Magnesium as an Adjuvant to Postoperative Analgesia: A Systematic Review of Randomized Trials

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BACKGROUND: Randomized trials have reached different conclusions as to whether magnesium is a useful adjuvant to postoperative analgesia.

METHODS: We performed a comprehensive search (electronic databases, bibliographies, all languages, to 4.2006) for randomized comparisons of magnesium and placebo in the surgical setting. Information on postoperative pain intensity and analgesic requirements was extracted from the trials and compared qualitatively. Dichotomous data on adverse effects were combined using classic methods of meta-analysis.

RESULTS: Fourteen randomized trials (778 patients, 404 received magnesium) tested magnesium laevulinate, gluconate or sulfate. With magnesium, postoperative pain intensity was significantly decreased in four (29%) trials, was no different from placebo in seven (50%), and was increased in one (7%); two trials (14%) did not report on pain intensity. With magnesium, postoperative analgesic requirements were significantly reduced in eight (57%) trials, were no different from placebo in five (36%), and were increased in one (7%). Magnesium-treated patients had less postoperative shivering (relative risk 0.38, 95% confidence interval 0.17–0.88, number-needed-to-treat 14). Seven trials reported on magnesium serum levels. In all, serum levels were increased in patients who received magnesium; in six, serum levels were decreased in those who received placebo.

CONCLUSIONS: These trials do not provide convincing evidence that perioperative magnesium may have favorable effects on postoperative pain intensity and analgesic requirements. Perioperative magnesium supplementation prevents postoperative hypomagnesemia and decreases the incidence of postoperative shivering. It may be worthwhile to further study the role of magnesium as a supplement to postoperative analgesia, since this relatively harmless molecule is inexpensive, and the biological basis for its potential antinociceptive effect is promising.

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Magnesium inhibits calcium entry into the cell via a noncompetitive blockade of the *N*-methyl-D-aspartate (NMDA) receptor (1). Magnesium and the NMDA receptor are thought to be involved in the modulation of pain (2). Magnesium is also a physiological calcium antagonist at different voltage-gated channels (3), which may be important in the mechanisms of antinociception (4).

In a rat model, intrathecal magnesium sulfate induced spinal anesthesia (5). In clinical trials, magnesium treatment improved symptoms of primary dysmenorrhea (6), and had a beneficial effect in patients affected by menstrual migraine (7), or headache (8). Patients undergoing major surgery without magnesium supplementation are at risk of developing hypomagnesemia in the first postoperative 24 h (9). This decrease is probably due to the large loss of fluids and fluid movement between body compartments. Thus, perioperative magnesium supplementation may prevent postoperative hypomagnesemia and have a beneficial effect on postoperative pain. However, results from randomized, controlled trials studying the impact of magnesium on the quality of postoperative analgesia have been conflicting (10–12). It remains unclear whether magnesium has a clinically relevant effect on postoperative pain and analgesia requirements, and what the optimal regimen is. We performed a systematic review of all relevant, published, randomized trials on magnesium and postoperative pain outcomes.

METHODS

We followed the recommendations of the QUOROM statement (13).

Literature Search

Requirements for inclusion were 1) Randomized treatment allocation; 2) Placebo or no treatment control group; 3) Pre- or intraoperative, with or without

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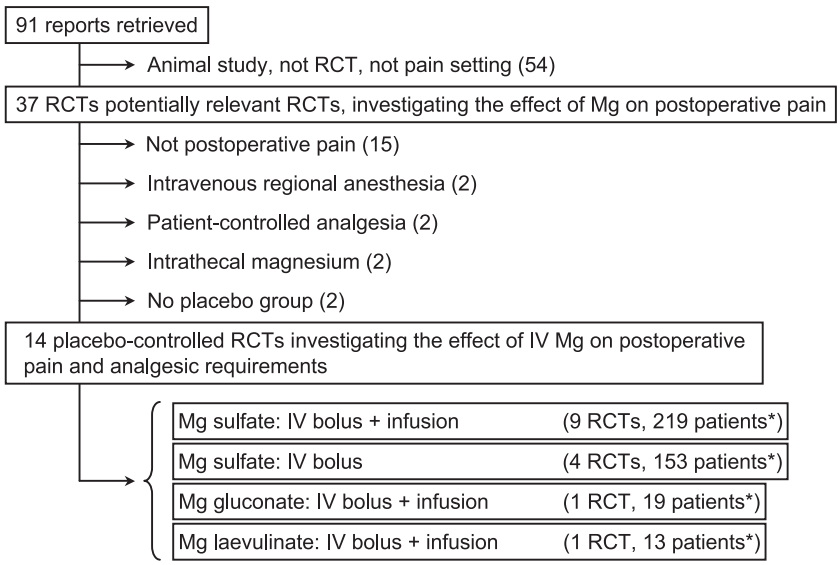

