Intravenous and Nebulized Magnesium Sulfate for Treating Acute Asthma in Children
A Systematic Review and Meta-Analysis

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Objective: This study aimed to evaluate the efficacy of intravenous (IV) and nebulized magnesium sulfate in acute asthma in children.
Methods: The PubMed, Cochrane Library, and EMBASE databases were searched. Randomized controlled trials and quasi-randomized controlled trials of IV and nebulized magnesium sulfate in pediatric acute asthma were included. The outcomes subject to meta-analysis were pulmonary function, hospitalization, and further treatment. If statistical heterogeneity was significant, random-effects models were used for meta-analysis, otherwise, fixed-effects models were applied.
Results: Ten randomized and quasi-randomized trials (6 IV, 4 nebulized) were identified. Intravenous magnesium sulfate treatment is associated with significant effects on respiratory function (standardized mean difference, 1.94; 95% confidence interval [CI], 0.80-3.08; $P = 0.0008$) and hospital admission (risk ratio, 0.55; 95% CI, 0.31-0.95; $P = 0.03$). But nebulized magnesium sulfate treatment shows no significant effect on respiratory function (standardized mean difference, 0.19; 95% CI, −0.01–0.40; $P = 0.07$) or hospital admission (risk ratio, 1.11; 95% CI, 0.86–1.44; $P = 0.42$).
Conclusions: The meta-analysis revealed that IV magnesium sulfate is an effective treatment in children, with the pulmonary function significantly improved and hospitalization and further treatment decreased. But nebulized magnesium sulfate treatment showed no significant effect on respiratory function or hospital admission and further treatment.

Key Words: magnesium sulfate, asthma, systematic review

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Asthma is one of the most common chronic inflammatory diseases in children that affects the airways and is characterized by an obstruction of airflow. The prevalence of pediatric asthma varies from 10% to 30% worldwide.[1] Sometimes, standard treatment and general management for the children with moderate to severe acute asthmatic attacks may have inadequate improvement, leading to severe morbidity, even mortality. Poorly controlled asthma in children leads to significant morbidity and socioeconomic consequences.[2] So, there is an increasing need to find new effective bronchodilating agents for improving moderate to severe acute asthmatic attacks. Magnesium sulfate (MgSO4) seems to be the agent as an alternative treatment option in patients resistant to standard therapy.[3,4] The mechanisms of action of magnesium sulfate in acute asthma are complex. Investigators found that magnesium sulfate is involved with cellular homeostasis, acetylcholine, and histamine release. It is also a calcium antagonist that inhibits bronchial smooth muscle contraction and promotes bronchodilation.[5] Several studies have reported that intravenous (IV) magnesium sulfate in adults with moderate to severe acute asthma had significantly improved short-term pulmonary function, but only few studies of nebulized magnesium sulfate in acute asthma have been conducted, and the conclusions are inconsistent.[6–10] The potential clinical benefits of IV and nebulized magnesium sulfate in children with asthma have been studied and research publications have produced conflicting results. So, we performed a meta-analysis to evaluate the efficacy of IV and nebulized magnesium sulfate in acute asthma in children to determine their roles in hospitalization and pulmonary function.

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All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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METHODS

Database and Search Strategy

Electronic searches were conducted in the MEDLINE, Cochrane Library, and EMBASE databases without language restriction. All databases were searched from inception to June 2015. Search terms used were *magnesium sulfate*, *asthma*, *bronchial asthma*, and *asthma, bronchial*. The limit applied to the search was *child: birth-18 years* and *randomized controlled trial*. Reference lists of review articles, reference lists of articles chosen for inclusion, and relevant trials were also searched to identify other potentially eligible trials.

Study Selection Criteria and Quality Assessment

Included trials were selected based on the following criteria: randomized controlled and quasi-randomized controlled study design, examined therapy with IV or nebulized magnesium sulfate for the patients with acute asthmatic attacks, and patient aged 18 years or younger. Exclusion criteria were as follows: (1) reviews and case reports, (2) trials for adult patient (>18 years), and (3) trials for comparing magnesium sulfate with β2-agonists. The Cochrane Collaboration tool was used to assess the methodological quality of the included trials. All articles were screened independently by 2 reviewers and assigned a value of "high", "low", or "unclear" to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any disagreement in data extraction or in quality assessment was resolved by discussion.

