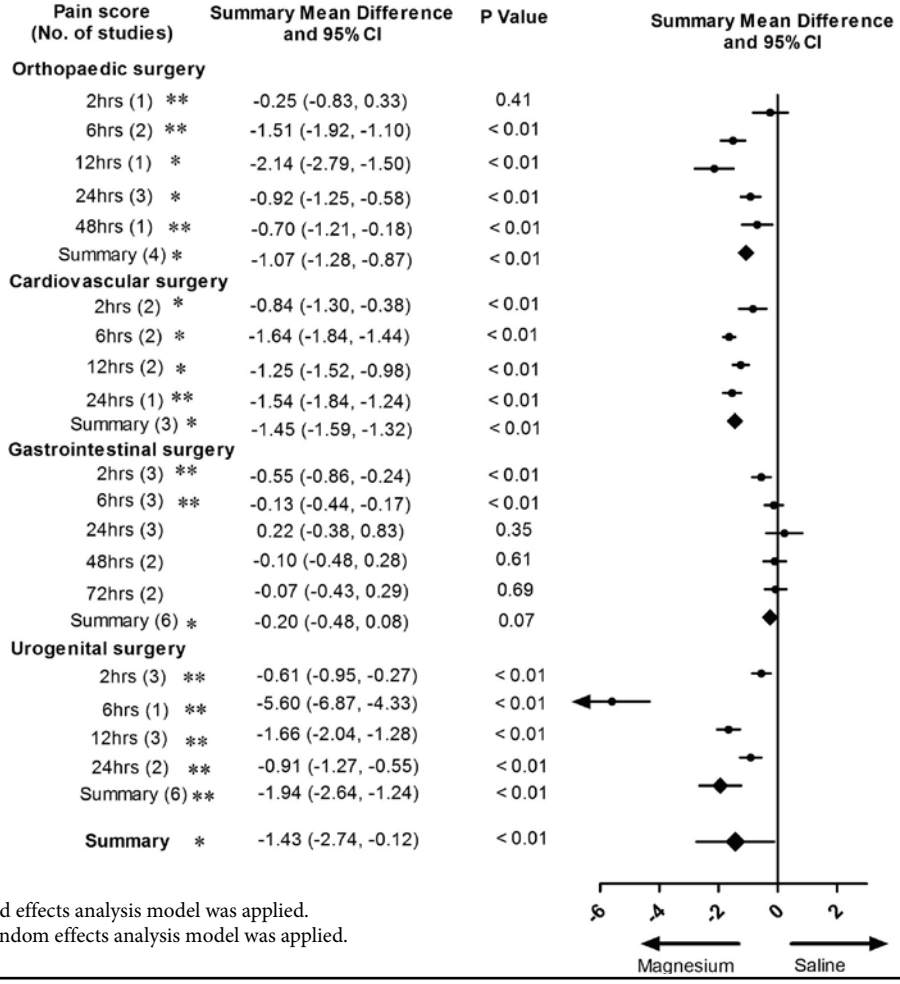

Fig. 2. *The effect of peri-operative magnesium on pain score. Solid symbols denote the values for the summarized unadjusted relative risk. The horizontal lines extending to the right and left of the black circles indicate the widths of the 95 percent confidence intervals (CIs).*

