Systematic Review and Meta-Analysis

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Influence of magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy

A meta-analysis of randomized controlled studies

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Abstract

Background: The impact of magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of magnesium sulfate on hemodynamic responses for laparoscopic cholecystectomy.

Methods: We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through June 2018 for randomized controlled trials (RCTs) assessing the effect of magnesium sulfate on hemodynamic responses for laparoscopic cholecystectomy. Meta-analysis is performed using the random-effect model.

Results: Four RCTs involving 208 patients are included in the meta-analysis. Overall, compared with control group in laparoscopic cholecystectomy, intravenous magnesium sulfate is associated with systolic blood pressure at 30 minutes [Std. MD = −1.34; 95% confidence interval (95% CI) = −1.86 to −0.82; $P<.00001$], diastolic blood pressure at 30 minutes (Std. MD = −1.40; 95% CI = −1.86 to −0.94; $P<.00001$), mean arterial pressure at 30 minutes (Std. MD = −1.19; 95% CI = −1.91 to −0.46; $P=.001$), systolic blood pressure at 10 minutes (Std. MD = −1.61; 95% CI = −2.08 to −1.13; $P<.00001$), diastolic blood pressure at 10 minutes (Std. MD = −1.54; 95% CI = −2.68 to −0.40; $P=.008$), heart rate at 30 minutes (Std. MD = −2.09; 95% CI = −2.87 to −1.32; $P<.00001$), but results in prolonged extubation time (Std. MD = 0.96; 95% CI = 0.18–1.74; $P=.02$).

Conclusion: Magnesium sulfate can reduce blood pressure, but with the increase in extubation time for laparoscopic cholecystectomy.

Abbreviations: CI = confidence interval, RAAS = renin angiotensin aldosterone system, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: hemodynamic responses, laparoscopic cholecystectomy, magnesium sulfate, meta-analysis' randomized controlled trials

1. Introduction

Laparoscopic cholecystectomy is known as one of the most common laparoscopic surgeries worldwide.[1–3] Carbon dioxide (CO_2) is used for pneumoperitoneum, which may result in the adverse cardiovascular effects.[4–6] They mainly include an abrupt elevation of mean arterial pressure, systemic vascular resistance, and decreased cardiac output because of the release of both catecholamines and vasopressin.[7–9] In addition, the reverse Trendelenburg position in these surgeries can further decrease cardiac output.[10]

Many drugs have been developed for the attenuation of these vasopressor responses, and include opioids, beta blockers, magnesium, and α2 agonists.[11–13] Especially, magnesium is widely used to attenuate intubation-induced vasopressor response by blocking the release of catecholamines release from both adrenal medullae and from nerve terminals.[14] In addition, magnesium sulfate is reported to attenuate vasopressin-induced vasoconstriction by directly acting on blood vessels causing vasodilation.[10] With accumulating evidence, we perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy of magnesium sulfate to control hemodynamic responses in laparoscopic cholecystectomy.

2. Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[15]

2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to June 2018): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following combination keywords

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"magnesium sulfate" and "laparoscopic cholecystectomy." We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: population: patients undergoing laparoscopic cholecystectomy; intervention: magnesium sulfate; comparison: saline; study design: RCT; and studies published in English. Studies without hemodynamic data are excluded.

2.2. Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, weight, surgical duration, etc. Data have been extracted independently by 2 investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary. No simplifications and assumptions are made. The primary outcomes are systolic blood pressure and diastolic blood pressure at 30 minutes after pneumoperitoneum. Secondary outcomes include mean arterial pressure at 30 minutes, systolic blood pressure and diastolic blood pressure at 10 minutes, heart rate at 30 minutes, and extubation time.

2.3. Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale.[16] There are 3 items for Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality.[17]

2.4. Statistical analysis

We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (systolic blood pressure and diastolic blood pressure at 30 minutes after pneumoperitoneum, mean arterial pressure at 30 minutes, systolic blood pressure and diastolic blood pressure at 10 min, heart rate at 30 minutes, and extubation time). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity.[18] Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting 1 study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number (<10) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics, and quality assessment

A detailed flowchart of the search and selection results is shown in Fig. 1. Four hundred fifty-five potentially relevant articles are identified initially. Finally, 4 RCTs that meet our inclusion criteria are included in the meta-analysis.