Data Extraction

We used a standardized data collection form to extract data and extracted the following information from each trial: title, first author, year of publication, number of patients, age, asthma severity, study design, clinical setting, and outcome data.

Outcomes and Statistical Analysis

We calculated the risk ratio (RR) with 95% confidence interval (CI) to express the dichotomous outcomes (hospitalization and further treatment) and the standardized mean difference (SMD) with 95% CI to express the continuous outcomes (pulmonary functions). Heterogeneity across trials was evaluated, and a *P* value

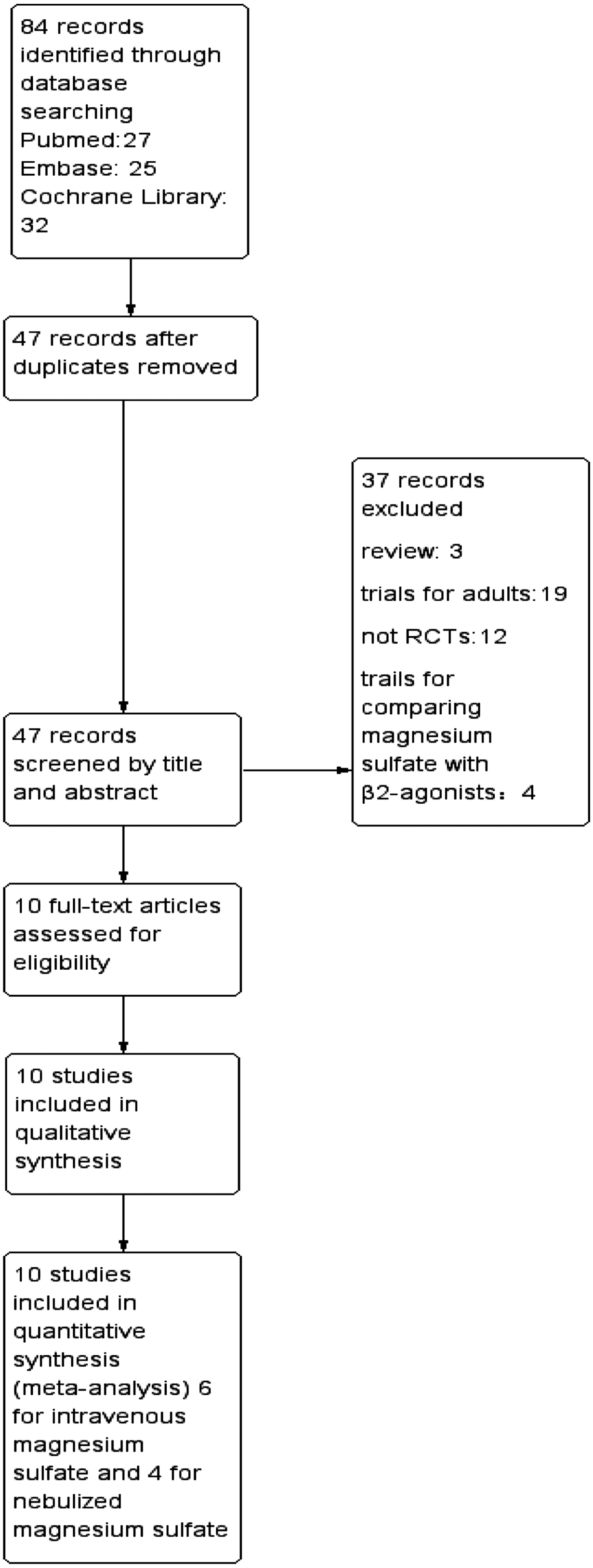

FIGURE 1. Flow chart showing the selection of trials in the review. RCTs, randomized controlled trials.

of 0.10 or less was considered to be statistically significant. Statistical heterogeneity across the trials was tested by using the I^2 statistic, and I^2 values of 25%, 50%, and 75% were considered low, medium, and high levels of heterogeneity, respectively. If statistical heterogeneity was significant, random-effects models were used for meta-analysis; otherwise, fixed-effects models were applied. All statistical analyses were performed using Review Manager 5.1.0, Cochrane, UK. Publication bias was not performed because of the small number of studies.