Figure 1. Flowchart of retrieved, excluded, and analyzed randomized controlled trials (RCT). Mg, magnesium; IV, intravenous. *Number of patients receiving magnesium. Number of trials does not add up since one trial tested IV bolus and IV bolus + infusion.

postoperative, IV or IM magnesium administration; 4) Reporting on postoperative analgesic requirements or postoperative pain intensity. Studies on intrathecal magnesium, on magnesium added to a patient-controlled analgesia opioid pump, animal studies, experimental studies in healthy volunteers, or trials that reported on intraoperative outcomes only (for instance, anesthetic requirements) were not considered. Relevant full reports were searched in Medline, Embase, Biosis, Cinahl, and the Cochrane Controlled Trials Register. Keywords used alone and in combination were *magnesium; surgery* OR *surgical* OR *postoperative* OR *post* adj *operative; randomized* OR *randomised; human;* and *pain* OR *analgesia* OR *nociception*. The last electronic search was in April 2006. We also checked bibliographies of retrieved reports.

Critical Appraisal

Two authors screened all retrieved papers. Reports that did not meet inclusion criteria were excluded at this stage. The remaining papers were read by two authors independently and scored for methodological validity using a modified 7-point Oxford scale (14,15). Authors met to agree consensus; discrepancies were resolved by discussion.

Analyses

From the individual reports we extracted data on type of surgery, number of randomized and analyzed patients, magnesium regimens, outcomes, and adverse effects. There was an intention to combine data from independent trials using classic methods of meta-analyses and to express summary estimates with 95% confidence intervals (CI). However, the relevant trials tested many different magnesium regimens and reported on a large variety of efficacy end-points; meta-analysis of pain outcomes was deemed inappropriate. Instead, we extracted from the original studies information on postoperative pain intensity and analgesic requirements and compared the results qualitatively. Results of statistical significance were taken as reported in the original trials. Dichotomous data on further outcomes (for instance, adverse effects) were combined using a fixed effect model and were expressed as relative risks with 95% CI and numbers-needed-to-treat (NNT) or -harm (16–18).

RESULTS

Retrieved Trials

We retrieved 37 potentially relevant randomized trials; 23 had to be subsequently excluded (Fig. 1). Fifteen were not on postoperative surgical pain: they studied prevention of pain on injection with propofol (20) or of succinylcholine-induced myalgia (21), experimental pain in healthy volunteers (22), dysmenorrhea (6), headache (23), fibromyalgia (24), migraine (25–28), neuropathic pain (29,30), or intraoperative anesthetic requirements (31–33). Eight trials had to be excluded for a variety of reasons: they tested magnesium added to tramadol or morphine in a patient-controlled analgesia pump (34,35), intrathecal magnesium (36,37), magnesium as an adjuvant to IV regional anesthesia (Bier's block) for acute (38) or chronic pain (39), magnesium as part of a multimodal analgesia regimen and the effect of magnesium could not be isolated (40), and one did not include an inactive control group (41).

We eventually analyzed data from 14 placebo or no treatment controlled trials (Tables 1 and 2) (10–12,42–52). Data from 778 patients were analyzed; 404 received magnesium. The quality scale ranged from 2 to 7 (median, 3); 2 trials scored 2, 5 scored 3, 3 scored 4, 1 each scored 5 or 6, and 2 scored 7. One trial was performed in children (52), all others in adults.

