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Review Article

Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis

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Summary

Intravenous magnesium has been reported to improve postoperative pain; however, the evidence is inconsistent. The objective of this quantitative systematic review is to evaluate whether or not the peri-operative administration of intravenous magnesium can reduce postoperative pain. Twenty-five trials comparing magnesium with placebo were identified. Independent of the mode of administration (bolus or continuous infusion), peri-operative magnesium reduced cumulative intravenous morphine consumption by 24.4% (mean difference: 7.6 mg, 95% CI −9.5 to −5.8 mg; $p < 0.00001$) at 24 h postoperatively. Numeric pain scores at rest and on movement at 24 h postoperatively were reduced by 4.2 (95% CI −6.3 to −2.1; $p < 0.0001$) and 9.2 (95% CI −16.1 to −2.3; $p = 0.009$) out of 100, respectively. We conclude that peri-operative intravenous magnesium reduces opioid consumption, and to a lesser extent, pain scores, in the first 24 h postoperatively, without any reported serious adverse effects.

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Magnesium has been reported to produce important analgesic effects including the suppression of neuropathic pain [1], potentiation of morphine analgesia, and attenuation of morphine tolerance [2]. Although the exact mechanism is not yet fully understood, the analgesic properties of magnesium are believed to stem from regulation of calcium influx into the cell [3] and antagonism of N-methyl-D-aspartate (NMDA) receptors in the central nervous system [1, 4]. Since the completion of the first positive randomised controlled trial investigating magnesium as an analgesic adjuvant in 1996 [5], several additional trials have been published, with conflicting results [6–8]. Two narrative review articles [9, 10] recently concluded that peri-operative magnesium does not confer any important analgesic benefit, but these conclusions were drawn from a small number of trials [9] and subject to inaccuracies in data reporting [10]. The administration of intravenous magnesium in the peri-operative setting is not without risk and should be based on evidence, as it may prolong neuromuscular blockade after administration of neuromuscular blocking drugs [11, 12], increase sedation [13] and contribute to serious cardiac morbidity [14]. Consequently, the aim of this review is to define quantitatively the effect of peri-operative intravenous magnesium on acute postoperative pain.

Methods

The investigators followed the recommendations of the « Preferred Reporting Items for Systematic Reviews and Meta-Analyses» (PRISMA) statement [15]. The authors searched the electronic databases MEDLINE (until January 2012), EMBASE (until January 2012), and the Cochrane Central Register of Controlled Clinical Trials (until January 2012) using the following population search terms: magnesium OR magnesium compounds. These search results were combined with peri-operative care OR peri-operative period. Results were further limited by combining with analgesia OR analgesics OR pain OR pain management OR pain measurement OR pain threshold. The following words were searched as keywords: magnesium*, periop*, peri-op*,perop*, intra-op*, intra-op*, postop*, post-op*, analg*, and pain*. Finally, the references of the retrieved articles were manually examined for any relevant trials not identified in the original search. Search results were limited to randomised controlled trials, English, French and German language, humans, adults and magnesium sulphate. Only trials comparing the administration of intravenous magnesium to placebo were included in the present review. Trials investigating magnesium as a perineural local anaesthetic adjunct, trials using magnesium as an adjuvant for intravenous regional anaesthesia or for general anaesthesia, and trials using an epidural catheter for treating postoperative pain were excluded.

The quality of the method of each randomised trial was rated using the Jadad score [16] and assigned from 1 (minimum) to 5 (maximum) points. Two authors (EA, KK) independently reviewed and scored each trial using this method and extracted data for the analyses with disagreements in data or scoring were resolved through discussion with a third author (RB). Extracted trial characteristics included type of surgery, type of surgical anaesthesia, mode and total dose of administered magnesium, the use and type of multimodal analgesia. Calculations of total magnesium doses were made assuming a mean weight of 70 kg when not otherwise specified.

Specific outcomes sought in each article were based on the American Society of Regional Anesthesia and Pain Medicine's Acute Postoperative Pain Database initiative [17]. The primary acute pain-related endpoint evaluated was cumulative intravenous morphine consumption at 24 h postoperatively. Secondary acute pain-related endpoints sought were pain scores at rest and on movement measured at 24 h postoperatively, early postoperative (0–6 h) intravenous morphine consumption, early postoperative (0–6 h) pain scores at rest and on movement, time to first analgesic request, and incidences of postoperative nausea, vomiting (PONV) and pruritus within the first 24 h postoperatively. If not otherwise stated, it was assumed that pain scores were assessed at rest.