The baseline characteristics of the 4 eligible RCTs in the meta-analysis are summarized in Table 1. The 4 studies are published between 2013 and 2017, and sample sizes range from 32 to 60 with a total of 208. All included RCTs report injection magnesium sulfate 50 mg/kg before pneumoperitoneum versus matched saline.

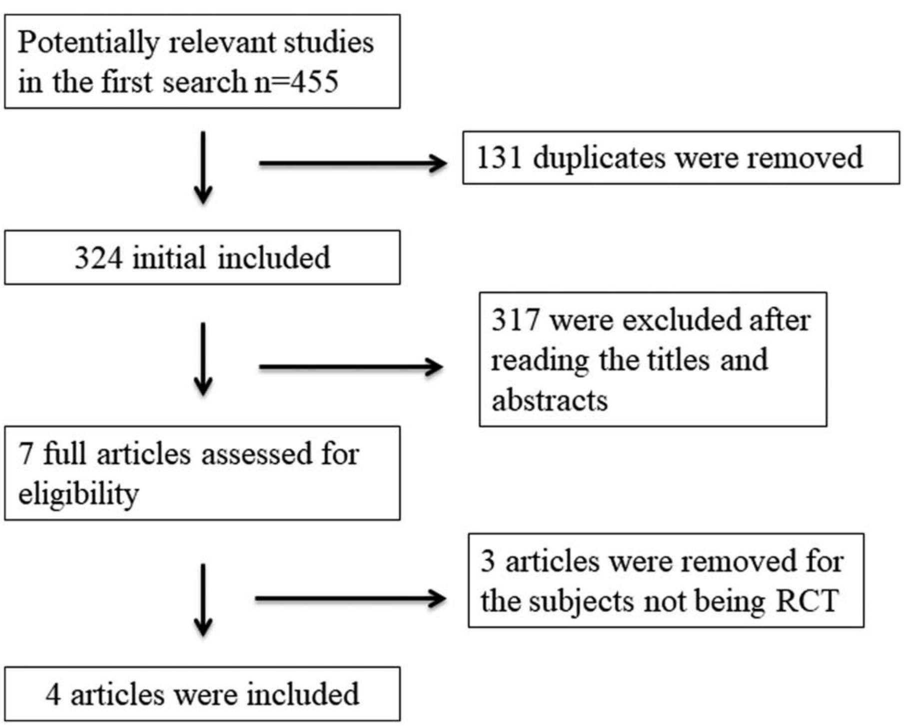

Figure 1. Flow diagram of study searching and selection process.

Table 1

Characteristics of included studies.

No.	Author	Magnesium sulfate group						Control group						Jada scores
		Number	Age, y	Female (n)	Weight, kg	Surgical duration	Methods	Number	Age, y	Female (n)	Weight, kg	Surgical duration	Methods	
1	Kamble et al[10]	30	41.20±13.30	12	66.00±10.66	1.48±0.45 h	Injection magnesium sulfate 50 mg/kg diluted in 10 mL normal saline over 10 min, before pneumoperitoneum	30	40.93±12.89	13	64.27±9.86	1.40±0.41 h	10 mL normal saline intravenously over 10 min, before pneumoperitoneum	5
2	Paul et al[19]	30	43.7±8.56	20	51.28±8.14	45.4±6.24 min	Magnesium sulfate 30 mg/kg intravenously as a bolus before pneumoperitoneum	30	41.4±6.83	19	49.18±7.64	46.26±5.42 min	Same volume of 0.9% saline	4
3	Kalra et al[13]	29	40.2±8.5	14	61.2±9.6	47.3±7.8 min	50 mg/kg of magnesium sulfate in normal saline (total volume 50 mL) before pneumoperitoneum	27	38.3±9.1	16	60.7±9.4	50±6.4 min	50 mL normal saline over a period of 15 min after induction and before pneumoperitoneum	4
4	Jee et al[14]	17	48.2	7	64.4±10.4	51.9±14.2 min	Magnesium sulphate 50 mg/kg immediately before pneumoperitoneum	15	46.6	7	60.2±8.1	54.3±10.7 min	0.5 mL/kg saline	3

Among the 4 studies included here, 2 studies report systolic blood pressure and diastolic blood pressure at 30 minutes after pneumoperitoneum,[10,14] 2 studies report mean arterial pressure at 30 minutes,[10,19] 2 studies report systolic blood pressure and diastolic blood pressure at 10 minutes,[10,14] 2 studies report heart rate at 30 minutes,[10,19] and 3 studies report extubation time.[10,13,14] Jadad scores of the 4 included studies vary from 3 to 5, and all 4 studies are considered to be high-quality ones according to quality assessment.