Magnesium Regimens

Magnesium was tested as laevulinate (50) or gluconate (49) in one trial each, and as sulfate in all others. In nine trials, magnesium sulfate was administered as a pre- or intraoperative IV bolus followed by

Table 1. Analyzed Randomized Controlled Trials—Part I

Ref.	Quality of data reporting R	C	B	F	Comparison: All magnesium regimens were given intravenously (no. of analyzed patients) {duration of infusion} [not analyzed data]	Surgery	Postoperative analgesic requirements and pain intensity: Magnesium	Placebo	*P**
Magnesium sulfate ($MgSO_4$): intravenous bolus + continuous infusion									
41	1	0	2	0	1. $MgSO_4$ 5 mg/kg + 500 mg/h {24 h} (25) 2. Saline (25)	Minor surgery	*Time to first analgesia* 264 ± 155 min	190 ± 154 min	<0.05
							Morphine consumption per 24 h 31.8 ± 30.7 mg	60 ± 73.1 mg	<0.05
							Pain intensity (VAS) at 12 h (mean, from graph) 10	15	<0.05
42	2	0	1	1	1. $MgSO_4$ 50 mg/kg + 15 mg/kg/h during surgery {77′} (25) 2. Saline (25)	Cholecystectomy	*Morphine consumption per 24 h* No difference		ns
							Pain intensity on coughing (VAS) at 24 h No difference		ns
43	1	0	1	0	1. $MgSO_4$ 30 mg/kg + 500 mg/h {20 h} (12) 2. Saline (12)	Abdominal hysterectomy	*Morphine consumption (PCA 24 h)* 35.6 ± 4.8 mg	43.4 ± 7.2 mg	<0.05
							Pain intensity (VAS) at rest; during coughing In favor of Mg at 30′ and at 18 h (no data reported)		<0.05
44	1	0	1	2	1. $MgSO_4$ 50 mg/kg + 15 mg/kg/h {6 h} (29) 2. Saline (29)	Abdominal hysterectomy	*Epidural bupivacaine-fentanyl consumption* No difference		ns
							Pain intensity (VAS) at rest; forced expiration No difference		ns
45	1	0	2	0	1. $MgSO_4$ 50 mg/kg + 8 mg/kg/h during surgery {123′} (23) 2. Saline (23)	Knee arthroscopy	*Fentanyl consumption during 4 h; from graph* 0.004 ± 0.002 μg/kg/min	0.02 ± 0.015 μg/kg/min	<0.01
							Pain intensity No data reported		n/a
47	1	0	1	0	1. $MgSO_4$ 30 mg/kg + 6 mg/kg during surgery {75′} (21) 2. Saline (21)	Abdominal hernioplasty	*Fentanyl consumption during 2 h* 0.81 ± 0.23 μg/kg	1.72 ± 0.35 μg/kg	<0.01
							Pain intensity (VAS) during first 2 h No difference		ns
49	2	0	1	0	[1. $MgSO_4$ 40 mg/kg + saline {4 h} (20)] 2. $MgSO_4$ 40 mg/kg + 10 mg/kg {4 h} (20) 3. $MgSO_4$ 40 mg/kg + 20 mg/kg {4 h} (20) 4. Saline (20) Group 1: see "$MgSO_4$: IV bolus"	Abdominal hysterectomy	*Morphine consumption (PCA 24 h)* Mg10 0.59 ± 0.23 mg/kg Mg20 0.53 ± 0.21 mg/kg	Sal 0.88 ± 0.14 mg/kg	<0.001
							Pain intensity No data reported		n/a
10	2	1	2	1	1. $MgSO_4$ 3 g + 0.5 g/h {20 h} (21) 2. Saline (21)	Abdominal hysterectomy	*Morphine consumption per 48 h (mean)* 65	91	<0.03
							Pain intensity (VAS) at rest; on movement to 1 mo No difference		ns
11	1	0	2	2	1. Placebo + $MgSO_4$ 30 mg/kg + 10 mg/kg/h {20 h} (23) [2. Nifedipine 60 mg PO + saline (22)] [3. Placebo PO + nimodipine 30 μg/kg/h (23)] 4. Placebo PO + saline (24)	Colorectal	*Morphine consumption (48 h)* No difference		ns
							Pain intensity (VAS) at rest; on movement to 5 d No difference		ns

Randomization: 0 = none; 1 = yes, not specified; 2 = yes, adequate. Concealment of treatment allocation: 0 = none; 1 = yes. Blinding: 0 = none; 1 = patient or investigator or observer blinded; 2 = patient and investigator and observer blinded. Follow-up: 0 = none; 1 = incomplete; 2 = complete.

