Systematic Review and Meta-Analysis

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Effect of magnesium sulfate on renal colic pain

A PRISMA-compliant meta-analysis

Liang-Fu Chen, MD[a,b], Chih-Hao Yang, MD[a,b], Ting-Yi Lin, MD[c], Po-Jia Pao, MD[c], Karen Chia-Wen Chu, MD[a,b], Chin-Wang Hsu, MD[a,b], Chyi-Huey Bai, PhD[d], Ming-Hai Du, MD[a,b,*], Yuan-Pin Hsu, MD[a,b,e,*]

Abstract

Background: Magnesium sulfate ($MgSO_4$) is widely used in analgesia for different conditions. Recent randomized controlled trials (RCTs) have evaluated the effects of $MgSO_4$ on renal colic; however, this new evidence has not been synthesized. Thus, we conducted a systematic review and meta-analysis to assess the efficacy and safety of $MgSO_4$ in comparison with control for renal colic.

Methods: PubMed, EMBASE, and Scopus databases were searched from inception to February 2020. We included RCTs that evaluated $MgSO_4$ vs control for patients with renal colic. Data were independently extracted by 2 reviewers and synthesized using a random-effects model.

Results: Four studies with a total of 373 patients were analyzed. Intravenous $MgSO_4$ 15 to 50 mg/kg did not significantly reduce renal colic pain severity at 15 minutes (mean difference [MD] = 0.35, 95% confidence interval [CI] −0.51 to 1.21; 2 RCTs), 30 minutes (MD = 0.19, 95% CI −0.74 to 1.13; 4 RCTs), and 60 minutes (MD = −0.28, 95% CI −0.72 to 0.16; 3 RCTs) in comparison with controls. In patients who failed to respond to initial analgesics, intravenous $MgSO_4$ 15 mg/kg or 2 ml of 50% solution provided similar pain relief to ketorolac or morphine at 30 minutes ($P = .90$) and 60 minutes ($P = .57$). No significant hemodynamic changes were observed with short-term use of MgSO4 in these studies.

Conclusion: $MgSO_4$ provides no superior therapeutic benefits in comparison with control treatments. MgSO4 may be used as a rescue medication in patients not responding to initial analgesics. The short-term use of $MgSO_4$ did not affect hemodynamic values.

Abbreviations: CCB = calcium channel blocker, CI = confidence interval, MD = mean difference, MET = medical expulsive therapy, $MgSO_4$ = magnesium sulfate, NSAID = nonsteroidal anti-inflammatory drug, RCT = randomized controlled trial, VAS = visual analog scale.

Keywords: magnesium sulfate, renal colic, urolithiasis

Editor: Bernhard Schaller.

M-HD and Y-H contributed equally to this work.

This manuscript was edited by Wallace Academic Editing.

The authors are very grateful for the financial support by the project No. 109-wf-eva-25 of Wan Fang Hospital, Taipei Medical University, Taiwan.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Emergency Department, Wan Fang Hospital, Taipei Medical University, [b] Department of Emergency Medicine, School of Medicine, College of Medicine, Taipei Medical University, [c] General Medicine Department, Wan Fang Hospital, Taipei Medical University, [d] Department of Public Health, School of Medicine, College of Medicine, Taipei Medical University, [e] Research Center of Big Data and Meta-Analysis, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.

[*] Correspondence: Yuan-Pin Hsu, Emergency Department, Wan Fang Hospital, Taipei Medical University, No.111, Sec. 3, Xinglong Rd., Taipei 11696, Taiwan (e-mail: koakoahsu@gmail.com).

How to cite this article: Chen LF, Yang CH, Lin TY, Pao PJ, Chu KW, Hsu CW, Bai CH, Du MH, Hsu YP. Effect of magnesium sulfate on renal colic pain: a PRISMA-compliant meta-analysis. Medicine 2020;99:46(e23279).

Received: 6 May 2020 / Received in final form: 20 September 2020 / Accepted: 21 October 2020

http://dx.doi.org/10.1097/MD.0000000000023279

1. Introduction

Renal colic is a common manifestation of nephrolithiasis, accounting for 7.9% of emergency department visits in the United States; it is 1 of the top 10 major medical complaints, costing more than US$4000 per visit.[1] The prevalence of nephrolithiasis ranges from 0.1% to 18.5%.[2] Its incidence increased remarkably from 0.42% to 1.47% within 2 decades in Germany,[3] and an even greater increase was noted in the Middle East.[4] Renal colic arises from partial or complete obstruction caused by urolithiasis, which induces increased intraluminal pressure, stretching forces that stimulate nerve endings, and prostaglandin release.[5] Most patients have acute attacks of renal colic that reaches its peak pain intensity within 2 hours of onset.[6] Patients experiencing unbearable pain from renal colic require prompt pain management.

