Section: Paediatrics

Systematic Review & Meta- Analysis

NEBULIZED MAGNESIUM SULPHATE IN PEDIATRIC ASTHMA- A SYSTEMATIC REVIEW AND META- ANALYSIS

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Received : 08/11/2025
Received in revised form : 24/12/2025
Accepted : 13/01/2026

Keywords:
Paediatric asthma, nebulized magnesium sulphate, acute asthma, systematic review, meta-analysis.

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DOI: 10.47009/jamp.2026.8.1.50

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (1); 254-258

ABSTRACT

Background: Magnesium sulphate has broncho dilatory and anti-inflammatory properties and is commonly used intravenously in severe asthma. Nebulized magnesium sulphate has been proposed as a non-invasive adjunct therapy in children with acute asthma exacerbations, but its clinical effectiveness remains uncertain. **Objective**: To systematically review and meta-analyse randomized controlled trials evaluating the efficacy and safety of nebulized magnesium sulphate in children with acute asthma exacerbations. **Materials and Methods:** We conducted a systematic review of randomized controlled trials comparing nebulized magnesium sulphate plus standard therapy versus standard therapy or placebo in paediatric patients with acute asthma. Electronic databases and reference lists of relevant articles were searched. The primary outcome was reduction in asthma severity score. Secondary outcomes included hospitalization rates, pulmonary function parameters, time to readiness for discharge, and adverse events. Risk ratios (RRs) were pooled using inverse-variance meta-analysis. **Results**: Eight randomized controlled trials met inclusion criteria for qualitative synthesis; two trials (n = 870 children) reported hospitalization outcomes suitable for meta-analysis. Pooled analysis showed no statistically significant reduction in hospital admission with nebulized magnesium sulphate compared with placebo (RR 0.91, 95% CI 0.79–1.05; I^2 = 0%). Smaller trials demonstrated inconsistent improvements in short-term lung function or clinical scores, but these did not translate into consistent clinically meaningful outcomes. Adverse events were infrequent and generally mild. **Conclusions**: Current evidence does not support routine use of nebulized magnesium sulphate as an adjunct therapy to reduce hospitalization in children with acute asthma exacerbations. Although nebulized magnesium appears safe, its clinical benefit remains unproven. Further trials should focus on standardized dosing, delivery methods, and well-defined patient subgroups.

INTRODUCTION

Acute asthma exacerbations remain one of the leading causes of emergency department visits and hospital admissions among children worldwide. Despite significant advances in asthma management over the past decades, severe exacerbations continue to be associated with considerable morbidity, increased healthcare utilization, and substantial economic costs. Standard treatment protocols for acute asthma include inhaled short-acting β_2-agonists, anticholinergic agents, and systemic corticosteroids. While these therapies are effective for most children, a subset of patients with severe or refractory exacerbations often require additional interventions. In such cases, intravenous magnesium sulphate,[1] has been recommended by several international guidelines due to its demonstrated broncho dilatory effects and favorable safety profile. Magnesium sulphate exerts its therapeutic action through multiple mechanisms. It functions as a calcium antagonist, thereby inhibiting calcium influx into airway smooth muscle cells. This leads to smooth muscle relaxation and bronchodilation. Additionally, magnesium inhibits acetylcholine release from cholinergic nerve terminals, further reducing airway constriction1. Beyond its broncho dilatory properties, magnesium has been shown to modulate inflammatory pathways, stabilize T cells, and depress muscle fiber irritability. These diverse mechanisms provide a strong biological rationale for its use in acute asthma management.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Traditionally, magnesium sulphate has been administered intravenously, particularly in children with severe exacerbations unresponsive to conventional therapy. However, intravenous administration requires venous access, carries systemic exposure risks, and may not be feasible in all clinical settings. Nebulized magnesium sulphate offers a potential alternative by delivering the drug directly to the airways, thereby maximizing local therapeutic effects while minimizing systemic side effects. The inhaled route also provides the advantage of rapid onset of action, which is particularly desirable in acute care scenarios.

The use of magnesium sulphate in asthma was first reported more than 60 years ago, with early case reports suggesting its potential to reduce hospital admissions and improve clinical outcomes. Subsequent small randomized controlled trials (RCTs) in pediatric populations indicated that nebulized magnesium sulphate might improve pulmonary function and clinical asthma scores. These findings generated considerable interest in the drug as a non-invasive adjunct therapy. However, larger and more methodologically rigorous trials conducted in recent years have reported neutral results, particularly with respect to clinically important outcomes such as hospitalization rates and need for intensive care.