3.2. Primary outcomes: systolic blood pressure and diastolic blood pressure at 30 minutes

These outcome data are analyzed with the random-effects model, and the pooled estimate of the 2 included RCTs suggested that compared with control group during laparoscopic cholecystectomy, magnesium sulfate can significantly decrease the systolic blood pressure at 30 minutes [Std. MD = −1.34; 95% confidence interval (95% CI) = −1.86 to −0.82; $P < .00001$], with low heterogeneity among the studies ($I^2 = 21\%$, heterogeneity $P = .26$) (Fig. 2). Consistently, magnesium sulfate results in substantially reduced diastolic blood pressure at 30 minutes (Std. MD = −1.40; 95% CI = −1.86 to −0.94; $P < .00001$), with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .57$) (Fig. 3).

3.3. Sensitivity analysis

Low or even no heterogeneity is observed among the included studies for the primary outcomes. Thus, we do not perform sensitivity analysis by omitting 1 study in each turn to detect the source of heterogeneity.

3.4. Secondary outcomes

Compared with control group in laparoscopic cholecystectomy, magnesium sulfate is associated with significantly reduced mean arterial pressure at 30 minutes (Std. MD = −1.19; 95% CI = −1.91 to −0.46; $P = .001$; Fig. 4), systolic blood pressure at 10 minutes (Std. MD = −1.61; 95% CI = −2.08 to −1.13; $P < .00001$; Fig. 5), diastolic blood pressure at 10 minutes (Std. MD = −1.54; 95% CI = −2.68 to −0.40; $P = .008$; Fig. 6), heart rate at 30 minutes (Std. MD = −2.09; 95% CI = −2.87 to −1.32; $P < .00001$; Fig. 7), but leads to the increase in extubation time (Std. MD = 0.96; 95% CI = 0.18–1.74; $P = .02$; Fig. 8).

4. Discussion

Elevated intra-abdominal pressure induced by pneumoperitoneum and CO_2 can produce some adverse effects on the cardiovascular system.[20,21] Plasma level of catecholamines and vasopressin is found to increase immediately after pneumoperitoneum.[22,23] Increased catecholamine level further activates the renin-angiotensin aldosterone system (RAAS) and some characteristic hemodynamic alterations, including decreased cardiac output, elevated arterial pressure, and increased systemic/pulmonary vascular resistance.[24,25] Vasopressin also results in elevation of arterial pressure and systemic vascular resistance.[8]

Magnesium has a vasodilator action, thus contributing to the reduction of blood pressure. Magnesium sulfate has been reported to attenuate the adverse hemodynamic response of endotracheal intubation in one previous study.[26] One RCT reveals effectively blunted hemodynamic responses to pneumoperitoneum and lower arterial pressure and heart rate after using

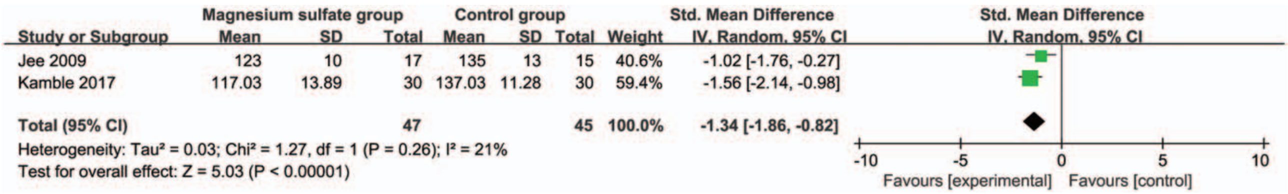

Figure 2. Forest plot for the meta-analysis of systolic blood pressure at 30 min (mm Hg).