Primary treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. A systematic review and meta-analysis revealed superior pain-relieving effects of NSAIDs as the first-line treatment compared with those of opioids.[7,8] Although using NSAIDs or opioids or a combination of both soothes renal colic, 16% to 42% of patients were unsatisfied with the effect and required rescue analgesia.[9] Considering the adverse effects of the cumulative usage of NSAIDs and opioids, which include the risks of anaphylaxis, gastrointestinal insult, and renal impairment for NSAIDs and nausea, vomiting, and respiratory suppression for opioids, identifying alternative or add-on medications to reduce pain intensity and analgesia requirements is imperative.

Tocolytic agents are considered an alternative or adjunct medication for the management of acute renal colic. Magnesium sulfate ($MgSO_4$) induces analgesic effects through the antagonism of the N-methyl-D-aspartate receptor.[10] Once the N-methyl-D-aspartate receptor is blocked, the permeability of calcium channel on cell membrane decreases and alters the emission of neurotransmitter that generalizes pain stimuli.[11] Additionally, $MgSO_4$ reportedly relaxes the smooth muscle by reducing the depolarizing effect of acetylcholine on neuromuscular junctions.[12] $MgSO_4$ is also effective in treating acute headaches of various etiologies.[13] Moreover, Ng et al demonstrated that the use of intravenous magnesium as part of multimodal analgesia may reduce postoperative pain.[14] Interest in the use of $MgSO_4$ as an alternative or adjunct medication to reduce pain intensity in patients with renal colic has been increasing among researchers.

Numerous randomized controlled trials (RCTs) have been conducted to investigate the effect of $MgSO_4$ on patients with renal colic.[6,15–17] Verki indicated that $MgSO_4$ did not affect renal colic severity,[15] whereas Majidi considered $MgSO_4$ a safe adjunct pain-control medication.[17] Therefore, evidence for the efficacy of $MgSO_4$ in reducing acute renal colic remains inconclusive. We performed a systematic review and meta-analysis to assess the effects of $MgSO_4$ on pain intensity in patients with acute renal colic.

2. Methods

We conducted our systematic review and meta-analysis according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[18] Ethical approval or patient consent was not required because the present study was a review of published articles. We have registered our protocol on PROSPERO (PROSPERO ID: CRD42020173718).

2.1. Search strategy and study selection

We searched PubMed, EMBASE, Scopus, and the Cochrane Library from inception to April 2020 (Supplementary Table 1, http://links.lww.com/MD/F221). We used the following search keywords to identify eligible studies: *magnesium*, *magnesium sulfate renal colic*, *ureteral stone*, *ureteral calculi*, and *urolithiasis*. No language restrictions were applied. We scrutinized the references of identified studies for other potentially eligible articles and collected unpublished studies from the ClinicalTrials.gov registry (http://clinicaltrials.gov/). Subsequently, we combined results and removed duplicates by using EndNote X8 reference manager (Thompson ISI Research-Soft, Philadelphia, PA). Then, the titles, abstracts, and full-text articles were independently examined by 2 researchers (CHY and TYL) to identify potentially eligible studies. We included all published human RCTs that evaluated the effects of intravenous $MgSO_4$ on renal colic pain management. We excluded animal studies, retrospective cohort studies, case series, and case reports. Studies in which patients received shock wave lithotripsy were also excluded. In included studies, $MgSO_4$ could be administered in any dose and by any route for analgesia in acute renal colic. Our primary outcomes of interest were pain severity measured using the visual analog scale (VAS) after the administration of $MgSO_4$ or control. Secondary outcomes were hemodynamic parameter changes, such as blood pressure, heart rate, respiratory rate, and oxygen saturation.

2.2. Data extraction and management

Two reviewers (PJP and KCWC) independently extracted the following data: the general characteristics of the study (author, year of publication, study location, and sample size), study design, study population characteristics, inclusion and exclusion criteria, procedures, intervention route, and outcomes of interest parameters. Disagreements regarding recorded data were resolved through discussion between the aforementioned reviewers or by referral to a third reviewer (YPH).

2.3. Assessment of the risk of bias in included studies

Two authors (CHY and TYL) independently appraised the methodological quality of each study by using the revised Cochrane risk of bias tool for parallel-group RCTs. The tool includes the following 6 domains: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurements of outcomes, bias in the selection of reported results, and other biases. Discrepancies were resolved by consensus and arbitration (YPH).

2.4. Statistical analysis

We analyzed continuous outcomes by using mean differences (MDs) and 95% confidence intervals (CIs). We used the DerSimonian and Laird random-effects model to synthesize results. The I^2 statistic was used to evaluate heterogeneity among studies with predetermined thresholds for low (25%–49%), moderate (50%–74%), and high (>75%) levels.[19] We performed a subgroup analysis if patients failed to respond to initial analgesics and if $MgSO_4$ was added to the first-line analgesic. We assessed publication bias by detecting asymmetry in funnel plots. Data analysis was performed using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). A 2-sided P value of $<.05$ was considered statistically significant.