Additional relevant endpoints evaluated were magnesium-related adverse effects including hypotension, bradycardia and sedation, quality of neuromuscular blockade and serum magnesium levels. Serum magnesium expressed as $mg.dl^{-1}$ was converted to $mmol.l^{-1}$ for analysis.

Meta-analyses were performed with the assistance of Review Manager software (RevMan version 5.1.6; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). This software estimates the weighted mean differences for continuous data or categorical data between magnesium and placebo groups, with an overall estimate of the pooled effect. Data were analysed using a random effects model, as most were heterogeneous, and are presented as mean difference or relative risk (RR) with 95% CI. Means and SD were extracted from the text, tables or graphs from each source study. All opioids were converted into equianalgesic doses of intravenous morphine [18–20] and pain scores reported as verbal or numeric rating scales were converted to a standardised 0–100 analogue scale for quantitative evaluations. The authors of trials that failed to report the sample size or results as a mean and SD or SEM were contacted to request the missing data. Our primary endpoint (cumulative intravenous morphine consumption at 24 h postoperatively) was analysed in subgroups according to mode of magnesium administration (bolus only, bolus and infusion, and infusion), and type of surgery. A meta-analysis was conducted if two or more trials reported the endpoint of interest. I^2 was used to evaluate heterogeneity with thresholds for low (25–49%), moderate (50–74%), and high (>75%) levels [21] and the likelihood of publication bias was assessed by calculating a funnel plot of standard error of the mean difference (y-axis) as a function of the mean difference (x-axis). A Pearson or Spearman

correlation, depending on the distribution of the variable, was calculated between the total dose of magnesium administered in 24 h and the reduction in morphine consumption at 24 h postoperatively using the JMP 9 statistical package (SAS Institute, Cary, NC, USA). A two-sided p value < 0.05 was considered significant

Results

Of the 43 trials identified (40 from literature search strategy, 3 from scanning bibliographies), 25 met the inclusion criteria, representing a total of 1461 patients (Fig. 1). Table 1 presents the trial characteristics. The median Jadad score was 4 out of 5 with 64% of trials receiving a score of either 4 or 5. The trials were mostly conducted on patients who underwent abdominal surgery (48%) [6–8, 13, 22–29], hysterectomy (24%) [5, 22, 30–33], and orthopaedic surgery (24%) [22, 34–38].

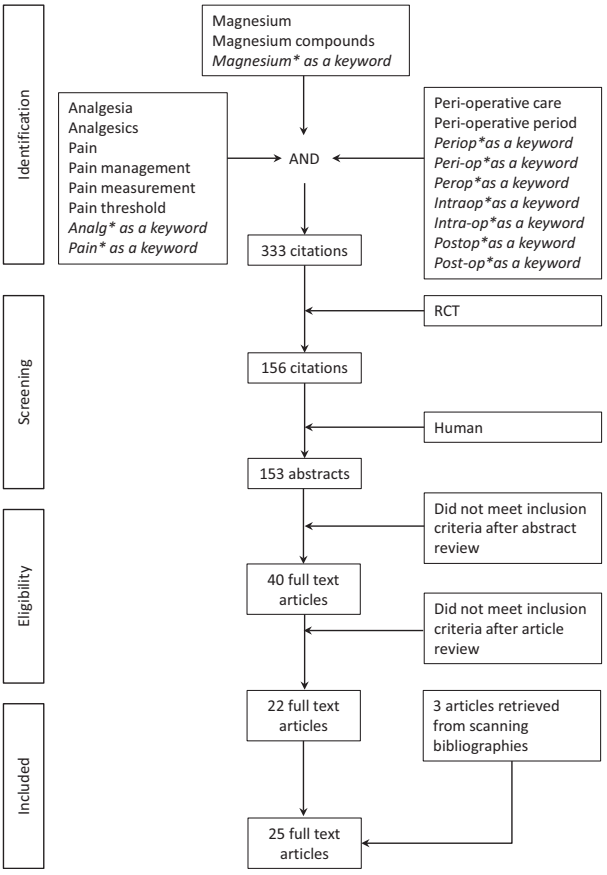

Figure 1 PRISMA flow diagram showing literature search results. Twenty-five randomised controlled trials (RCTs) were ultimately used for the analysis.