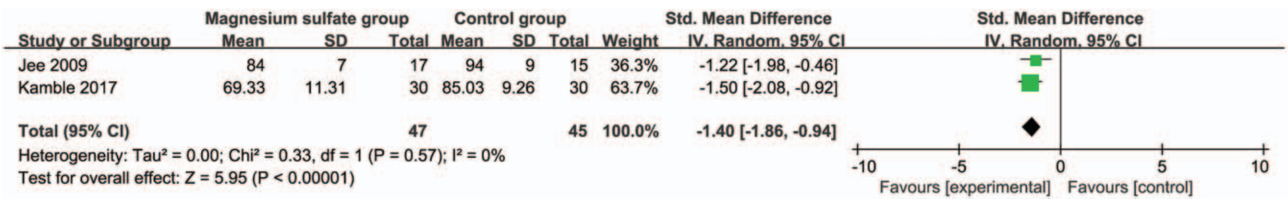

Figure 3. Forest plot for the meta-analysis of diastolic blood pressure at 30 min (mm Hg).

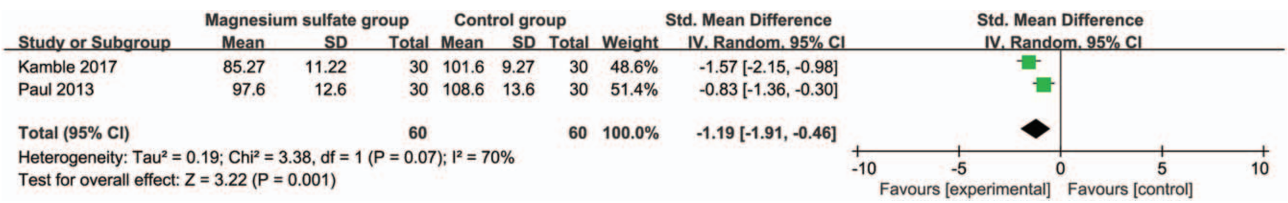

Figure 4. Forest plot for the meta-analysis of mean arterial pressure at 30 min (mm Hg).

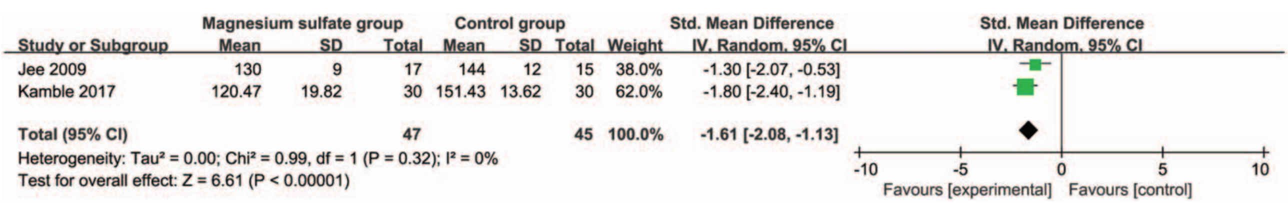

Figure 5. Forest plot for the meta-analysis of systolic blood pressure at 10 min (mm Hg).

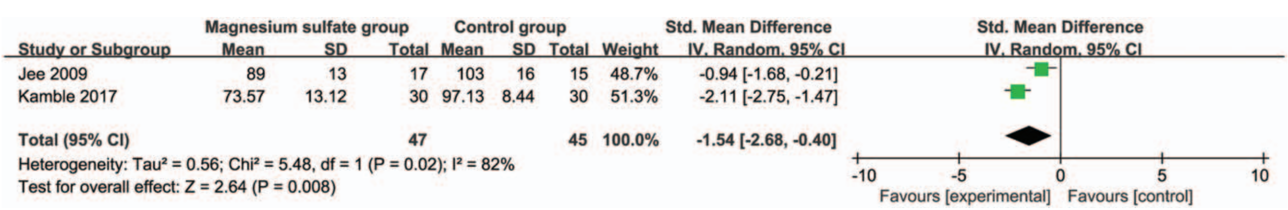

Figure 6. Forest plot for the meta-analysis of diastolic blood pressure at 10 min (mm Hg).