3. Results

3.1. Search results

The flowchart of the article selection process is illustrated in Figure 1. In addition to consulting PubMed, EMBASE, Scopus, the Cochrane Library, and clinicaltrials.gov, we also hand-searched for relevant articles; this process yielded 243 records. We removed 44 duplicate articles and excluded 192 studies after reading titles and abstracts. Two full-text studies were excluded for being ongoing and another was excluded because no target population was specified. Finally, 4 RCTs were included for qualitative and quantitative synthesis.

3.2. Study characteristics

The characteristics of the included studies are summarized in Table 1. Of the studies, 3 were conducted in Iran and 1 in Egypt. All studies were conducted within the past decade, ranging from 2017 to 2020. All studies were performed in emergency departments. The mean age of participants ranged from 32.0 to 39.4 years. All studies recruited more male than female patients, with the proportion of female participants ranging from 11.1% to 42%. Three studies excluded patients who had received

Table 1

Characteristics of the included studies.

Author, publication year	Country/ setting	Inclusion criteria	Exclusion criteria	Diagnosis of renal colic	Sample size, N	Age, mean (SD)	Sex, F (%)	Intervention/ control	Comedication	Outcome measure
Jokar et al,[15] 2017	Iran/ED	Renal colic; age 18-55	CCB use	Clinical judgement by symptoms	$MgSO_4$: 50	$MgSO_4$: 33.6 (8.6)	$MgSO_4$: 40.0%	$MgSO_4$ 15mg/kg/ saline	0.1 mg/kg morphine sulfate + 30 mg ketorolac	VAS at baseline, 30 min, 60 min
					Control: 50	Control: 35.2 (9.0)	Control: 42.0%			
Maleki Verki et al,[14] 2018	Iran/ED	Renal colic; age 18-65	α-blocker use	Clinical judgement and x-ray, ultrasound or computed tomography	$MgSO_4$: 44	$MgSO_4$: 39.4 (12.1)	$MgSO_4$: 11.4%	$MgSO_4$ 50mg/kg IV/ saline	Ketorolac 30 mg IV	VAS at baseline, 15 min, 30 min
					Control: 43	Control: 37.2 (10)	Control: 20.9%			
Sayel et al,[6] 2019	Egypt/ ED	Renal colic; age 18–60; no response to initial 30 mg IV ketorolac	CCB use	Clinical judgement by symptoms	$MgSO_4$: 48	$MgSO_4$: 32.0 (8.3)	$MgSO_4$: 43.8%	$MgSO_4$ 15mg/kg/30 mg ketorolac IV + saline	N/A	VAS at baseline, 30 min, 60 min
					Control: 48	Control: 32.0 (8.1)	Control: 39.6%			
Majidi et al,[16] 2020	Iran/ED	Renal colic; age 18–60; no response to initial morphine 0.1 mg/kg	CCB use	Clinical judgement by symptoms	$MgSO_4$: 45	$MgSO_4$: 35.6 (10.8)	$MgSO_4$: 40.0%	$MgSO_4$ 50% solution 2mL/ morphine 0.1 mg/kg	N/A	VAS at baseline, 20, 30, 60, 120, 180 min
					Control: 45	Control: 39.1 (13.2)	Control: 28.9%			

C = control group, CCB = calcium channel blocker, ED = emergency department, F = female, I = intervention group, IV = intravenous, $MgSO_4$ = magnesium sulfate, N/A = not applicable, SD = standard deviation, VAS = visual analogue scale.