Attempts were made to contact seven authors [5, 24, 28–30, 33–35], and three provided the additional data requested [33–35].

Magnesium was administered as a single bolus in six trials (24%) [7, 13, 26, 33, 37, 39], as a bolus followed by infusion in 15 trials (60%) [5, 6, 8, 22–25, 27, 30–32, 35, 36, 38, 40], as an infusion only in two trials (8%) [34, 41], and combined with tramadol in a patient-controlled analgesia pump in two trials (8%) [28, 29]. Among the 21 trials that employed a bolus dose of magnesium, 19 used a bolus dose ranging between 30 and 50 $mg.kg^{-1}$. The total peri-operative dose administered ranged from 1.03 g [34] to 23.5 g [40]. There was no correlation between the total dose of magnesium administered over the first 24 h postoperatively and cumulative intravenous morphine consumption at 24 h postoperatively (Spearman coefficient = −0.16, p = 0.17).

Cumulative intravenous morphine consumption was reduced by an average of 24.4% in favour of the magnesium group (mean difference: 7.6 mg; 95% CI −9.5 to −5.8 mg; p < 0.00001) at 24 h postoperatively (Fig. 2). This difference persisted whether magnesium was administered as a bolus (reduction of 29.6%; p = 0.01), as a bolus and infusion (reduction of 23.6%; p < 0.0001) or as an infusion (reduction of 21.9%; p < 0.00001). The cumulative amount of intravenous morphine consumed at 24 h postoperatively was not statistically different between subgroups (p = 0.38). Cumulative intravenous morphine consumption at 24 h postoperatively was reduced in all types of surgery (Fig. 3). Specifically, morphine consumption was reduced by an average of 15% in gastrointestinal surgery (p = 0.02), 12.7% in gynaecological surgery (p < 0.00001), 37.9% in orthopaedic surgery (p < 0.0001), and 33.8% in other types of surgery (p = 0.009).

The funnel plots for our primary endpoint were inverted and symmetrical, centred around the mean difference on the x-axis, indicating a low potential for publication bias. Heterogeneity was assessed with I^2 values of 92% for both analyses.

Table 2 presents secondary acute pain-related endpoints. Mean pain scores at rest and on movement at 24 h postoperatively were reduced by 4.2 (95% CI −6.3, −2.1; p < 0.0001) and 9.2 (95% CI −16.1, −2.3; p = 0.009) out of 100, respectively. Immediate postoperative intravenous morphine consumption was

Table 1 Trial characteristics.

Reference	Jadad score	Number of patients in magnesium group / placebo group	Surgery	Sex	Anaesthesia strategy	Bolus	Infusion	Total dose in 24 h	Time of administration	Multimodal analgesia	Method of data extraction	Comment
[22]	4	25 / 25	Urological, general, gynaecological & lower extremity surgery	Both	Spinal	5 $mg.kg^{-1}$	500 $mg.h^{-1}$ for 24 h	12.35 g	Intra-operative	No	Text / table / graph	–
[23]	4	24 / 24	Open choleystectomy, gastrojejunal surgery	Both	General	50 $mg.kg^{-1}$	500 $mg.h^{-1}$ up to 6 h after surgery	7.35 g	Intra-operative	No	Text / table / graph	–
[24]	3	25 / 25	Open cholecystectomy	Both	General	50 $mg.kg^{-1}$	15 $mg.kg^{-1}.h^{-1}$ during surgery	4.04 g	Intra-operative	No	Text / table	–
[34]	4	30 / 30	Lower limb orthopaedic surgery	Both	Spinal	–	8 $mg.kg^{-1}.h^{-1}$ during surgery	1.03 g	Intra-operative	No	Text / table / author	–
[41]	4	114 / 114	Coronary artery bypass graft surgery	Both	General	–	8 $mg.kg^{-1}.h^{-1}$ during surgery	3.3 g	Intra-operative	No	Text / table	–
[35]	4	20 / 20	Total hip arthroplasty	Both	Spinal	50 $mg.kg^{-1}$	15 $mg.kg^{-1}.h^{-1}$ during surgery	5 g	Intra-operative	Ketorolac	Text / table / graph / author	–
[6]	5	21 / 21	Abdominal surgery	Both	General	50 $mg.kg^{-1}$	10 $mg.kg^{-1}.h^{-1}$ for 24 h	18.2 g	30 min before induction	No	Text / table	–
[30]	1	12 / 12	Abdominal hysterectomy	Female	General	30 $mg.kg^{-1}$	500 $mg.h^{-1}$ during next 20 h	12 g	Intra-operative	No	Text / table	–
[31]	4	20 / 20	Abdominal hysterectomy	Female	General	30 $mg.kg^{-1}$	500 $mg.h^{-1}$ during surgery	2.75 g	Intra-operative	No	Text / table	–
[13]	4	50 / 50	Inguinal hernia repair	Both	General	50 $mg.kg^{-1}$	–	3.5 g	Intra-operative	Pethidine in PACU (data not reported), diclofenac on the ward	Table	–
[36]	2	23 / 23	Knee arthroscopic surgery	Both	General	50 $mg.kg^{-1}$	8 $mg.kg^{-1}.h^{-1}$ during surgery	4.9 g	Intra-operative	No	Text / table / graph	–