* *P* values as reported in the original trials; ns = not significant.

a continuous infusion that lasted up to 24 h; in those, the median cumulative dose of magnesium sulfate was 8.5 g (range, 2.6–16.3).

Pain Intensity

Four trials (29% of all) reported on a significant decrease in postoperative pain intensity in patients treated with magnesium compared with placebo (42,44,49,51); observation times were between 7 and 24 h. From only one of those trials, could actual pain intensity data be extracted; with placebo, average pain intensity at 12 h was 15 mm on a 100 mm visual analog scale, with magnesium, it was reported to be 10 mm (42). Seven trials (50%) were unable to find

Table 2. Analyzed Randomized Controlled Trials—Part II

Ref.	Quality of data reporting: Randomization	Concealement	Blinding	Follow-up	Comparison: All magnesium regimens were given intravenously (No. of analyzed patients) {duration of infusion} [not analyzed data]	Surgery	Postoperative analgesic requirements and pain intensity: Magnesium	Placebo	*P**
Magnesium gluconate: intravenous bolus + continuous infusion									
49	1	0	1	1	1. Mg gluconate 86.5 mg/kg + 13.8 mg/kg/h {12 h} (19) 2. Saline (20)	Cardiac	*Remifentanil consumption up to 12 h* 0.04 ± 0.02 μg/kg/min	0.06 ± 0.02 μg/kg/min	0.008
							Inadequate pain control (>3/6) before extubation (no.) 9	23	<0.05
							Pain intensity (VAS) at 7 and 8 h (from graph) "Significantly lower with Mg compared with saline"		<0.05
Magnesium laevulinate: intravenous bolus + continuous infusion									
50	1	0	2	1	1. Mg laevulinate 200 mg + 200 mg/h {5 h} (13) 2. Saline (11)	Abdominal hysterectomy	*Morphine consumption up to 4 h* No difference		ns
							Pain intensity (5-point score) at 3 h 2	1	<0.04**
							No. of episodes with severe or unbearable pain 21/130	7/110	<0.02**
							No. of episodes without any pain during first 4 h No difference		ns
Magnesium sulfate: intravenous bolus									
51	2	0	1	0	1. $MgSO_4$ 50 mg/kg bolus {30′} (12) 2. Saline (12)	Major orthopaedic	*Piritramide consumption at 12 h (from graph)* 20 ± 7 mg	32 ± 12 mg	<0.05
							Piritramide consumption at 24 h (from graph) 30 ± 11 mg	47 ± 15 mg	<0.05
							Pain intensity (VAS) (at 24 h) "Significantly lower with Mg"		<0.05
52	2	1	2	2	[1. Ketamine 0.15 mg/kg (18)] 2. $MgSO_4$ 30 mg/kg (20) [3. Ketamine 0.15 mg/kg + $MgSO_4$ 30 mg/kg (19)] 4. Saline (20)	Pediatric tonsillectomy	*Codeine consumption per 24 h (from graph)* 1.6 mg/kg	1.0 mg/kg	<0.03**
							Other analgesics (fentanyl, acetaminophen) no difference		ns
							Objective pain scale (5 items, 0–10 points) no difference		ns
48	2	0	1	0	1. $MgSO_4$ 40 mg/kg + Saline (20) [2. $MgSO_4$ 40 mg/kg + 10 mg/kg/4 h (20)] [3. $MgSO_4$ 40 mg/kg + 20 mg/kg/4 h (20)] 4. Saline (20) Groups 2 and 3: see "$MgSO_4$: IV bolus + cont infusion"	Abdominal hysterectomy	*Morphine consumption (PCA 24 h)* 0.73 ± 0.17 mg/kg	0.88 ± 0.14 mg/kg	<0.01
							Pain intensity No data reported		n/a
12	2	1	2	2	1. $MgSO_4$ 4 g (101) 2. Saline (99)	Inguinal hernia Varicose vein	*Analgesic consumption (first 4 h, days 1–3)* no difference		ns
							Pain intensity (VAS) (first 4 h, days 1–3) no difference		ns
							Pain relief (first 4 h, days 1–3) no difference		ns

Randomization: 0 = none; 1 = yes, not specified; 2 = yes, adequate. Concealement: 0 = none; 1 = yes. Blinding: 0 = none; 1 = patient or investigator or observer; 2 = patient and investigator and observer. Follow-up: 0 = none; 1 = incomplete; 2 = complete.