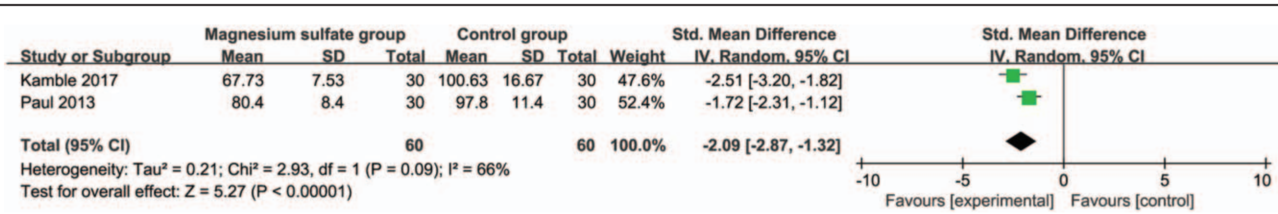

Figure 7. Forest plot for the meta-analysis of heart rate at 30 min.

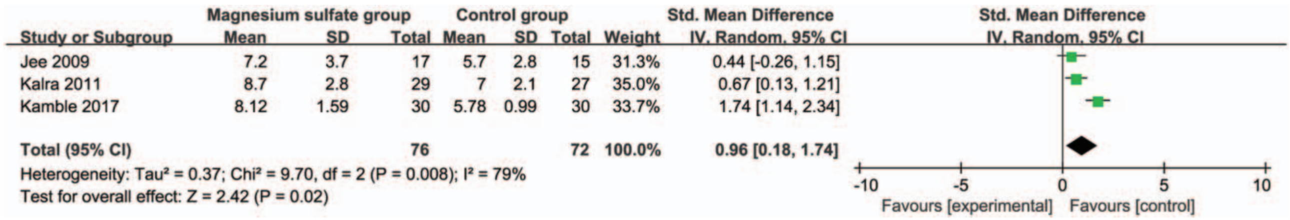

Figure 8. Forest plot for the meta-analysis of extubation time (min).

magnesium sulfate for laparoscopic cholecystectomy than those in control intervention.[19]

Magnesium sulfate at a dose of 50 mg/kg over 2 to 3 minutes before pneumoperitoneum is reported to effectively attenuate the hemodynamic responses, without severe hypotension or bradycardia through reducing the plasma catecholamines and vasopressin levels.[14] These effects of magnesium can act at serum concentrations of 2 to 4 mmol/L, and a dose of 50 mg/kg has been shown to achieve these levels.[14,27,28] Our meta-analysis suggests that intravenous magnesium sulfate at a dose of 50 mg/kg is associated with significantly reduced blood pressure at 10 and 30 minutes after pneumoperitoneum, as well as heart rate at 30 minutes during laparoscopic cholecystectomy.

Magnesium is effective to attenuate vasopressin-stimulated vasoconstriction and adverse hemodynamic response of endotracheal intubation.[29] In addition, magnesium sulfate in a dose of 30 mg/kg bolus before induction and 10 mg/kg/h continuous infusion has the ability to decrease anesthetic requirement.[30] Prolonged time to verbal response observed occurs because of central nervous system depressant action. Magnesium sulfate is able to produce general anesthesia and enhance the activity of local anesthetic drugs.[31]

Magnesium sulfate can potentiate the neuromuscular blockade of nondepolarizing relaxants and this is evident one with a prolonged time to extubation.[10,32] Consistently, the increase in extubation time is observed after the use of magnesium sulfate in our meta-analysis. Regarding the incidence of adverse effects, one included RCT involves 30 patients in each magnesium sulfate group and control group. The results reveal that only single patient suffers from hypotension in magnesium sulfate group, and 12 patients have hypertension just in control group. No bradycardia is found in 2 groups.[19]

This meta-analysis has several potential limitations that should be taken into account. Firstly, our analysis is based on only 4 RCTs and all of them have a relatively small sample size ($n < 100$). More RCTs with a large sample size should be conducted to confirm this issue. Next, it is not available to perform the meta-analysis of some important adverse events such as hypotension and hypertension based on current included RCTs. Finally, some unpublished and missing data may lead bias to the pooled effect.

5. Conclusion

Magnesium sulfate is effective to attenuate the hemodynamic responses during laparoscopic cholecystectomy, but results in the prolonged extubation time.

Author contributions

Data curation: Juyi Zhang.
Funding acquisition: Juan Yang.
Investigation: Juyi Zhang.
Methodology: Juyi Zhang, Yubin Wang.
Software: Hao Xu.
Supervision: Juan Yang.
Writing – original draft: Yubin Wang.
Writing – review & editing: Hao Xu.

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