Table 1 *Continued.*

Reference	Jadad score	Number of patients in magnesium group / placebo group	Surgery	Sex	Anaesthesia strategy	Bolus	Infusion	Total dose in 24 h	Time of administration	Multimodal analgesia	Method of data extraction	Comment
[37]	4	12/12	Lumbar arthrodesis	Both	General	50 $mg.kg^{-1}$	–	3.5 g	Intra-operative	No	Graph	–
[25]	2	21/21	Abdominal hernioplasty	Both	General	30 $mg.kg^{-1}$	6 $mg.kg^{-1}.h^{-1}$ during surgery	2.6 g	Intra-operative	No	Text/table	–
[26]	3	41/42	Laparoscopic cholecystectomy	Both	General	50 $mg.kg^{-1}$	–	3.5 g	Intra-operative	No	Text/table/graph	–
[38]	5	25/25	Lumbar disc surgery	Both	General	30 $mg.kg^{-1}$	10 $mg.kg^{-1}.h^{-1}$ during surgery	6.5 g	Intra-operative	No	Text/table/graph	–
[40]	3	12/12	Thoracotomy	Both	General	30 $mg.kg^{-1}$	10 $mg.kg^{-1}.h^{-1}$ for 48 h	23.5 g	Postoperative	Tenoxicam	Text/table/graph	–
[32]	3	25/25	Abdominal hysterectomy	Female	General	50 $mg.kg^{-1}$	15 $mg.kg^{-1}.h^{-1}$ during surgery	5.3 g	Intra-operative	Ketorolac	Text/table/graph	–
[27]	5	40/40	Laparoscopic cholecystectomy	Both	General	50 $mg.kg^{-1}$	25 $mg.kg^{-1}.h^{-1}$ during surgery	6.7 g	15 min before induction	No	Text/table/graph	Three groups were included: saline; magnesium; and lidocaine. Only data from the saline and magnesium groups were extracted.
[33]	4	20/20	Abdominal hysterectomy	Female	General	40 $mg.kg^{-1}$	–	3 g	15 min before induction	No	Text/table/author	Four groups were included: saline; single-bolus magnesium; and bolus magnesium followed by infusion of 10 or 20 $mg.kg^{-1}.h^{-1}$. Only data from the saline and single-bolus magnesium groups were extracted.
[39]	4	15/15	Radical retropubic prostatectomy	Male	General	50 $mg.kg^{-1}$	–	4.1 g	Intra-operative	Wound infiltration with ropivacaine + paracetamol + tramadol	Text/table/graph	–