RESULTS

Search and Selection Results

Eighty-four potential records were identified. According to the inclusion and exclusion criteria, 10 relevant records (6 IV, 4 nebulized) were included for the meta-analysis (Fig. 1).[11–20]

Study Characteristics

The characteristics of the included trials are presented in Tables 1 and 2. These trials were published between 1996 and 2014. The sample size of the studies ranged from 20 to 508. The quality assessment of the trials is as follows: 5 trials[10,15,17,19,20] were judged to be at low risk of bias; 5 trials[11–14,16] were judged to be at unclear risk of bias. One is an open-label, randomized and controlled trial.[10] But those who treated patients were different from those who collected the data and also different from those who processed and analyzed the data. So, the trial was judged to be at low risk of bias. The interventions and cointerventions used in each trial were shown in Tables 3 and 4.

Intravenous Magnesium Sulfate in Acute Asthma

For IV magnesium sulfate, 6 studies were included with a total of 325 pediatric patients comprising 165 in the IV magnesium sulfate group and 160 in the control group.[11–14,17,18] Four studies were included for the analyses of the effects of IV magnesium sulfate on respiratory function.[11–14] Three studies were included for the analyses of the effects on hospital admission[11,12,17] and 1 for requirement of mechanical ventilation support.[18] All the patients were treated with β2-agonists and systemic steroids. According to the result of heterogeneity tests, SMDs for pulmonary functions and RRs for hospital admission were pooled using random-effect model. According to the statistical analyses, IV magnesium sulfate treatment is associated with significant effects on respiratory function (SMD, 1.94; 95% CI, 0.80–3.08; $P = 0.0008$) (Fig. 2) and hospital admission (RR, 0.55; 95% CI, 0.31–0.95; $P = 0.03$) (Fig. 3).

Nebulized Magnesium Sulfate in Acute Asthma

For nebulized magnesium sulfate, 4 studies were included with a total of 870 pediatric patients comprising 433 in the nebulized magnesium sulfate group and 437 in the control group.[15,16,19,20] In a trial,[20] lung function of children with acetylcholine-induced asthma was compared between 3 groups: magnesium sulfate [M], albuterol and saline [A + S], and a combination of magnesium sulfate and albuterol [M + A]. According to our inclusion criteria, we extracted the data of the [A + S] group and [M + A] group for our meta-analysis. Three studies were included for the analyses of the effects of nebulized magnesium sulfate on respiratory function.[15,16,20] Two studies were included for the analyses of the effects on hospitalization and further treatment.[15,19] Patients were treated with systemic steroids in 3 studies.[15,16,19] According to the result of heterogeneity tests, SMDs for pulmonary functions and RRs for hospital admission were pooled using fixed-effect model. According to the statistical analyses, nebulized magnesium

TABLE 1. Characteristics of the Included Trials of IV Magnesium Sulfate

Study	Year	Location	Sample Size	Age Range, y	Asthma Severity	Outcomes
Ciarallo	1996	USA	31	6–18	Moderate-severe	PEFR (percent change from baseline)*, FEV1, FVC, and admissions
Devi	1997	India	47	1–12	Severe	PEFR (percent predicted) and pulmonary index score
Gurkan	1999	Turkey	20	6–16	Moderate-severe	PEFR (percent change from baseline)* and asthma score
Scarfone	2000	USA	54	1–18	Moderate-severe	Admissions and pulmonary index score
Ciarallo	2000	USA	30	6–18	Moderate-severe	PEFR (change in percent predicted)*, FEV1, FVC, and admissions
Silvio	2012	Argentina	143	2–15	Severe	Requirement of invasive or noninvasive mechanical ventilation support

*If more than one pulmonary function test was used, the measure marked with an asterisk was used in the analysis.

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PEFR, peak expiratory flow rate.

TABLE 2. Characteristics of the Included Trials of Nebulized Magnesium Sulfate

Study	Year	Location	Sample Size	Age Range, y	Asthma Severity	Outcomes
Mahajan	2004	USA	62	5–17	Mild-moderate	FEV1 (percent predicted) and admission
Powel	2013	UK	508	2–16	Severe	The Yung Asthma Severity Score (ASS) and stepping down of treatment
Mohammadzadeh	2014	Iran	80	5–14	Moderate-severe	Pulmonary index and PEFR
Sun	2014	China	220	4–16	Mild, acetylcholine-induced asthma	FEV1, PEF

sulfate treatment shows no significant effect on respiratory function (SMD, 0.19; 95% CI, −0.01–0.40; *P* = 0.07) (Fig. 4) or hospital admission (RR, 1.11; 95% CI, 0.86–1.44; *P* = 0.42) (Fig. 5). By omitting a study,[20] the one in which patients were not treated with systemic steroids, the conclusion was not changed.