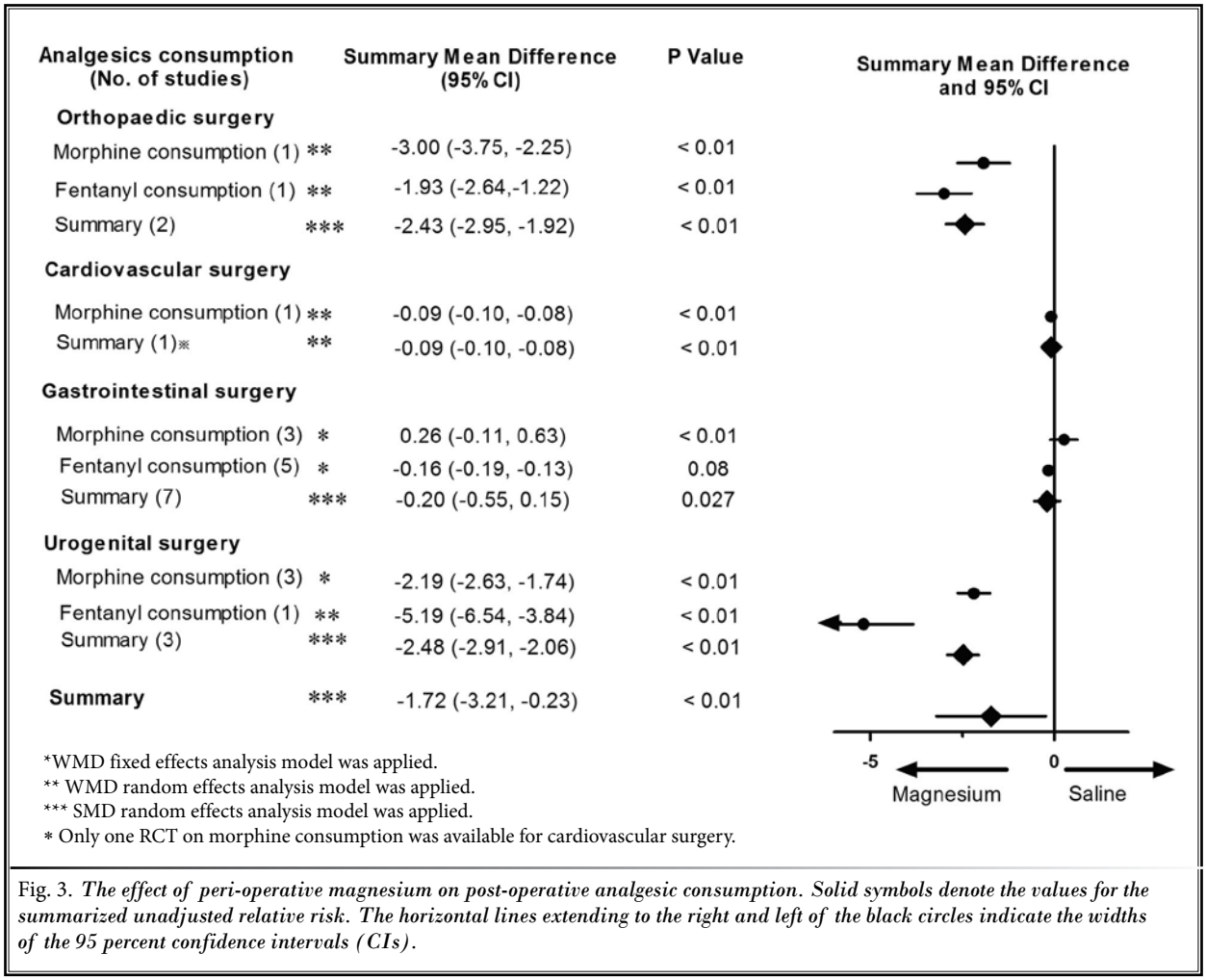

Fig. 3. *The effect of peri-operative magnesium on post-operative analgesic consumption. Solid symbols denote the values for the summarized unadjusted relative risk. The horizontal lines extending to the right and left of the black circles indicate the widths of the 95 percent confidence intervals (CIs).*

score was significant at 2 (-0.61, 95% CI, -0.95 to -0.27; $P < 0.01$, from 3 RCTs), 12 (-1.66, 95% CI, 2.04 to -1.28; $P < 0.01$, from 3 RCTs), and 24 hours (-0.91, 95% CI, -1.27 to -0.55; $P < 0.01$, from 2 RCTs) after surgery. However, the decrease in pain score at 6 hours after surgery was observed in only one single RCT, therefore, a concrete conclusion at this time-point cannot be drawn.