Table 1 *Continued.*

Reference	Jadad score	Number of patients in magnesium group / placebo group	Surgery	Sex	Anaesthesia strategy	Bolus	Infusion	Total dose in 24 h	Time of administration	Multimodal analgesia	Method of data extraction	Comment
[5]	5	21 / 21	Abdominal hysterectomy	Female	General	3000 mg	500 $mg.h^{-1}$ during next 20 h	13 g	Intra-operative	No	Text / table	–
[7]	5	60 / 60	Varicose vein surgery / inguinal hernia repair	Both	General	4000 mg	–	4 g	Intra-operative	diclofenac + paracetamol + dextropropoxyphene	Table	Two subgroups of patients were included: patients with inguinal hernia repair had a routine ilioinguinal + iliohypogastric nerve block; patients with varicose vein surgery did not have any regional technique. Only data from patients with varicose vein surgey were extracted for pain-related outcomes. For magnesium-related side-effects, data from all patients were used.
[28]	3	23 / 21	Major abdominal surgery	Both	General	–	N / A	5.5 g	Postoperative (PCA)	No	Text / table	Three groups were included: tramadol; tramadol-magnesium; and tramadol-ketamine. Only data from the tramadol and tramadol-magnesium groups were extracted.
[29]	3	29 / 28	Major abdominal surgery	Both	General	–	N / A	3.7	Postoperative (PCA)	No	Text	Three groups were included: morphine; morphine-magnesium; and morphine-ketamine. Only data from the morphine and morphine-magnesium groups were extracted.
[8]	4	23 / 24	Colorectal surgey	Both	General	30 $mg.kg^{-1}$	10 $mg.kg^{-1}.h^{-1}$ during the next 20 h	16.3 g	Intra-operative	Propacetamol + metamizole	Text / table / graph	Four groups were included: IV saline; IV magnesium; oral nifedipine; and IV nimodipine. Only data from the saline and magnesium groups were extracted

PCA, patient-controlled analgesia; IV, intravenous

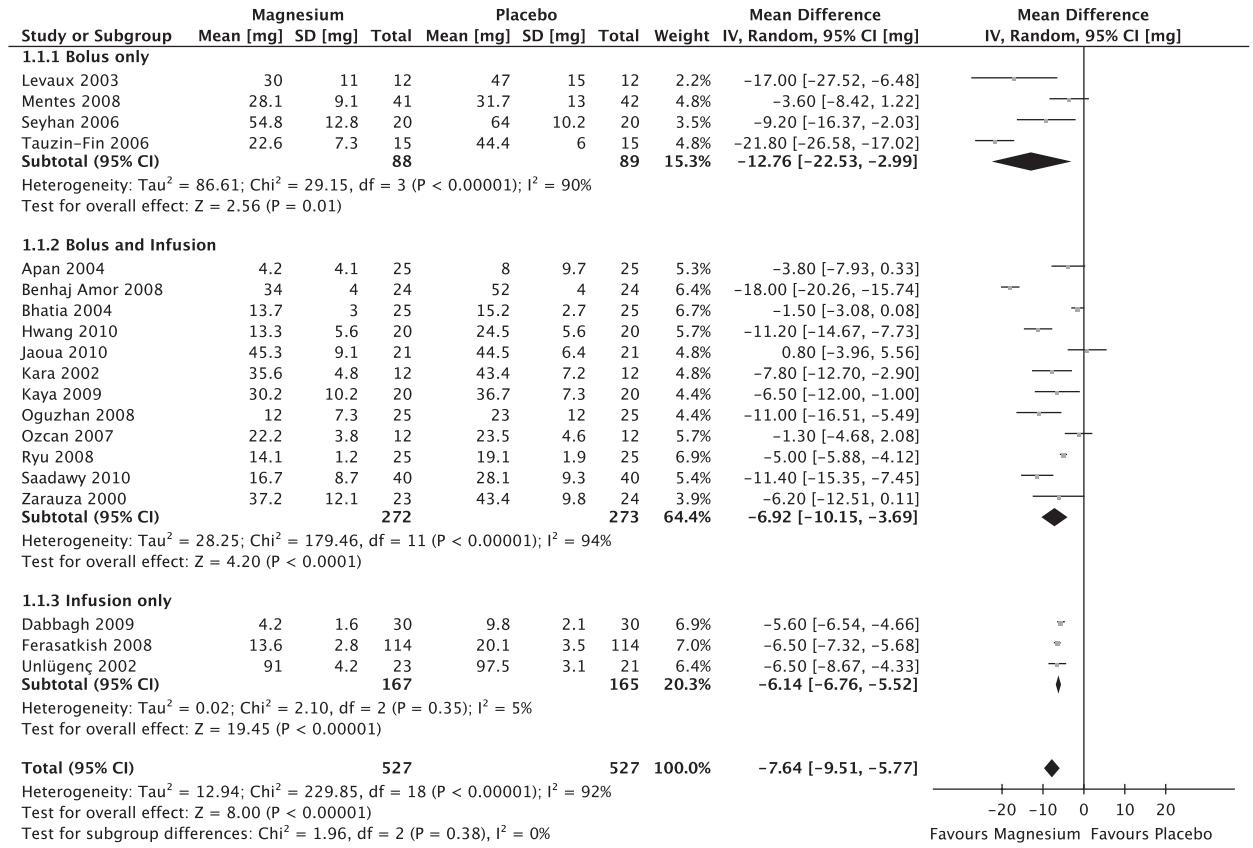

Figure 2 Cumulative intravenous morphine consumption at 24 h postoperatively according to the mode of administration (bolus only, bolus and infusion, infusion only).