DISCUSSION

This systematic review and meta-analysis attempted to synthesize the most comprehensive review to date of the role of magnesium sulfate in acute asthma in children. There are only a few trials of IV and nebulized magnesium sulfate in children with acute asthma attacks. According to our analysis, combined with standard therapy, IV magnesium sulfate is an effective treatment in moderate to severe acute asthma in children, with the pulmonary function significantly improved and hospitalization and further treatment decreased. But nebulized magnesium sulfate treatment shows no significant effect on respiratory function or hospital admission and further treatment. Magnesium sulfate has a low risk of serious adverse effects, but the exact dose of magnesium sulfate for IV and nebulized administration in children is still controversial. In the present study, the IV dose was from 25 mg/kg to 100 mg/kg (with the max, 2–2.5 mg); the nebulized dose was 2 to 3 mL.

There are some meta-analyses on the effects of magnesium sulfate on acute asthma that have been done. The only research synthesis on children, Cheuk et al,[21] identified 5 trials and concluded that IV magnesium sulfate probably provides additional benefit in moderate to severe acute asthma in children treated with bronchodilators and steroids. In the most recent research synthesis, Kew et al[22] identified 13 trials and concluded that a single infusion of 1.2 or 2 g IV magnesium sulfate through 15 to 30 minutes reduces hospital admission and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulized short-acting β2-agonists, and IV corticosteroids. Mohammed et al[23] and Shan et al[24] did the similar

TABLE 3. Treatment Regimens and Cointerventions Used in Studies of IV Magnesium Sulfate

Study	Magnesium Regimen	Control Regimen	β-Agonist Regimen	Corticosteroid Regimen	Cointerventions
Ciarallo1996	40 mg/kg through 20 min (max, 2 g)	100 mL saline solution	Albuterol	2 mg/kg MP IV (max, 100 mg)	Ipratropium
Devi1997	100 mg/kg through 35 min	Saline solution equivalent volume	Salbutamol 0.15 mg/kg	Hydrocortisone IV/oral (no dose provided)	Aminophylline
Gurkan1999	40 mg/kg through 20 min (max, 2 g)	Saline solution equivalent volume	Salbutamol 0.15 mg/kg	2 mg/kg IV MP (max, 100 mg)	None stated
Scarfone2000	75 mg/kg through 20 min (max, 2.5 g)	Saline solution	Albuterol 0.15 mg/kg 0, 40, 80, 120 min	1.0 mg/kg IV MP (max, 125 mg)	None stated
Ciarallo2000	25 mg/kg through 20 min (max, 2 g)	Saline solution equivalent volume	Albuterol 0.15 mg/kg	2 mg/kg IV MP	None stated
Silvio2012	25 mg/kg (max, 2 g) in a 20-minute period	No placebo	Salbutamol 0.15 mg/kg	1 mg/kg IV MP	None stated

IV MP, intravenous methylprednisolone.

TABLE 4. Treatment Regimens and Cointerventions Used in Studies of Nebulized Magnesium Sulfate

Study	Magnesium Regimens	Control Regimen	Bronchodilator Regimen	Corticosteroid Regimen	Cointerventions
Mahajan2004	2.5 mL isotonic MgSO4 (6.3% solution) single dose	2.5 mL saline solution	Albuterol 2.5 mg (0.5 mL)	2 mg/kg prednisolone	None stated
Powel2103	2.5 mL isotonic MgSO4 (250 mmol/L; 151 mg per dose)	2.5 mL of isotonic saline	Salbutamol 2.5 mg (for children aged 2–5 y) or 5 mg (for those 6 y or older)	Conventional treatment	Ipratropium bromide 0.25 mg
Mohammadzadeh2014	3 mL isotonic MgSO4	3 mL saline solution	0.15 mg/kg salbutamol	Conventional treatment	None stated
Sun2014	2 mL isotonic MgSO4 (286 mOsm/l, 7.5% solution, 150 mg)	1.5 mL saline solution	Albuterol 2.5 mg (0.5 mL)	None stated	None stated