Systemic Magnesium Delivery and Extubation Time

According to the results, there was strong evidence for the efficacy of magnesium in reducing extubation time among cardiovascular surgery patients. Sensitivity analysis revealed strong evidence for the reduction of extubation time for cardiovascular (Table 2, WMD,-74.00, 95% CI, -84.38 to -63.62; $P < 0.00001$), but not urogenital (Table 2, WMD, -2.26, 95% CI, -10.48 to 5.96; $P = 0.59$) or gastrointestinal (Table 2, WMD, 12.00, 95% CI, -43.52 to 67.52; $P = 0.67$) surgery patients.

Systemic Magnesium Delivery and Intraoperative Hemodynamics

There was strong evidence for reduction in both HR and MAP at one hour after surgery. Table 2 gives a comparison of the effect sizes for different type of patients and operations. Peri-operative magnesium-induced significant HR decrease was observed for urogenital (Table 2, WMD, -11.60, 95% CI, -16.79 to -6.41, $P < 0.0001$), but not gastrointestinal (Table 2, WMD, -0.97, 95% CI, -2.08 to 0.14, $P = 0.09$) or orthopedic (Table 2, WMD, -4.44, 95% CI, -11.23 to 2.34, $P = 0.20$) surgery patients. Also peri-operative magnesium-induced significant MAP decrease was observed among urogenital (Table 2, WMD, -9.10, 95% CI, -13.74 to -4.46, $P = 0.0001$), gastrointestinal (Table 2, WMD, -6.73, 95% CI, -9.90 to -3.57, $P < 0.0001$), and orthopedic (Table 2, WMD, -8.16, 95% CI,

Table 2. The effect of peri-operative magnesium on haemodynamics and adverse events.

Outcomes		No. of studies	Patients receiving magnesium No.	Effect size (95% CI)	Test of over effect *P* value
Orthopaedic surgery					
HR		2	51	-4.44 (-11.23, 2.34)*	0.20
MAP		3	76	-8.16 (-10.24, -6.07)*	<0.00001
ET*		—	—	—	—
Cardic surgery					
HR*		—	—	—	—
MAP*		—	—	—	—
ET		1	109	-74.00 (-84.38, -63.62)**	<0.00001
Gastrointestinal surgery					
HR		3	66	-0.97 (-2.08, 0.14)*	0.09
MAP		4	96	-6.73 (-9.90, -3.57)*	< 0.0001
ET		1	21	12.00 (-43.52, 67.52)**	0.67
Side effects †	Vomit	5	18	0.65 (0.33, 1.28)***	0.21
	Pruritus	3	64	0.95 (0.18, 4.93)***	0.95
Gynaecological surgery					
HR		1	20	-11.60 (-16.79, -6.41)**	< 0.0001
MAP		1	20	-9.10 (-13.74, -4.46)**	0.0001
ET		3	60	-2.26 (-10.48, 5.96)*	0.59

* WMD fixed effects analysis model was applied in these effect size analyses.
** WMD random effects analysis model was applied in these effect size analyses.
*** OR fixed effects analysis model was applied in these effect size analyses.
* No data can be involved in these effect size analyses.
† Only side effects reported from digestive system operation related RCT were applied in these effect size analyses.
Abbreviations: HR, heart rate; MAP, mean arterial pressure; ET, extubated time

-10.24 to -6.07, $P < 0.00001$) surgery patients. The effect data in cardiovascular surgery for both HR and MAP were not reported in the selected studies.

Systemic Magnesium Delivery and Serum Magnesium Concentration

The current meta-analysis revealed that the magnesium concentration was significantly increased right after surgery (Table 3, WMD, 0.52, 95% CI, 0.47 to 0.56; $P < 0.00001$). This difference existed for gastrointestinal (Table 3, WMD, 0.18, 95% CI, 0.06 to 0.30; $P = 0.003$), orthopedic (Table 3, WMD, 0.56, 95% CI, 0.51 to 0.61; $P < 0.00001$), and cardiovascular (Table 3, WMD, 1.06, 95% CI, 0.76 to 1.36; $P < 0.00001$) surgery patients.