reduced by an average of 3.6 mg in favour of the magnesium group (95% CI −5.2 to −2.1 mg; p < 0.00001). Early postoperative pain scores at rest and on movement were reduced by 6.9 (95% CI −9.6 to −4.2; p < 0.00001) and 6.5 (95% CI −10.0 to −2.9; p < 0.00001) out of 100, respectively. There were no significant differences in time to first analgesic request (mean difference: 7.2 min; 95% CI −1.9 to 16.2 min; p = 0.12), incidence of PONV (RR: 0.88; 95% CI 0.69, 1.12; p = 0.30) or incidence of pruritus (RR: 0.75; 95% CI 0.15–3.75; p = 0.73), respectively.

Table 3 summarises the adverse effects of intravenous magnesium administration. The incidence of bradycardia was higher in the magnesium group (RR: 1.76; 95% CI 1.01–3.07; p = 0.04), but without an increased incidence of hypotension (RR: 1.49; 95% CI 0.88–2.52; p = 0.14). Sedation scores were similar in both groups (mean difference: 0.17; 95% CI −0.42 to 0.76; p = 0.57). Measured serum magnesium levels were higher in the magnesium groups compared to placebo groups (mean difference: 0.42 $mmol.l^{-1}$; 95% CI 0.21–0.64 $mmol.l^{-1}$; p < 0.0001). It was not possible to perform any meta-analysis on neuromuscular blockade due to the variability in reporting. Five trials reported a reduction in consumption of neuromuscular blocking drugs [6, 27, 32, 33, 38], whereas five others did not find any difference [5, 24, 25, 30, 39]. Finally, one study reported a longer time to obtain four clinical responses to train-of-four stimulation in the magnesium group [37].

Discussion

This is the first systematic review of the literature and meta-analysis to assess the analgesic effect of peri-operative intravenous magnesium administration. Our results suggest that peri-operative magnesium can provide a clinically important reduction in opioid consumption, and to a lesser extent, pain scores, in the first 24 h postoperatively, in all types of surgery studied. We were unable to detect any advantage of one mode of