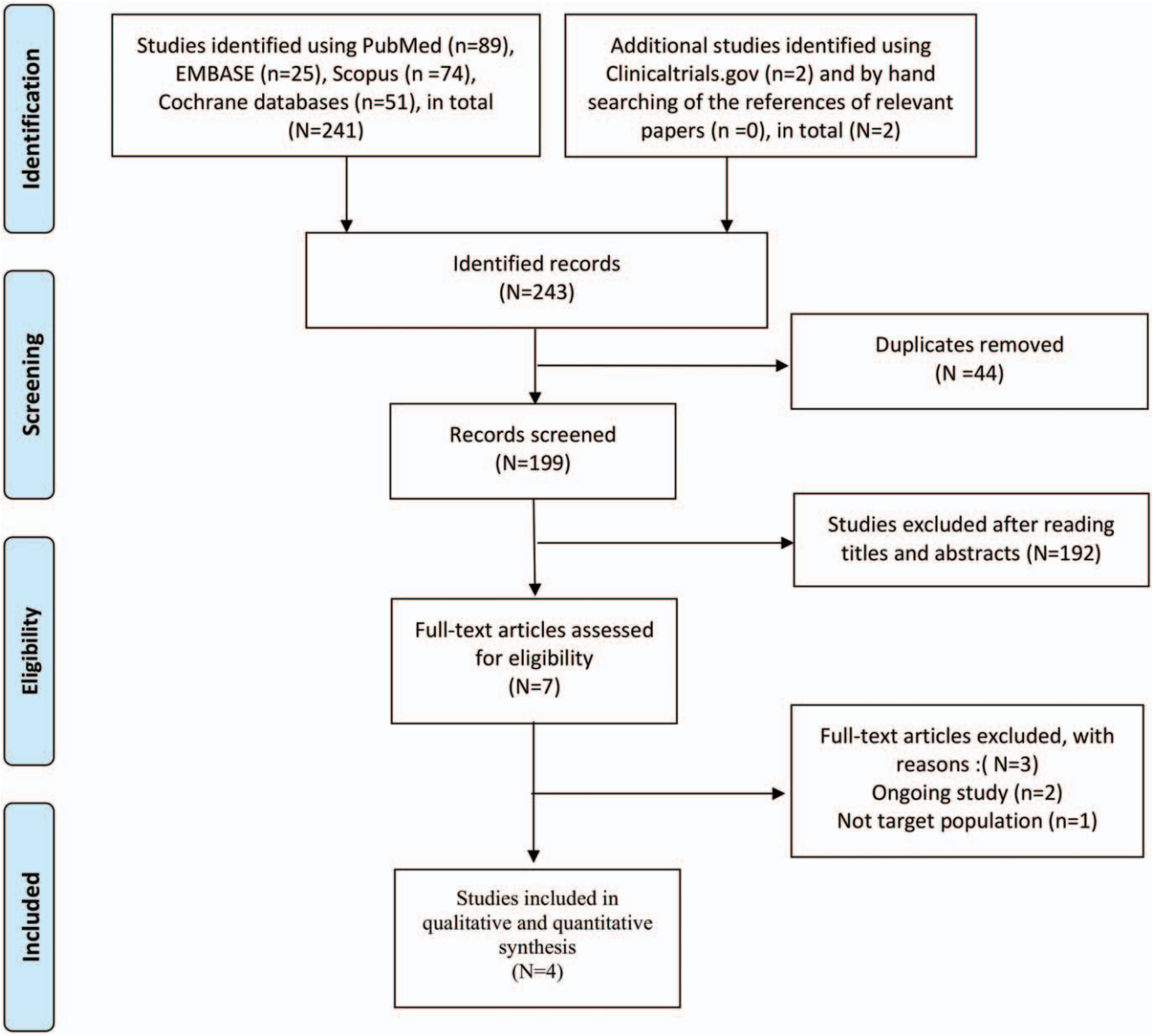

Figure 1. Flowchart of the article selection process.

calcium channel blockers (CCBs) and one excluded those who had received α-blockers. All the studies made the diagnosis of acute renal colic based on clinical symptoms and only one study confirmed the presence of stone by imaging tools including x-ray, sonography, and computed tomography. Two of the studies compared $MgSO_4$ with normal saline, ketorolac, or ketorolac plus morphine as comedication. The other 2 studies compared $MgSO_4$ with ketorolac or morphine. All studies used the VAS to assess pain severity at various time points after the administration of the intervention or control. The results of the risk of bias assessment are displayed in Figure 2. One study had a high risk of bias because of the randomization process, bias in the measurement of outcome, and unclear risk of bias in selection of the reported result. Another study had a high risk of bias in the measurement of outcome and unclear risk of bias because of the randomization process and in the selection of reported results. The remaining 2 studies were rated as having a low risk of bias.

3.3. Primary outcome: pain severity

All RCTs evaluated the pain severity of renal colic by comparing intravenous $MgSO_4$ with the control. The results of the meta-analysis are presented in Figure 3. Compared with control, using $MgSO_4$ to treat renal colic did not significantly reduce pain severity at 15 minutes (n = 177, MD = 0.35, 95% CI −0.51 to 1.21; Fig. 3A, 2 RCTs), 30 minutes (n = 373, MD = 0.19, 95% CI −0.74 to 1.13; Fig. 3B, 4 RCTs) and 60 minutes (n = 286, MD = −0.28, 95% CI −0.72 to 0.16; Fig. 3C, 3 RCTs). The limited data from the included studies regarding patients who did not respond to the initial analgesic dose or who received intravenous $MgSO_4$ as an add-on treatment were pooled. For patients who did not respond to the initial analgesic dose, those receiving intravenous $MgSO_4$ did not report significantly decreased pain severity at 30 minutes (n = 186, MD = −0.05, 95% CI −0.74 to 0.65; Fig. 4A, 2 RCTs) and 60 minutes (n = 186, MD = −0.16, 95% CI −0.70 to 0.39; Fig. 4B, 2 RCTs) than did those treated with secondary analgesics. Using