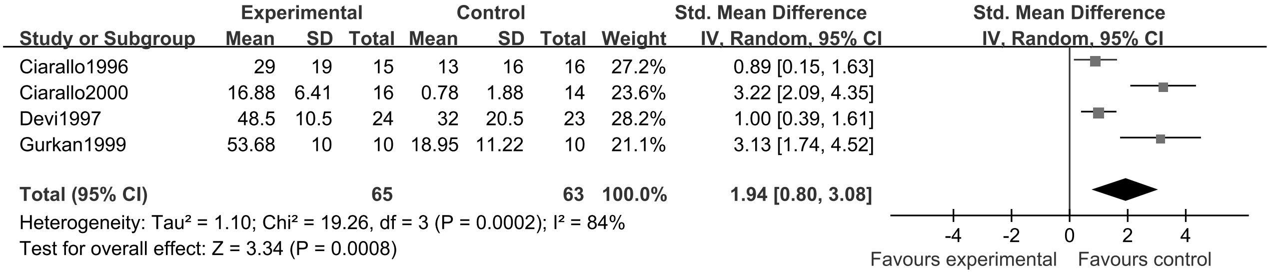

FIGURE 2. Effect of IV magnesium sulfate on respiratory function.

meta-analysis to estimate the effects of IV and nebulized magnesium sulfate in treating adults and children with acute asthma. But their results were inconsistent. Mohammed et al[23] concluded that only IV magnesium sulfate in children seems to be an effective treatment. But Shan et al[24] concluded that IV magnesium sulfate improved pulmonary function in both adults and children and reduced the number of hospital admissions by 30% in children. They also concluded that nebulized magnesium sulfate improved pulmonary function and reduced the number of hospital admissions by 37% in adults. Blitz et al[25] and Powell et al[26] undertook a