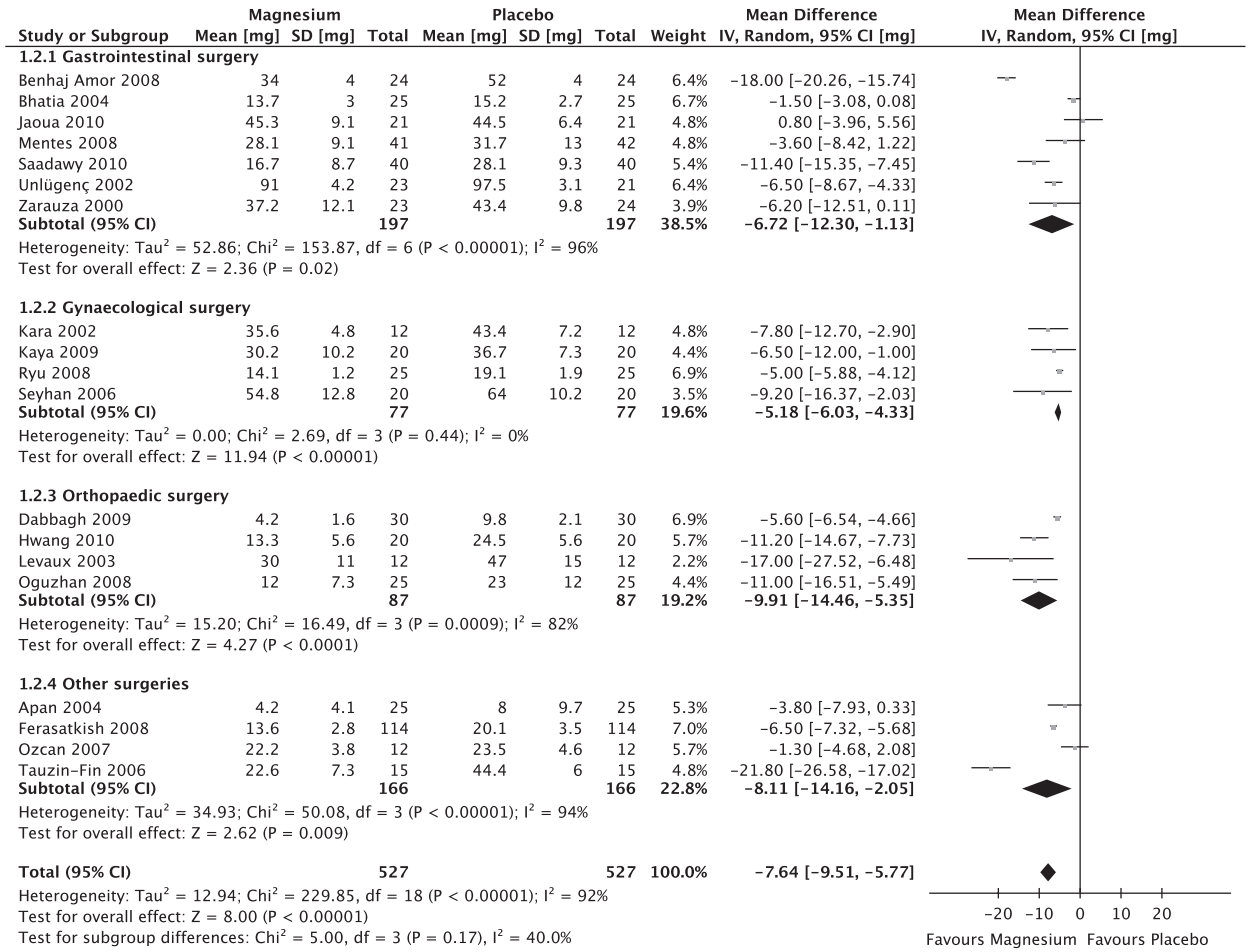

Figure 3 Cumulative intravenous morphine consumption at 24 h postoperatively according to the type of surgery.

administration (bolus, bolus and infusion, or infusion) over another for our acute pain-related endpoints. Moreover, we could not demonstrate any correlation between the total dose administered and reduction in morphine consumption at 24 h postoperatively, but this may be a result of the small size of the effect when magnesium is administered as an infusion over 24 h rather than a single bolus dose. Considering the potential logistic challenges of a prolonged postoperative magnesium infusion, there is no compelling reason to select this modality over a single bolus dose. Although our data suggest that a single bolus administration of between 40 [33] and 50 mg.kg^{-1} [26, 37, 39] reduces postoperative morphine consumption, it remains uncertain whether or not a different bolus dose may result in a greater effect. It is also noteworthy that none of the trials reviewed herein justified their selected doses for magnesium, and we are unable to find any dose-finding studies in the literature to support such dose selection.

Of the trials that evaluated magnesium-related adverse effects, there was no difference between groups in the incidence of sedation or hypotension. It was impossible to quantitatively assess the effect of magnesium on neuromuscular blockade due to inconsistent reporting of this endpoint. Although bradycardia was more common after magnesium administration, there were no reports of persistent haemodynamic instability or bradycardia that did not respond to first-line pharmacologic therapy. It must be noted that only six trials evaluated the incidence of either hypotension [5, 6, 8, 31, 35, 37] or bradycardia [5–7, 31, 35, 41], while two assessed the incidence of sedation [13, 31]. Thus, the incidence of adverse effects may be underestimated. Interestingly, however, three studies administered doses as high as 16.3 g [8], 18.2 g [6], or 23.5 g [40] over a

Table 2 Secondary acute pain-related endpoints.