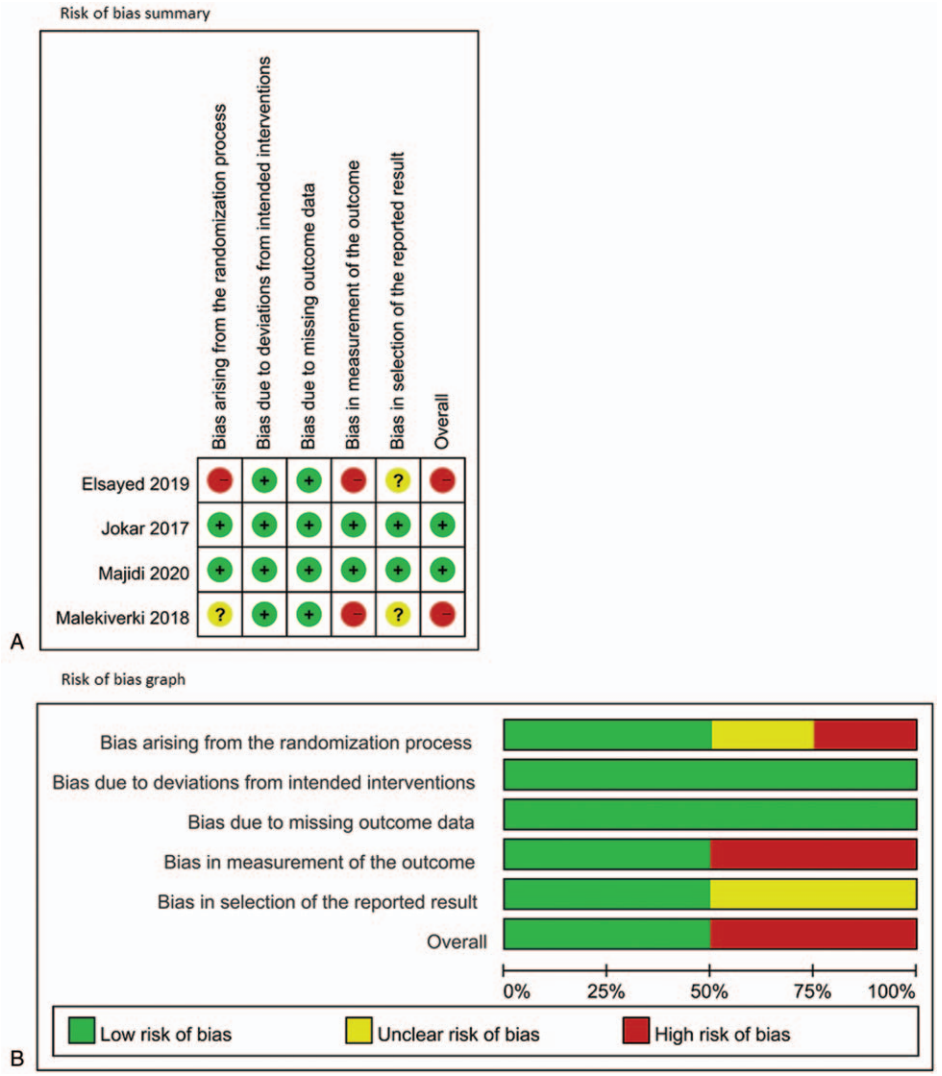

Figure 2. Risk of bias assessment of the included studies.

intravenous $MgSO_4$ as an add-on treatment was not superior to using analgesics alone in reducing pain severity at 30 minutes (n = 187, MD = 0.50, 95% CI −2.31 to 3.31; Fig. 4C, 2 RCTs). Publication bias was disregarded because no asymmetry was detected in funnel plots. (Supplementary Fig. 1, http://links.lww.com/MD/F220)

3.4. Secondary outcome: hemodynamics and vital signs monitoring

The meta-analysis results of secondary outcomes are summarized in Table 2. Of the 4 studies, 3 considered the change in hemodynamics and other vital signs at 30 and 60 minutes following treatment. No significant changes were observed in blood pressure, respiratory rate, heart rate, oxygen saturation, or body temperature between the $MgSO_4$ and control groups.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to compare the effects of $MgSO_4$ with those of control for renal colic. In this meta-analysis of 4 clinical trials, using $MgSO_4$ failed to reveal superior effects in comparison with control at 15, 30, and 60 minutes. The results of the subgroup analysis indicated that in patients who were unsatisfied with the initial ketorolac and opioid, $MgSO_4$ provided similar pain relief as other analgesics at 30 and 60 minutes. Using $MgSO_4$ as an add-on treatment when patients received analgesics did not provide additional pain reduction at 30 minutes. The short-term use of $MgSO_4$ did not affect hemodynamic or respiratory status.

Renal colic often manifests in waves lasting 20 to 60 minutes, requiring immediate pain relief. The European Association of Urology guidelines suggests NSAIDs as the first-line treatment for renal colic, with opioids being the second choice.[8] Combining drugs as a the first-line treatment was not mentioned. We found that patients who had received NSAIDs or morphine for renal colic may not benefit from additional $MgSO_4$ administration. Moreover, the aforementioned guidelines did not address the management of patients who do not respond to NSAIDs, opioids, or both. The literature describing the management of renal colic refractory to standard therapy is also limited. Our subgroup