* *P* values as reported in the original trials; ns = not significant.

** Significance in favor of placebo.

any difference in pain intensities between magnesium and placebo (10–12,43,45,47,52). In one trial (7%), patients treated with magnesium laevulinate had significantly increased pain scores at 3 h postoperatively; on a 5-point verbal rating scale, pain intensity increased from 1 with placebo to 2 with magnesium (50). Two trials did not report on postoperative pain intensity.

Analgesic Requirements

Eight trials (57% of all) reported a significant decrease in postoperative analgesic requirements in patients treated with magnesium compared with those who received placebo. In 4 of those, cumulative morphine consumption at 24 or 48 h was decreased on average by 12% to 47% (median, 28%) (10,42,44,48); in 2, fentanyl consumption at 2 and 4 h postoperatively was decreased by 53% and 80% (46,47); and in 1 each, remifentanil consumption at 12 h and piritramide consumption at 24 h was decreased by 67% and 36%, respectively (49,51). Five trials (36%) were unable to find any difference in the postoperative consumption of epidural bupivacaine-fentanyl (45), or morphine (11,43,50), or different opioids (morphine, fentanyl, meperidine) and nonopioid analgesics (nonsteroidal antiinflammatory drugs, acetaminophen) (12). In one trial (7%), children treated with magnesium consumed significantly more codeine postoperatively, but not fentanyl or acetaminophen (52).

Four trials reported on both a significant decrease in pain intensity and analgesic requirements with magnesium (42,44,49,51). Four trials reported on absence of both a significant decrease in pain intensity

Table 3. Additional Beneficial and Harmful Effects

Endpoint	No. of patients with endpoint/total no. of patients (%)		RR (95% CI)	NNT/H (95% CI)	Refs.
	Magnesium	Control			
Shivering	7/155 (4.5)	18/153 (11.8)	0.38 (0.17–0.88)	NNT 14 (8–84)	10; 12; 49; 51
Vomiting	22/212 (10.4)	26/209 (12.4)	0.82 (0.49–1.37)	NNT 48	10–12; 45; 49; 50
Dizziness	12/124 (9.7)	14/123 (11.4)	0.85 (0.41–1.76)	NNT 57	11; 12
Nausea	42/166 (25.3)	31/163 (19.0)	1.30 (0.88–1.93)	NNH 16	11; 12; 45; 49; 50
Hypotension	23/186 (12.4)	16/185 (8.6)	1.43 (0.82–2.47)	NNH 27	10–12; 45; 51
Bradycardia	27/182 (14.8)	15/140 (10.7)	1.64 (0.90–2.98)	NNH 24	10–12; 45; 48

Table 4. Magnesium Serum Concentrations in Patients Treated with Magnesium and in Controls

Ref.	Surgery	Total amount of Mg (mg)	Magnesium				Control			
			Pretreatment	Posttreatment	*P**	% change	Pretreatment	Posttreatment	*P**	% change
42	Minor	12,370	1.95 ± 0.20	2.53 ± 0.50	n/a	31	1.85 ± 0.20	1.86 ± 0.20	n/a	1
44	Abdominal hysterectomy	11,950	1.48 ± 0.24	2.66 ± 0.18	<0.05	80	1.79 ± 0.18	1.30 ± 0.11	<0.05	−27
45	Abdominal hysterectomy	8,038	1.96 ± 0.20	3.51 ± 0.42	<0.001	79	1.91 ± 0.26	1.65 ± 0.26	<0.001	−14
46	Knee arthroscopy	4,950	0.76 ± 0.07	1.40 ± 0.37	<0.01	84	0.76 ± 0.11	0.69 ± 0.12	<0.05	−9
47	Abdominal hernioplasty	2,550	1.52 ± 0.14	2.40 ± 0.31	<0.05	58	1.63 ± 0.22	1.38 ± 0.24	<0.06	−15
49	Cardiac	25,688	0.79 ± 0.18	1.20 ± 0.19	<0.05	65	0.79 ± 0.18	0.76 ± 0.19	n/a	−4
10	Abdominal hysterectomy	13,000	0.74 ± 0.09	1.34 ± 0.09	<0.0001	81	0.74 ± 0.09	0.66 ± 0.05	<0.002	−11

Values are means ± SD ; n/a = not reported.