Outcome	Number of trials	References	Total number of patients or number of patients with outcome/ total number of patients (%)					p value	
			Magnesium	Placebo	RR; 95% CI	Mean difference; 95% CI	I^2; %	Heterogeneity	Overall effect
Pain scores (VAS, VRS or NRS) at 24 h postoperatively at rest	14	[22], [23], [34], [41], [35], [13], [26], [38], [40], [32], [27], [33], [39], [8]	464	466	–	−4.2 (−6.3 to −2.1)	78	< 0.00001	< 0.0001
Pain scores (VAS, VRS or NRS) at 24 h postoperatively on movement	5	[23], [26], [32], [27], [8]	112	113	–	−9.2 (−16.1 to −2.3)	86	< 0.00001	0.009
Early postoperative IV morphine consumption (mg)	9	[35], [36], [37], [25], [40], [32], [27], [33], [39]	188	188	–	−3.6 (−5.2 to −2.1)	93	< 0.00001	< 0.00001
Early postoperative pain scores (VAS, VRS or NRS) at rest	15	[22], [23], [34], [35], [13], [36], [26], [38], [40], [32], [27] [33], [39], [7], [8]	433	435	–	−6.9 (−9.6 to −4.2)	79	< 0.00001	< 0.00001
Early postoperative pain scores (VAS, VRS or NRS) on movement	5	[23], [26], [32], [27], [7]	190	191	–	−6.5 (−10.0 to −2.9)	35	0.19	0.0004
Time to first analgesic request (min)	4	[22], [23], [27], [7]	149	149	–	7.2 (−1.9 to 16.2)	90	< 0.00001	0.12
Postoperative nausea and vomiting	15	[23], [24], [6], [31], [37], [26], [38], [40], [32], [27], [39], [7], [28], [29], [8]	92/419 (22.0%)	105/418 (25.1%)	0.88 (0.69 – 1.12)	–	–	0.86	0.30
Pruritus	2	[23], [6]	2/44 (4.5%)	3/44 (6.8%)	0.75 (0.15 – 3.75)	–	–	0.55	0.73

PCA, patient-controlled analgesia; IV, intravenous

Table 3 Magnesium-related adverse effects.

Outcome	Number of trials	References	Total number of patients or number of patients with outcome/total number of patients (%)		RR; 95% CI	Mean difference; 95% CI	I^2; %	p value	
			Magnesium	Placebo				Heterogeneity	Overall effect
Hypotension	6	[35], [6], [31], [37], [5], [8]	22/116	14/117	1.49 (0.88–2.52)	–	–	0.89	0.14
Bradycardia	6	[41], [35], [6], [31], [5], [7]	32/296 (10.8%)	16/294 (5.4%)	1.76 (1.01–3.07)	–	–	0.69	0.04
Sedation	2	[31], [13]	70	70	–	0.2 (–0.4–0.8)	87	0.002	0.57
Serum magnesium (mmol.l^{-1})	9	[22], [23], [35], [30], [36], [25], [40], [39], [5]	173	173	–	0.42 (0.21–0.64)	99	< 0.00001	< 0.00001

period of 24 h, and none of these reported any major adverse effects of magnesium. In the obstetric setting, Duley and colleagues previously studied more than 10 000 preeclamptic parturients in whom the total dose of magnesium administered was 28 g over 24 h (bolus dose of 4 g followed by an infusion of 1 g.h^{-1}) [42]. This group of investigators also found no differences in serious morbidity compared with placebo. In rats, the median lethal dose is in excess of 150 mg.kg^{-1} when administered as a bolus and greater than 200 mg.kg^{-1}.h^{-1} when administered as an infusion [43]. All studies included in our meta-analysis administered magnesium doses well below these levels.

This meta-analysis is limited by the absence of systematic definitions for certain endpoints and by wide variability in methods used in the trials included. Only seven trials allowed patients access to non-opioid analgesics such as non-steroidal analgesic drugs [7, 8, 13, 32, 35, 40], paracetamol [7, 8, 39], or wound infiltration of local anaesthetic [39]. This permitted a precise assessment of the analgesic contribution of magnesium, but limits generalisation of our results to modern anaesthetic practice where multimodal agents are commonly employed. Finally, despite the large number of studies examined, only a small number of trials could be included in the analysis for some of our important predefined endpoints, such as the time to first analgesic request [7, 22, 23, 27] and the incidence of pruritus [6, 23].

In summary, peri-operative intravenous magnesium can reduce opioid consumption, and to a lesser extent, pain scores, in the first 24 h postoperatively, without any reported serious adverse effects. Magnesium can be considered as an efficacious adjunct for postoperative analgesia in the setting of conventional opioid-based therapy.

Competing interests

EA has received grants from the Swiss Academy for Anaesthesia Research (SACAR), Lausanne, Switzerland and from the Foundation SICPA, Prilly, Switzerland.

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