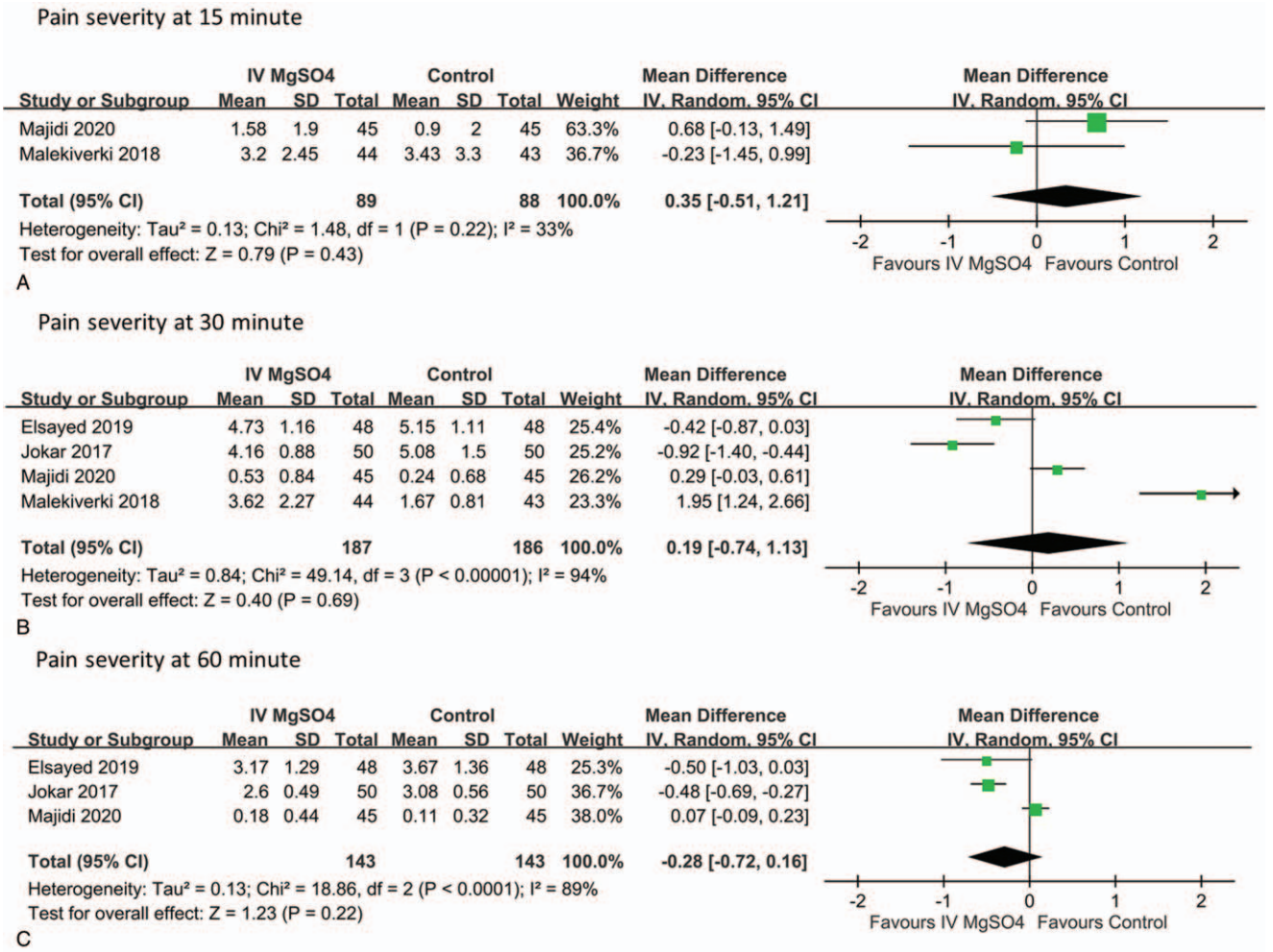

Figure 3. Meta-analysis evaluating the pain severity of renal colic after $MgSO_4$ administration (A) at 15 minutes, (B) at 30 minutes, and (C) at 60 minutes.

analysis suggested that MgSO4 may be an option for rescue treatment.

$MgSO_4$ was first used as an antieclampsia drug in the early 20th century, and interest in its anesthetic abilities developed in the 1990s.[20] A meta-analysis of 21 RCTs reported that intravenous $MgSO_4$ reduced migraine severity within 15 to 45 minutes, 120 minutes, and 24 hours after initial infusion, and oral $MgSO_4$ alleviated the frequency and intensity of migraine as well.[21] Moreover, another meta-analysis, which included 20 RCTs, indicated that systemic administration of $MgSO_4$ could reduce early (0–4 hours) and late (24 hours) postoperative pain and morphine consumption.[22] These results support our findings that $MgSO_4$ exerts analgesic effects on patients with renal colic; these effects could be attributed to the relaxation effects of $MgSO_4$ on the smooth muscle.

Nonetheless, a previous guideline recommended NSAIDs and paracetamol as the standards of care for initial treatment on renal colic pain management.[8] A wide variety of NSAIDs had been tried in the attempt of relieving renal colic pain.[23] A systematic review and network meta-analysis had demonstrated that diclofenac and ketorolac provided comparable pain-relief effect.[24] Paracetamol in intravenous form had similar effect of pain-relief when compared with diclofenac, according to a large RCT.[25] However, in our study, none of the 4 RCTs compared $MgSO_4$ with NSAIDs (except ketorolac) and acetaminophen. Therefore, more robust evidence is warranted before any generalization in favor or against the use of $MgSO_4$.