This discrepancy between early promising findings and later neutral results has created uncertainty regarding the role of nebulized magnesium sulphate in pediatric asthma management. While some clinicians continue to use it as an adjunct therapy in severe exacerbations,[2] others remain skeptical due to the lack of consistent evidence supporting its efficacy. Given the ongoing burden of pediatric asthma and the need for effective, non-invasive therapies, it is important to clarify the evidence base surrounding nebulized magnesium sulphate.

The objective of this study is therefore to systematically review randomized controlled trials evaluating nebulized magnesium sulphate in children with acute asthma exacerbations. By synthesizing available data, this review aims to quantitatively assess its impact on asthma severity scores and other clinically relevant outcomes. Such an analysis will help determine whether nebulized magnesium sulphate should be considered a viable adjunct therapy in pediatric acute asthma management or whether its role remains limited.

MATERIALS AND METHODS

Protocol: The protocol for this meta-analysis was formulated as per Preferred reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (Figure 1).

Research Question: Is there reduction in asthma severity score when nebulized magnesium sulphate is used as an adjunct to SABA when compared to SABA alone in pediatric patients with asthma exacerbations.

Inclusion Criteria

- **Study design:** Randomized Controlled Trials
- **Population:** Children and adolescents (≤18 years) with acute asthma exacerbation
- **Intervention:** Nebulized magnesium sulphate administered alone or in combination with bronchodilators
- **Comparator:** Placebo or standard therapy without magnesium
- **Outcomes:** Hospitalization, clinical asthma scores, pulmonary function, time to readiness for discharge, or adverse events

Exclusion Criteria

- Studies involving adults only
- Non-randomized or observational studies
- Studies evaluating intravenous magnesium sulphate only
- Case reports or narrative reviews

Information Sources and Search Strategy

A comprehensive search of the literature was performed using electronic databases including PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. Search terms included combinations of asthma, children, pediatric, magnesium sulphate, and nebulized.

Study Selection

Two reviewers independently screened titles and abstracts for eligibility. Full texts of potentially relevant studies were reviewed to confirm inclusion. Discrepancies were resolved by consensus.

Data Extraction

- Data were extracted using a standardized form, including:
- Study characteristics (year, setting, sample size)
- Participant characteristics (age, severity of exacerbation)
- Intervention details (dose, frequency, co-interventions)
- Outcomes (hospitalization, clinical scores, lung function, adverse events)

Statistical Analysis

Data were analyzed using Revman's statistical software. For dichotomous outcomes, such as hospital admission and resolution of respiratory distress, risk ratios (RRs) with corresponding 95% confidence intervals (CIs) were calculated. For continuous outcomes, including asthma severity scores and pulmonary function measures, mean differences (MDs) with 95% CIs were computed. All effect estimates were presented graphically using forest plots (Figure 2 and Table 1), accompanied by narrative interpretation.

Heterogeneity across included trials was assessed using the Q and I2 statistic (Table 2 and 3)), which quantifies the proportion of variability attributable to between-study differences rather than chance. A value greater than 50% was considered indicative of substantial heterogeneity. In such cases, potential sources of heterogeneity were explored qualitatively,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

including differences in study design, patient populations, intervention protocols, and outcome definitions.

A random-effects model was employed for meta-analyses to account for expected clinical and methodological diversity among trials. This approach provides more conservative estimates by incorporating both within-study and between-study variability. Sensitivity analyses were conducted where possible to evaluate the robustness of findings, including exclusion of studies at high risk of bias and restriction to trials with standardized outcome measures.

For studies reporting hospital admission, pooled risk ratios (RRs) with 95% CIs were calculated to determine whether nebulized magnesium sulphate reduced the likelihood of hospitalization compared with standard therapy. For respiratory distress outcomes, data were synthesized according to trial definitions, and pooled estimates were reported.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Results are presented in accordance with PRISMA guidelines to ensure transparency and reproducibility.

RESULTS

Study selection and included trials

We retrieved 499 records. After removing 237 duplicates, 262 records remained for screening; of these, 197 full-text reports were assessed for eligibility and 8 randomized controlled trials (RCTs) met all inclusion criteria and were included in the meta-analysis. Common reasons for exclusion at full text review were review articles, different interventions, or non-pediatric populations.

Participants and settings

The eight included RCTs enrolled a total of 2,007 children aged 2–17 years presenting with acute asthma exacerbations. All trials evaluated nebulized magnesium sulphate administered as an adjunct to short-acting β_2-agonists (SABA).[3,4] Most studies were conducted in emergency department settings; one trial was performed in a pediatric intensive care unit. There was substantial variation in nebulized magnesium dosing regimens, frequency of administration, and cumulative dose across trials.