* *P* values as reported in original trials.

Magnesium serum concentrations are in mg/dl or mmol/L.

and analgesic requirements (11,12,43,45). There was no obvious relationship between the tested magnesium regimens and pain outcomes.

Further Outcomes

Data on further, potentially magnesium-related, beneficial or harmful outcomes came from eight studies (Table 3). Shivering, vomiting, and dizziness occurred less often with magnesium. For shivering, the difference was statistically significant; the average incidence with placebo was 11.8%, with magnesium was 4.5% (NNT 14). Nausea, arterial hypotension, and bradycardia occurred more often with magnesium. None of the differences, however, was statistically significant. Some trials reported on decreased scores of discomfort (43), or insomnia during the first postoperative night (10,43,51), or increased scores of satisfaction (51) in patients who received magnesium. None of those results was statistically significant.

Magnesium Serum Concentrations

Seven trials reported on magnesium serum concentrations before and after the end of study drug administration (Table 4). Six tested an IV bolus and a subsequent continuous infusion of magnesium sulfate (10,41,43–45,47), and one tested an IV bolus and continuous infusion of magnesium gluconate (49). In five of the seven trials, average magnesium serum concentrations in control patients decreased significantly by −9% to −27%; the median of all average changes was −11%. In 6 of the 7 trials, average magnesium serum concentrations in patients receiving magnesium increased significantly by 31%–84%; the median of all average changes was +79%. No correlation between the administered cumulative doses of magnesium and the increase in the magnesium serum concentrations was apparent. The trials were too heterogeneous and data reporting was too inconsistent to allow for a relationship between the degree of hypomagnesemia and pain intensity in controls.

DISCUSSION

Three main results emerged from this systematic review. First, in some trials, magnesium had a beneficial effect on postoperative pain intensity and analgesic requirements. Second, magnesium treatment decreased the incidence of postoperative shivering. Third, in most trials, magnesium serum concentrations in control patients decreased.

The beneficial effects of magnesium were not unequivocal. In some trials, the benefit seemed to be obvious; others were unable to show any improvement or even showed some deterioration in patients treated with magnesium. Perhaps the clearest beneficial result was the decrease in postoperative analgesic consumption in patients who received magnesium. For instance, in four trials, the reported degree of morphine sparing (median, 28%) was similar to what has been reported with intraoperative ketamine (15) or postoperative nonsteroidal antiinflammatory drugs

(53). However, morphine-sparing *per se* is of questionable clinical relevance. The main issue is whether or not the decrease in morphine consumption is followed by a decrease in the incidence of morphine-related adverse effects. This was not the case; the incidence of nausea or vomiting, for instance, was not reduced with magnesium treatment. Further potentially morphine-related adverse effects, such as sedation, pruritus, or respiratory depression, were not reported in these trials. Yet another reason that would justify the concomitant use of a nonopioid adjuvant for postoperative opioid-based analgesia, would be a decrease in postoperative pain intensity compared with the opioid alone. Four trials reported on a significant decrease in pain intensity in magnesium-treated patients. However, one of those trials only provided actual visual analog scale data, and the reported average decrease in pain intensity with magnesium (from 15 to 10 mm) could not necessarily be regarded as clinically relevant. Against these trials that provided some evidence that magnesium supplementation may have a beneficial effect on analgesic requirements or pain intensity, all the trials need to be weighted that were unable to find any benefit for both outcomes.