Medical expulsive therapy (MET) is widely used as an effective treatment option to facilitate the expulsion of distal ureteral stones because the rate of spontaneous passage is low when stone size exceeds 5 mm.[26] The latest guidelines recommend treating these patients with MET for ureteral stones of >5 mm instead of immediate surgical intervention.[8] α-Blockers and CCBs are commonly used in MET.[27] An increasing number of patients have ureteral stones of >5 mm in width, and they may benefit from CCBs or α-blockers. However, when undergoing MET, patients may experience episodic colic before the stone is completely expelled.[26] These patients may experience severe and recurrent renal colic and consequently return to the emergency department. In our review, 1 study excluded patients receiving α-blockers and 3 studies excluded patients receiving CCBs. Therefore, the beneficial effect of intravenous $MgSO_4$ cannot be generalized to those with ureteral stones treated with MET using α-blockers or CCBs.

Concerns regarding the safety of $MgSO_4$ administration mainly refer to hemodynamic instability and respiratory distress risk.[28]

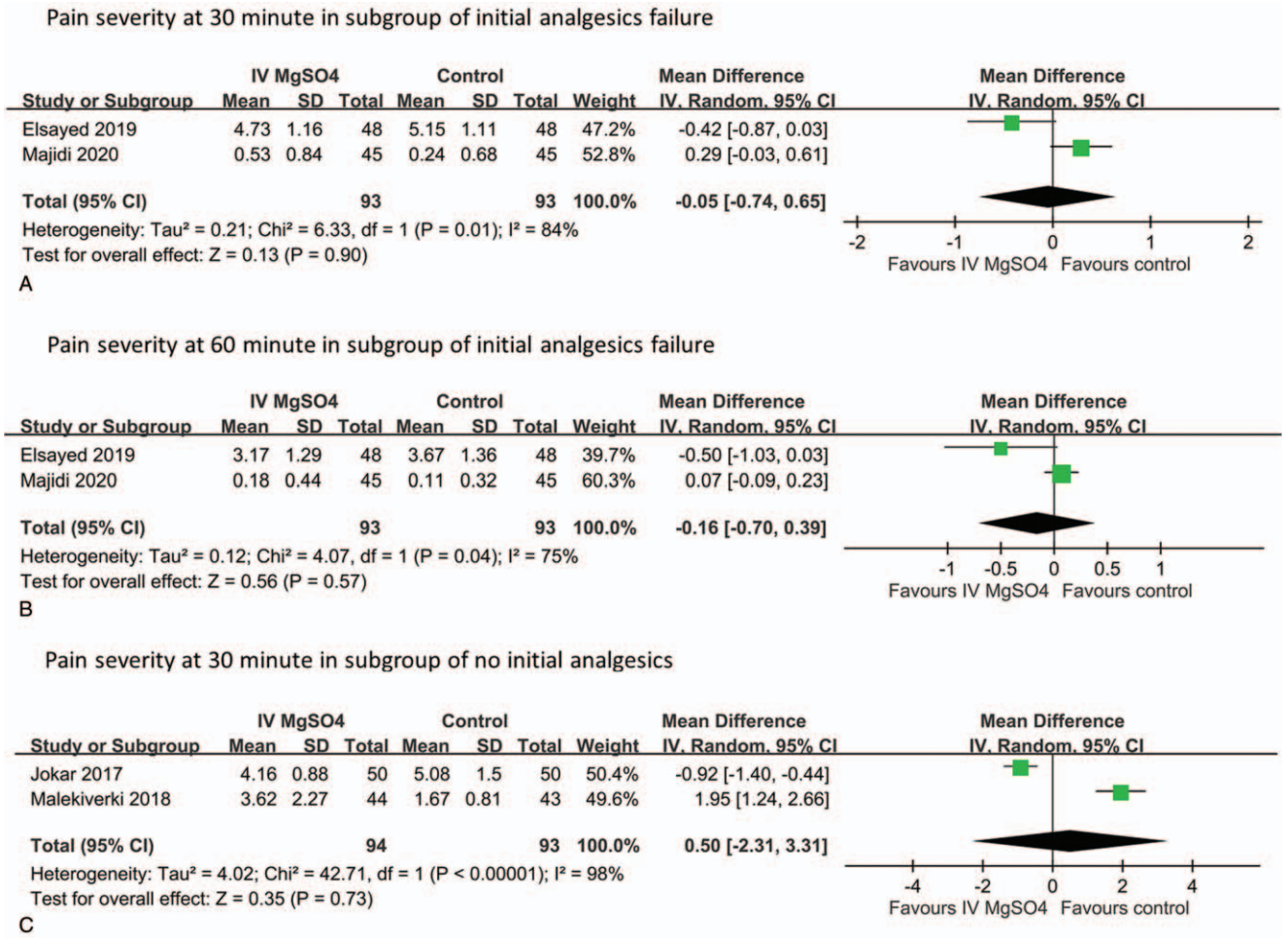

Figure 4. Meta-analysis evaluating the pain severity of renal colic after $MgSO_4$ administration in the subgroup with initial analgesic failure (A) at 30 minutes and (B) 60 minutes and in the subgroup with no initial analgesic (C) at 30 minutes.