The significantly increased magnesium concentration was also observed at 24 hours after surgery (Table 3, WMD, 0.16, 95% CI, 0.13 to 0.19; $P < 0.00001$), particularly for orthopedic surgery patients). Data for gastrointestinal and cardiovascular surgeries were not available.

Systemic Magnesium Delivery and Side Effects

Six studies provided the number of side effects with magnesium compared to placebo in a total of 269 patients receiving gastrointestinal surgery. Eighteen of 134 (13.4%) patients assigned to magnesium reported vomiting compared to 26 of 135 (19.2%) allocated to placebo. Three of 64 (4.7%) patients assigned to magnesium reported pruritus compared to 3 of 65 (4.6%) allocated to placebo. The evidence (Table 2) indicated that magnesium did not reduce the incidence of vomiting (Table 2, OR, 0.65; 95% CI, 0.33 to 1.28, $P = 0.21$) or pruritus (Table 2, OR, 0.95; 95% CI, 0.18 to 4.93, $P = 0.95$), with no heterogeneity detected between studies ($I2 = 0\%$, $P = 0.91$; $I2 = 0\%$, $P = 0.40$).

Validity Analysis

Seventeen studies had a Jadad score of 5; 6 studies, a score of 4; 3 studies, a score of 3; and one study, a score of 2 (14-40). Considering that some of the in-

Table 3. *The effect of peri-operative magnesium and serum magnesium concentration.*

	Before operation		0 minutes after operation		24 hours after operation	
	Effect size (95%CI)	Test of over effect *P* value	Effect size (95%CI)	Test of over effect *P* value	Effect size (95%CI)	Test of over effect *P* value
Orthopaedic surgery	-0.01 (-0.03, 0.01)*	0.39	0.56 (0.51, 0.61)*	< 0.00001	0.16 (0.13, 0.19)**	< 0.00001
Cardiovascular surgery	0 (-0.11, 0.11)†**	1	1.06 (0.76, 1.36)**	< 0.00001	—	—
Gastrointestinal surgery	-0.10 (-0.19, -0.01)*	0.03	0.18 (0.06, 0.30)*	0.003	—	—
Gynaecological surgery*	—	—	—	—	—	—
Total	-0.02 (-0.04, 0.01)*	0.17	0.52 (0.47, 0.56)*	< 0.00001	0.16 (0.13, 0.19)*	< 0.00001

* WMD fixed effects analysis model was applied in these effect size analyses.
** WMD random effects analysis model was applied in these effect size analyses.
*Data from Urogenital surgery were not available.

cluded articles in the previous meta-analysis have low Jadad scores, we made another evaluation of the RCTs with Jadad scores over 4, which resulted in the inclusion of 23 RCTs. Most of the results are similar to those before study deletion. Post-operative pain score for gastrointestinal surgery still showed no evident reduction but the statistical results for the total test and at 2 hours after surgery have been significantly changed (pain score, summary, SMD, -0.08, 95% CI, -0.28 to 0.11; $P = 0.40$; 2h, SMD, -0.37, 95% CI, -1.05 to 0.31; $P = 0.28$). For gastrointestinal surgery, post-operative pain score is significantly decreased at only 2 and 24 hours (pain score, 2 hours, SMD, -1.97, 95% CI, -2.65 to -1.28; $P < 0.00001$; 24 hours SMD, -0.97, 95% CI, -1.74 to -0.21; $P = 0.01$) after surgery. In conclusion, the exclusion of those studies did not change the overall conclusions.

Discussion

The primary aim of this meta-analysis was to determine the analgesic efficacy and safety of peri-operative systemic magnesium for post-operative pain. Strong evidence was demonstrated for the efficacy of magnesium in reducing post-operative pain and improving surgery quality (except in the case of gastrointestinal surgery). The beneficial effects of magnesium were observed in both orthopedic and cardiovascular surgeries at the first 24 hours after operation. The analgesic effect lasted until 48 hours after orthopedic surgery. The analgesic effect of magnesium declined after the first 24 hours in urogenital and cardiovascular surgeries, suggesting the necessity of combining other medications to extend analgesic duration.

