Effect of magnesium sulfate on renal colic pain
A PRISMA-compliant meta-analysis

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Abstract

Background: Magnesium sulfate (MgSO4) is widely used in analgesia for different conditions. Recent randomized controlled trials (RCTs) have evaluated the effects of MgSO4 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 MgSO4 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 MgSO4 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 MgSO4 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 MgSO4 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: MgSO4 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 MgSO4 did not affect hemodynamic values.

Abbreviations: CCB = calcium channel blocker, CI = confidence interval, MD = mean difference, MET = medical expulsive therapy, MgSO4 = magnesium sulfate, NSAID = nonsteroidal anti-inflammatory drug, RCT = randomized controlled trial, VAS = visual analog scale.

Keywords: magnesium sulfate, renal colic, urolithiasis

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.
2.2. Data extraction and management

Two reviewers (CHY and KYL) 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 KYL) 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 I² statistic was used to evaluate heterogeneity among studies with predetermined thresholds for low (25%–49%), moderate (50%–74%), and high (>75%) levels. We performed a subgroup analysis if patients failed to respond to initial analgesics and if MgSO₄ 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...
| 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 | MgSO4: 50      | MgSO4: 33.6 (8.6) | MgSO4: 40.0% | MgSO4 15mg/kg/ saline | 0.1 mg/kg morphine sulfate + 30 mg ketorolac | VAS at baseline, 30 min, 60 min |
| 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 | MgSO4: 44      | MgSO4: 39.4 (12.1) | MgSO4: 11.4% | MgSO4 50mg/kg N/ saline | Ketorolac 30 mg N | VAS at baseline, 15 min, 30 min |
| Sayel et al.[8] 2019     | Egypt/ ED        | Renal colic; age 18–60; no response to initial 30 mg IV ketorolac | CCB use            | Clinical judgement by symptoms | MgSO4: 48      | MgSO4: 32.0 (8.3) | MgSO4: 40.8% | MgSO4 15mg/kg/30 mg ketorolac + saline | N/A          | VAS at baseline, 30 min, 60 min |
| 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 | MgSO4: 45      | MgSO4: 35.6 (10.8) | MgSO4: 40.0% | MgSO4 50% solution 2mL/ morphine 0.1 mg/kg | N/A          | VAS at baseline, 20, 30, 60, 120, 180 min |

C = control group, CCB = calcium channel blocker, ED = emergency department, F = female, I = intervention group, IV = intravenous, MgSO4 = magnesium sulfate, N/A = not applicable, SD = standard deviation, VAS = visual analogue scale.
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 MgSO₄ with normal saline, ketorolac, or ketorolac plus morphine as comedication. The other 2 studies compared MgSO₄ 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 because of the randomization process, bias in the measurement of outcome, and unclear risk of bias in selection of the reported result. 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 MgSO₄ with the control. The results of the meta-analysis are presented in Figure 3. Compared with control, using MgSO₄ 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 MgSO₄ as an add-on treatment were pooled. For patients who did not respond to the initial analgesic dose, those receiving intravenous MgSO₄ 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
intravenous MgSO4 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 MgSO4 and control groups.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to compare the effects of MgSO4 with those of control for renal colic. In this meta-analysis of 4 clinical trials, using MgSO4 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, MgSO4 provided similar pain relief as other analgesics at 30 and 60 minutes. Using MgSO4 as an add-on treatment when patients received analgesics did not provide additional pain reduction at 30 minutes. The short-term use of MgSO4 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 suggest NSAIDs as the first-line treatment for renal colic, with opioids being the second choice. Combining drugs as a first-line treatment was not mentioned. We found that patients who had received NSAIDs or morphine for renal colic may not benefit from additional MgSO4 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
analysis suggested that MgSO₄ may be an option for rescue treatment.

MgSO₄ was first used as an antieclampsia drug in the early 20th century, and interest in its anesthetic abilities developed in the 1990s. A meta-analysis of 21 RCTs reported that intravenous MgSO₄ reduced migraine severity within 15 to 45 minutes, 120 minutes, and 24 hours after initial infusion, and oral MgSO₄ alleviated the frequency and intensity of migraine as well. Moreover, another meta-analysis, which included 20 RCTs, indicated that systemic administration of MgSO₄ could reduce early (0–4 hours) and late (24 hours) postoperative pain and morphine consumption. These results support our findings that MgSO₄ exerts analgesic effects on patients with renal colic; these effects could be attributed to the relaxation effects of MgSO₄ 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. A wide variety of NSAIDs had been tried in the attempt of relieving renal colic pain. A systematic review and network meta-analysis had demonstrated that diclofenac and ketorolac provided comparable pain-relief effect. Paracetamol in intravenous form had similar effect of pain-relief when compared with diclofenac, according to a large RCT. However, in our study, none of the 4 RCTs compared MgSO₄ with NSAIDs (except ketorolac) and acetaminophen. Therefore, more robust evidence is warranted before any generalization in favor or against the use of MgSO₄.

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. The latest guidelines recommend treating these patients with MET for ureteral stones of >5 mm instead of immediate surgical intervention. α-Blockers and CCBs are commonly used in MET. 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. 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 MgSO₄ cannot be generalized to those with ureteral stones treated with MET using α-blockers or CCBs.

Concerns regarding the safety of MgSO₄ administration mainly refer to hemodynamic instability and respiratory distress risk.
For patients who underwent surgery and received MgSO4 for postoperative analgesia, no significant hypotension was noted in comparison with the morphine group. Compared with controls, the incidence of bradycardia was also not significantly different in patients who received MgSO4 for postoperative analgesia after noncardiac surgery. 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 MgSO4 use in limited doses did not affect patients’ hemodynamics and breathing status.

### Table 2

| Outcome of Interest                  | No. of trials | No. of patients | PMD [95% CI]     | P value | I² (%) |
|-------------------------------------|---------------|----------------|------------------|---------|--------|
| 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      |
| O₂ saturation at baseline           | 2             | 196            | 0.01 [-0.26, 0.27] | .96     | 0      |
| O₂ saturation at 30 min             | 2             | 196            | -0.00 [-0.27, 0.26] | .98     | 0      |
| O₂ 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 subjectiveVAS 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 MgSO₄ dosages and the co-intervention 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 MgSO₄ 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 MgSO₄ 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

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