For patients who underwent surgery and received $MgSO_4$ for postoperative analgesia, no significant hypotension was noted in comparison with the morphine group.[22] Compared with controls, the incidence of bradycardia was also not significantly different in patients who received $MgSO_4$ for postoperative analgesia after noncardiac surgery.[14] No other fatal side effects have been identified in these meta-analyses in comparison with controls. We assessed similar adverse outcomes in our meta-analysis. We found that short-term $MgSO_4$ use in limited doses did not affect patients' hemodynamics and breathing status.

Table 2

Meta-analysis of the secondary outcome.

Outcome of interest	No. of trials	No. of patients	PMD [95% CI]	*P* value	I^2 (%)
Systolic blood pressure at baseline	2	196	0.04 [−0.24, 0.32]	.78	0
Systolic blood pressure at 30 min	2	196	−0.39 [−2.43, 1.64]	.71	0
Systolic blood pressure at 60 min	2	196	−0.13 [−2.00, 1.75]	.89	0
Pulse rate at baseline	2	196	0.20 [−0.24, 0.64]	.38	0
Pulse rate at 30 min	2	196	−1.61 [−4.94, 1.71]	.34	0
Pulse rate at 60 min	2	196	−1.95 [−5.92, 2.03]	.34	0
Respiratory rate at baseline	2	196	0.21 [−0.14, 0.55]	.25	0
Respiratory rate at 30 min	2	196	−0.38 [−1.16, 0.41]	.35	0
Respiratory rate at 60 min	2	196	−0.18 [−0.60, 0.25]	.42	0
O_2 saturation at baseline	2	196	0.01 [−0.26, 0.27]	.96	0
O_2 saturation at 30 min	2	196	−0.00 [−0.27, 0.26]	.98	0
O_2 saturation at 60 min	2	196	−0.04 [−0.31, 0.22]	.74	0

CI = confidence interval, PMD = pooled mean difference.

Our meta-analysis has some limitations. The results were based on a limited number of included RCTs with relatively small sample sizes. Most of the cases involved in the RCTs were diagnosed to have renal colic by mere clinical symptoms without imaging proof, which may bring to potential risk of biases. All 4 studies measure outcome in subjective VAS grading, which may vary in different populations and thus measurement bias cannot be completely avoided. We also found substantial heterogeneities in the primary outcome. These heterogeneities may be related to diverse $MgSO_4$ dosages and the cointervention used to treat renal colic. Although no publication bias was detected, the finding was not strong because of few RCTs included in the review. Furthermore, all 4 RCTs were conducted in the Middle East and North Africa, which may limit the generalization of findings to the general population. Additional studies including larger samples in diverse regions are recommended to further clarify the effects observed in the current review.

5. Conclusion

Our meta-analysis revealed that $MgSO_4$ did not provide superior therapeutic benefits in comparison with control treatments. MgSO4 may be used as a rescue medication in patients not responding to initial analgesics. Short-term use of $MgSO_4$ did not affect hemodynamic parameters. However, because of the low quality, the small number and the heterogeneity of studies were identified, these findings are inconclusive and cannot be generalized to the general population. Additional well-designed, large RCTs are warranted to clarify the effect.

Author contributions

Conceptualization: Karen Chia-Wen Chu, Yuan-Pin Hsu.
Data curation: Liang-Fu Chen, Chih-Hao Yang, Ting-Yi Lin, Po-Jia Pao, Karen Chia-Wen Chu, Yuan-Pin Hsu.
Formal analysis: Liang-Fu Chen, Chih-Hao Yang, Ting-Yi Lin, Chyi-Huey Bai, Yuan-Pin Hsu.
Funding acquisition: Liang-Fu Chen, Yuan Pin Hsu.
Investigation: Liang-Fu Chen, Chih-Hao Yang, Ting-Yi Lin, Yuan-Pin Hsu.
Methodology: Chih-Hao Yang, Ting-Yi Lin, Po-Jia Pao, Karen Chia-Wen Chu, Yuan-Pin Hsu.
Resources: Chin-Wang Hsu.
Software: Yuan-Pin Hsu.
Supervision: Chin-Wang Hsu, Chyi-Huey Bai, Ming-Hai Du, Yuan-Pin Hsu.
Validation: Liang-Fu Chen.
Visualization: Liang-Fu Chen.
Writing – original draft: Liang-Fu Chen, Chih-Hao Yang.
Writing – review & editing: Liang-Fu Chen, Yuan-Pin Hsu.

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