There might be significant age- or gender-related differences in magnesium-mediated analgesia. In the current meta-analysis, 2 RCTs focusing on the pediatric population demonstrated positive results (31,39). However, there was no significant difference between magnesium and placebo groups in different ages of adults. The results of the present investigation revealed that children appear to be more sensitive to magnesium than adults. Further, only 3 RCTs were designed for women and no matched male populations were included; therefore, conclusions of gender differences remain unclear. Therefore, future high-quality RCTs are needed to clarify the roles of age and gender on magnesium-mediated post-operative analgesia.

As for intraoperative hemodynamics, magnesium reduces HR and MAP, which can potentially lead to intra- and post-operative beneficial effects (2). Therefore, the use of magnesium in surgical operations can potentially avoid or minimize certain adverse cardiovascular and/or cerebrovascular events.

For serum magnesium concentration, a positive correlation between blood levels and post-operative analgesia was identified. However, the concentration of serum magnesium should be carefully monitored in order to prevent hypermagnesaemia, which can cause many adverse effects, including sedation, diarrhea, potentiation of neuromuscular blockade, cardiac arrhythmia, respiratory depression, and other adverse effects on the cardiovascular and renal systems (40). Notably, because of the potential adverse effects of hypermagnesaemia, a certain population may not be suitable to receive systemic magnesium. Unfortunately, studies on

this issue are lacking and further high quality RCTs on the contraindications of different magnesium delivery plans are needed.

This review has a number of limitations. First, there are differences with regard to the methods by which magnesium was administered in the studies. Because the number of RCTs which epidural and intra-articular pathways were utilized is limited, only intravenous magnesium was included in this investigation. However, we did notice the potential clinical role of other administration methods based on related literature (41). As a result, future research on this issue is warranted. Second, when to deliver and when to end magnesium varied and there is no consensus for magnesium dosages. We could not, therefore, stratify the effect of dose and time, though we are fully aware of their importance. And whether different dosages of magnesium may result in distinct side effects is difficult to analyze based on the current evidence. Thus, it is still too early for us to give comments on magnesium delivery plans, and more high-quality RCTs designed to assess the efficacy and safety of different magnesium delivery plans are needed, which is critically important for us to transfer this intervention into clinical practice. Third, there were limitations with some methods used in this article, such as using I2 for assessing the amount of heterogeneity in random-effects meta-analysis and fail-safe numbers for excluding a publication bias. Fourth, the conclusions obtained from the current meta-analysis are preliminary given that there are 7 ongoing RCTs and 11 completed RCTs without published data (Supplementary Tables 1 and 2).

Conclusion

In summary, the present investigation demonstrated that systemic magnesium during general anesthesia significantly decreases post-operative pain scores without increasing adverse events. Given that there are 18 ongoing RCTs without published data, it is still premature to draw conclusions on the long-term analgesic effects of magnesium as well as potential gender- or age-related differences.

Competing Interest Statement

All authors have completed the Unified Competing Interest form and declare: no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary Table 1. Ongoing RCTs on the topic of "magnesium and postoperative analgesia."