The quantity and quality of the trials did not allow for the necessary subgroup analyses to evaluate the degree of efficacy with various regimens of magnesium. There was a large variability in doses; some trials tested a single bolus, and in the majority, a subsequent infusion was added. The largest trial tested a single bolus dose of magnesium sulfate 4 g and was unable to find any benefit in favor of magnesium (12). Zarauza et al. (11) infused more than 16 g of magnesium sulfate in their patients and were unable to find a beneficial effect. On the other hand, Levaux et al. (51) injected a bolus dose of magnesium sulfate 3.6 g and reported a significant decrease in opioid consumption and pain intensity. As a consequence, we still do not know whether there is dose-responsiveness for the analgesic efficacy with magnesium. Similarly, it remains unknown whether there is a difference between magnesium sulfate, laevulinate, and gluconate. One trial tested a cumulative dose of magnesium laevulinate 1.2 g for 5 h (50). Cumulative morphine consumption up to 4 h after surgery, and the number of episodes without any pain, did not differ between patients treated with magnesium laevulinate and those receiving placebo. However, those who had received magnesium laevulinate reported significantly more episodes with severe or unbearable pain and they had higher pain scores. In another trial, a cumulative dose of magnesium gluconate that exceeded 25 g for 12 h was given (49). The number of patients with inadequate pain control before tracheal extubation, average pain intensity at 7 and 8 h after surgery, and remifentanil consumption during the first 12 h after surgery, were all significantly decreased in patients who had received magnesium gluconate. Thus, it remains unclear whether these differences in efficacy were due to differences in doses and regimens (1.2 g during 5 h vs 25 g during 12 h), or due to differences in the chemical form of magnesium (gluconate versus laevulinate), or due to other factors.

Not unexpectedly, magnesium treatment was shown to decrease the risk of postoperative shivering. This was perhaps the clearest beneficial effect of magnesium supplementation. In healthy volunteers, magnesium sulfate (80 mg kg^{-1} bolus followed by an infusion at 2 g h^{-1}) was shown to reduce the shivering threshold (54). In clinical practice, magnesium's beneficial effect on shivering is of minor importance (NNT about 14) compared with, for instance, the efficacy that was reported with meperidine or clonidine (NNT 3–4) (19).

In trials including patients undergoing abdominal hysterectomies and hernioplasties, average magnesium serum concentrations in control patients who did not receive magnesium supplementation decreased by 11%–27%. Serum levels, which are those generally measured, reflect only a small part of the total content of magnesium; the intracellular magnesium content can be low, despite normal serum levels (55). However, we may infer from the data reported in these trials and from observations from others (9) that longer and larger surgical interventions are more likely to lead to hypomagnesemia. It remains unclear what the clinical relevance of low magnesium serum levels in surgical patients is. There is evidence that the response of the NMDA receptor is greatly enhanced by reducing the extracellular magnesium concentration below the physiological level (56). It may be hypothesized that the reported outcomes in these trials, for instance, decrease in pain intensity or in morphine consumption, were not due to a direct analgesic effect of magnesium but, rather, to the prevention of hypomagnesemia, and thus prevention of subsequent NMDA activation.

Our analysis has two major limitations. First, most trials were small. Small trials may detect a beneficial treatment effect by random chance (57). The largest trial included 200 patients (12); that trial was negative but it tested only a bolus dose of magnesium sulfate. Thus, we do not know whether that trial was negative since it was large, and therefore the risk of random variation was minimal, or because the magnesium regimen in that trial was inadequate. Second, some trials reported on low pain scores in controls. For instance, in the trial by Ko et al. (45), patients postoperatively received epidural fentanyl and bupivacaine with or without systemic magnesium and pain scores were below 40 mm at all time points in both groups. That trial was part of those that were unable to show any benefit with magnesium. However, if there is not enough baseline pain, an experimental intervention has no scope to show analgesic efficacy (58).

In conclusion, these randomized trials do not provide convincing evidence that perioperative magnesium supplementation has favorable effects

on postoperative pain intensity and analgesic requirements. Nevertheless, it may be worthwhile to further study the role of magnesium as a supplement to postoperative analgesia, since this molecule is inexpensive, relatively harmless, and the biological basis for its potential antinociceptive effect is promising. There is the possibility that magnesium might have an additive or even synergistic effect with other NMDA antagonists, specifically ketamine or nitrous oxide. However, pharmacological interactions need to be formally tested. Future trials should be large enough to avoid random variations in outcomes, and they should report on clinically relevant end-points, such as pain intensity at short- and at long-term, and opioid-related adverse effects.

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