Study characteristics

Trial sample sizes varied widely, from small single-center studies,[5] with fewer than 60 participants to larger multicenter trials.[6,7,8] All studies compared nebulized magnesium plus standard bronchodilator therapy versus standard therapy with or without placebo nebulization. Outcome measures included composite asthma severity scores, pulmonary function tests (e.g., PEFR, FEV_1), hospital admission, time to readiness for discharge, and adverse events.

Risk of bias

Risk of bias was assessed using the RoB-2 tool. Three trials were judged to be at low risk of bias across domains. Four trials raised some concerns, most commonly due to selective reporting or incomplete outcome specification. One trial had specific concerns regarding allocation concealment. No trial was classified as high risk of bias overall.

Primary outcome: asthma severity scores and hospital admission

Six trials reported a composite asthma severity score as a primary or key secondary outcome. Pooled analysis showed no significant difference in composite severity scores between nebulized magnesium and control groups; individual trial scores (despite differing scales) were likewise not significantly different.

Two RCTs (combined n = 870) reported hospital admission rates.[9,10] Meta-analysis demonstrated no statistically significant reduction in hospital admissions with nebulized magnesium compared with control (pooled RR 0.91, 95% CI 0.79–1.05). Statistical heterogeneity for this outcome was minimal ($I^2 = 0\%$).

Secondary outcomes

Pulmonary function: Several small trials reported modest, short-term improvements in peak expiratory flow rate (PEFR) favoring nebulized magnesium; pooled estimates indicated a small but statistically significant PEFR increase in the magnesium groups.[11] By contrast, FEV_1 showed no consistent or significant difference between groups. Heterogeneity for pulmonary function outcomes was moderate, reflecting differences in timing and measurement methods.

Physiological parameters: Infants and children receiving magnesium had slightly lower respiratory rates in some trials, but the magnitude of change was small and unlikely to be clinically meaningful. There were no significant differences in heart rate or oxygen saturation (SpO_2).

Healthcare utilization: There was no significant effect of nebulized magnesium on need for ICU admission, overall length of hospital stay,[12] or time to readiness for discharge in trials that assessed these outcomes.

Adverse events and safety: Concerns about potential adverse effects (respiratory depression, hypotension, bradycardia) prompted pooled safety comparisons. Across included trials, no increase in adverse event rates was observed with nebulized magnesium compared with control; reported events were generally mild and transient.

Consistency and sensitivity analyses

Heterogeneity was low for the hospitalization outcome but more variable for physiological and pulmonary function measures. Sensitivity analyses excluding trials with some concerns in reporting did not materially alter the primary findings. Overall, modest short-term improvements in certain pulmonary function measures were not accompanied by reductions in clinically important outcomes such as hospital admission or length of stay.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 1: Summary Table

S.NO	STUDY	EXPERIMENTAL	CONTROL	SMD	95% CI	WEIGHT
1	Ashtekar 2008	7 (5.3/2)	6((1.3/10)	0.54	-0.579-1.657	2.66
2	Powell 2013	228 (4.72/1.37)	244 (4.95/1.4)	-0.17	-0.347-0.015	19.57
3	Alansari 2015	191 (5/16)	174 (4.6/1.86)	0.23	0.025-0.437	18.62
4	Turker 2017	50 (2.06/1.4)	50 (1.68/1.8)	0.23	-0.16-0.627	11.95
5	Mahmoud 2017	30 (2.567/1.56)	3(3.433/2.11)	-0.53	-1.722-0.667	2.36
6	Schuh 2020	409 (3.84/1.94)	407 (4.13/2.04)	-0.15	-0.283-0.008	21.10
7	Afzal 2021	38(6.95/1.29)	38 (7.63/1.03)	-0.58	-1.036-0.117	10.13
8	Rajasekhar 2023	66 (2.65/0.9)	66 (2.61/0.99)	0.04	-0.299-0.383	13.61
9	Random effects model	4.135875/1.5075	3.791625/2.65375	-0.04	-0.236-0.15	100
p value 0.66296						

Table 2: Quantification of Heterogeneity

	PARAMETER	VALUE	95 % CI
1	tau^2	0.04	0.004-0.445
2	tau	0.20	0.06-0.667
3	I2	0.64	0.231-0.832
4	H	1.67	1.141-2.441