Trial No.	Registered time	Title	Outcomes	Interventions	Country	Status
NCT01460563	October 2011	Valproic Acid, Magnesium Sulphate, Rocuronium Requirement, Postoperative Analgesia	total amount of anesthetics pain analgesics use	Magnesium Sulfate 0.9% saline	South Korea	Recruiting
NCT01795495	September 2013	Methadone vs Magnesium in Spinal Fusion	Intra- and Post-operative Pain Relief	Methadone hydrochloride Magnesium Sulfate Remifentanil	USA	Recruiting
NCT01542697	June 2011	Effect of Intraperitoneal Nebulisation of Magnesium Sulphate for Analgesia Following Laparoscopic Cholecystectomy	number of analgesic request VAS score	i.p. magnesium sulphate	Nepal	Recruiting
NCT02018276	December 2013	Effect of Perioperative Intravenous Lidocaine Infusion and Magnesium Infusion on the Functional Recovery After General Anesthesia in the Patients Undergoing Thyroid Surgery	QoR 40	Lidocaine Magnesium	South Korea	Recruiting
NCT01627353	January 2012	Post Hysterectomy Pain Prevention: Pre-op Wound Infiltration With Anesthetic Protocol Versus Standard of Care	Post Operative Morphine VAS score	Standard of care Pre-emptive wound infiltration	Canada	Recruiting
NCT02087202	March 2014	Hyperalgesia and NMDA Receptor Antagonist	pain	Magnesium Sulfate ketamine	South Korea	Not yet recruiting
NCT01923831	August 2013	Comparison of the Effect of Magnesium Sulfate and Dexamethasone on Postoperative Sore Throat After Spinal Surgery in Prone Position With Tracheal Intubation: a Double-blind, Randomized, Noninferiority Clinical Trial	NA	Magnesium Sulfate dexamethasone	South Korea	Not yet recruiting

Supplementary Table 2. *Completed RCTs on the topical of "magnesium and postoperative analgesia."*

Trial No.	Completion Date	Title	Outcomes	Interventions	Country
NCT00560092	October 2008	Intrathecal Magnesium and Postoperative Analgesia	Morphine consumption VAS score	i.t. magnesium sulfate	France
NCT01843296	April 2013	Effects of Addition of Magnesium Sulfate in Spinal Anesthesia on Sensory-Motor Blocks and Postoperative Pain in Lumbar Disk Herniation Surgery	Pain Score Time to first analgesic MABP, HR	Magnesium Sulfate Bupivacaine Fentanyl	Iran
NCT01679353	January 2013	Comparison of Analgesic Effect of Magnesium Added to Ropivacaine and Ropivacaine Alone in Caudal Analgesia on Postoperative Pain Control in Pediatric Patients Undergoing Inguinal Hernia Repair	Time to first analgesic	caudal block normal saline 0.5ml	South Korea
NCT01205997	January 2011	Comparison of Postoperative Analgesic Effect of Intrathecal Magnesium and Fentanyl Added to Bupivacaine in Patients Undergoing Lower Limb Orthopedic Surgery	Time to first analgesic MABP HR	Fentanyl placebo magnesium sulphate	Iran
NCT02011152	December 1999	Spinal Anesthesia Magnesium Infusion	Pain Score	NA	Iran
NCT01743144	February 2013	Magnesium Sulphate and Sevoflurane Induced Emergence Agitation in Children	postoperative pain: Children's Hospital Eastern Ontario Scale (CHEOPS)	Magnesium Sulfate normal saline	Egypt
NCT01433081	May 2013	The Effect of Magnesium Sulfate Infusion on the Quality of Recovery of Ambulatory Patients	Opioid consumption	Magnesium Sulfate normal saline	USA
NCT01360060	March 2011	Analgesia After Cesarean Section	Pain score: NRS serum magnesium level	Magnesium Sulphate	South Korea
NCT01261702	December 2012	Magnesium Infusion for Pain Relief After Thoracotomy. A Randomized Controlled Trial	24 hour morphine requirement	Magnesium Sulfate normal saline	Thailand
NCT01025245	January 2010	Effect of Intraoperative Magnesium on Remifentanil-induced Postoperative Hyperalgesia After Thyroidectomy	Tactile pain thresholds adjacent to the surgical wound	Remifentanil Magnesium Sulfate	South Korea
NCT01972659	December 2013	Effects of Magnesium Sulphate on Sugammadex Reversal of Rocuronium Induced Blockade in Gynaecology Patients	Morphine Consumption	Magnesium Sulphate Sugammadex placebo	Turkey

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