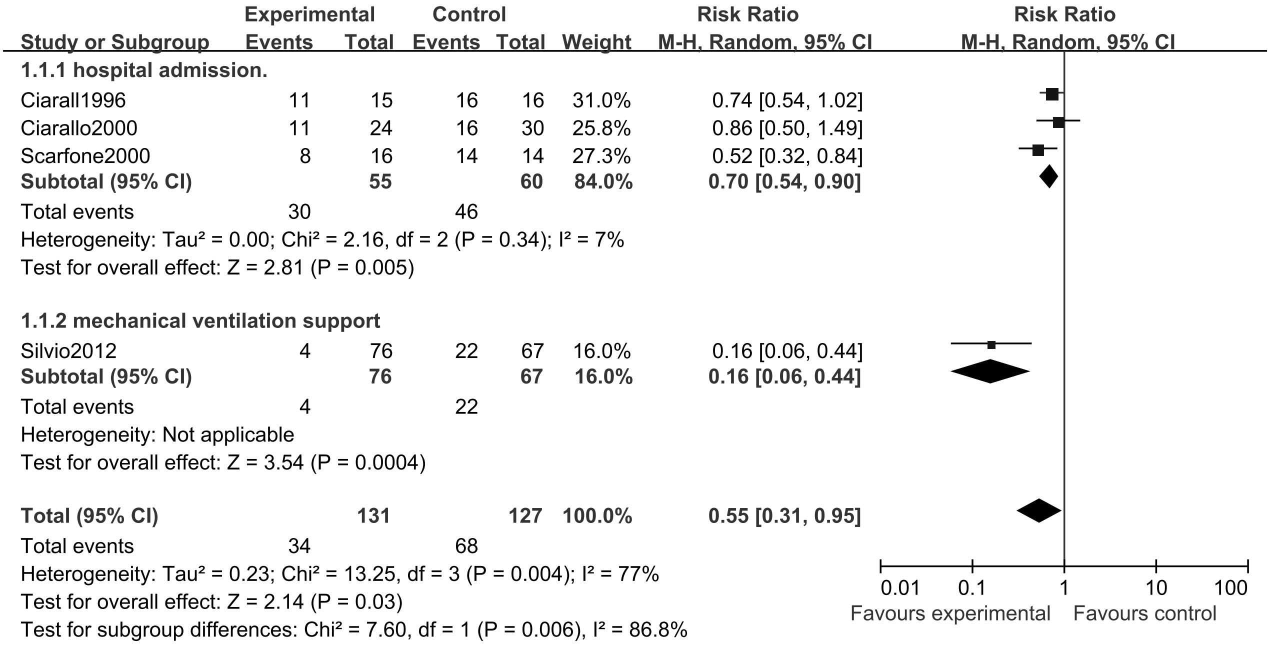

FIGURE 3. Effect of IV magnesium sulfate on hospital admission.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Mahajan2004	75.4	25.9	31	67.3	18	31	17.0%	0.36 [-0.14, 0.86]
Mohammadzadeh2014	171	48.1	40	149.3	39.7	40	21.6%	0.49 [0.04, 0.93]
Sun2014	100.17	17.47	110	99.39	19.31	110	61.4%	0.04 [-0.22, 0.31]
Total (95% CI)			**181**			**181**	**100.0%**	**0.19 [-0.01, 0.40]**

Heterogeneity: Chi² = 3.35, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 1.82 (P = 0.07)

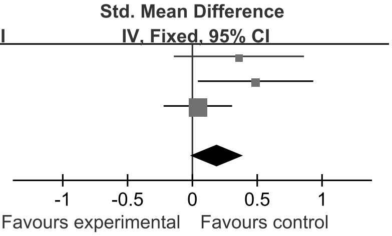

FIGURE 4. Effect of nebulized magnesium sulfate on respiratory function.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahajan 2004	2	31	1	31	1.3%	2.00 [0.19, 20.93]
Powel2013	82	248	76	253	98.7%	1.10 [0.85, 1.43]
Total (95% CI)		**279**		**284**	**100.0%**	**1.11 [0.86, 1.44]**
Total events	84		77			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

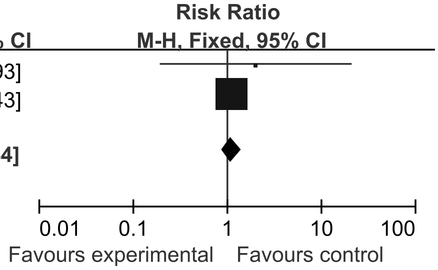

FIGURE 5. Effect of nebulized magnesium sulfate on hospital admission.

systematic review and meta-analysis of randomized and quasi-randomized trials of nebulized magnesium sulfate in acute asthma in 2006 and 2012, respectively. Their conclusions are broadly consistent with each other — there is a role for nebulized magnesium sulfate in acute severe exacerbations of asthma in adults but there are limited data to make firm conclusions about its role in children.

The British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines (2014) state that a single dose of IV magnesium sulfate to patients with acute severe asthma (peak expiratory flow < 50% best or predicted) who have not had a good initial response to inhaled bronchodilator therapy is safe and effective in adults. The guidelines for children are more equivocal, suggesting that IV magnesium sulfate is safe but its place in management is not yet established. Nebulized magnesium sulfate is not recommended for treatment in adults with acute asthma. For children with mild to moderate asthma attacks, nebulized magnesium sulfate is not recommended. But in the first hour, in children with a short duration of acute severe asthma symptoms presenting with oxygen saturation less than 92%, adding 150 mg magnesium sulfate to each nebulized salbutamol and ipratropium was recommended (evidence C).[27] Our conclusions are not entirely consistent with the guidelines. Our analysis suggests that IV magnesium sulfate is an effective treatment in moderate to severe acute asthma in children. For nebulized magnesium sulfate, there is no significant effect on respiratory function or hospital admission and further treatment.

Our meta-analysis has several potential limitations that must be taken into consideration. Firstly, because of the small number of studies, publication bias was not performed. Study selection bias may exist. Studies that were neither presented nor published in any form would not have been identified. But the 2 independent reviewers undertook a comprehensive literature search. References of relevant original papers, meta-analysis, and review articles were screened. Secondly, the most appropriate pulmonary function outcome measure to report does not have consensus. To avoid the influence of different outcome measures, we computed SMDs for pulmonary functions. For IV magnesium, some studies reported hospital admission as an outcome, whereas one reported further treatment and the requirement of mechanical ventilation support as an outcome.[18] We undertook a subgroup analysis for the second outcome. Thirdly, we did not stratify the studies by asthma severity because of the small number of studies.

Our analysis implies that IV magnesium sulfate should be an effective additional treatment for children with acute severe asthma that has not responded to initial standard treatment, whereas nebulized magnesium sulfate in children shows no significant effect and further investigation was required. Further randomized controlled trials with large sample sizes are also required to establish the optimal dosage.

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