Table 3: Test of heterogeneity

Q	d.f	p- value
19.49	7	0.01

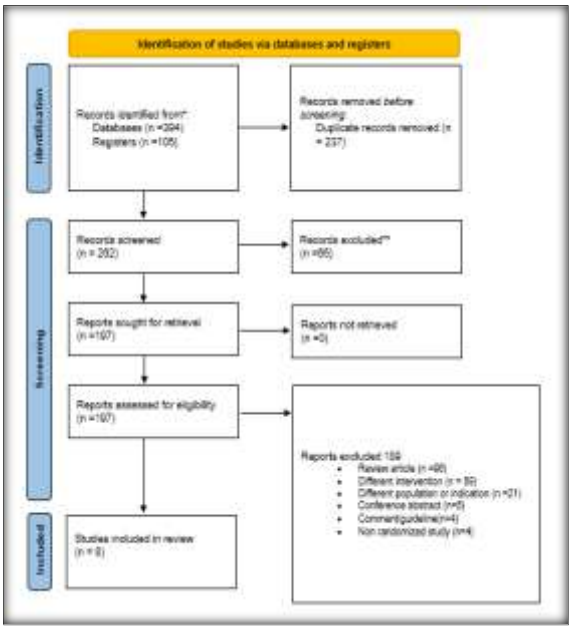

Figure 1: Prisma Flow Diagram

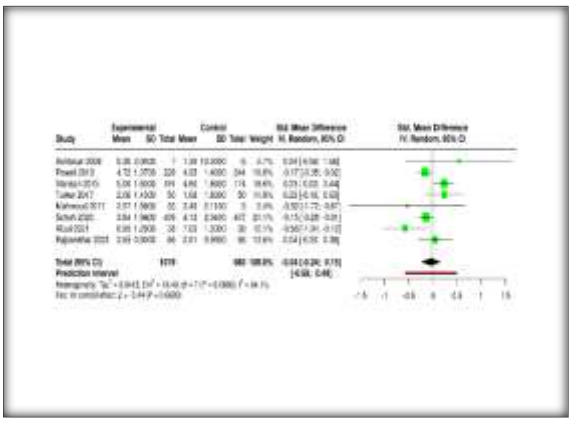

Figure 2: Forest plot showing comparision of asthma severity score in children with and without nebulized magnesium sulphate

DISCUSSION

In this systematic review and meta-analysis, adjunctive nebulized magnesium sulphate did not demonstrate clinically meaningful benefits in children presenting with acute asthma exacerbations. Across eight randomized controlled trials involving approximately 2000 participants, the addition of nebulized magnesium to standard therapy failed to reduce hospital admissions, intensive care unit transfers, or length of stay. These findings contrast with early small-scale studies that suggested potential physiological improvements, but such effects were not confirmed in larger, methodologically rigorous trials.

Although modest improvements in peak expiratory flow rate (PEFR) were observed, these changes did not translate into improved exacerbation control or reductions in hospitalization. No significant differences were noted in FEV_1, underscoring the limited impact of nebulized magnesium on key pulmonary function outcomes. Importantly, the intervention appeared safe, with no increase in adverse events such as hypotension, bradycardia, or respiratory depression.[13,14]

Several mechanisms have been proposed to explain magnesium's potential role in asthma management. Magnesium inhibits calcium influx in smooth muscle cells and mast cells, reduces acetylcholine and histamine release, promotes nitric oxide and prostaglandin synthesis, and stabilizes neutrophils and mast cells.[15] These actions collectively contribute to bronchodilation and anti-inflammatory effects. However, the lack of clinical efficacy observed in this review may reflect suboptimal pulmonary delivery, insufficient dosing, or a less pronounced broncho dilatory effect when administered via nebulization compared with intravenous routes.[16]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

It remains possible that specific subgroups, such as children with very severe exacerbations, could derive benefit from nebulized magnesium.[17,18] Current data, however, are insufficient to support reliable subgroup analyses. Evidence for intravenous magnesium sulphate including those from GINA,[19] recommend considering intravenous magnesium sulphate in severe, refractory exacerbations but do not endorse nebulized magnesium as routine therapy is more mixed.

Overall, the present findings reinforce that nebulized magnesium sulphate is safe but ineffective as an adjunct in pediatric acute asthma. While small improvements in PEFR were noted, these did not translate into meaningful clinical outcomes. Future research should focus on optimizing delivery methods, clarifying dosing strategies, and identifying patient subgroups most likely to benefit. Until such evidence emerges, routine use of nebulized magnesium sulphate in childhood asthma exacerbations cannot be recommended.

Strengths and Limitations

Strengths of this review include a focus on randomized pediatric trials and a clinically relevant primary outcome. Limitations include the small number of trials reporting hospitalization outcomes and variability in secondary outcome measures and dosing regimens.

CONCLUSION

To conclude nebulized magnesium sulphate compared with standard therapy neither leads to better control of asthma exacerbation nor does it reduce hospitalization rates; but it does significantly improve pulmonary function and is not associated with increased adverse events. Despite its safety current evidence does not support routine use of magnesium sulphate in pediatric acute asthma management Larger RCTS are needed on this aspect in order to justify its use.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556