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REVIEW

Safety and Effectiveness of Magnesium Sulphate for Severe Acute Asthma Management Among Under-five Children: Systematic Review and Meta-analysis

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Background: Asthma is the common chronic inflammatory disease affecting children. It is usually associated with airway hyper-responsiveness. Globally, the prevalence of asthma among pediatrics population varies from 10% to 30%. Its symptoms range from chronic cough to life-threatening bronchospasm. At emergency department, all patients with acute severe asthma should initially receive oxygen, nebulized β2-agonists, nebulized anticholinergic agent, and corticosteroids. Though bronchodilators act within minutes, corticosteroids may require hours. Magnesium sulphate ($MgSO_4$) was first considered for treating asthma about 60 years ago. Several case reports were published on its usefulness in decreasing admission and endotracheal intubation. So far, evidence is conflicting to fully employ $MgSO_4$ for asthma management in children under five.

Objective: This systematic review was aimed to evaluate the effectiveness and safety of $MgSO_4$ in the treatment of severe acute asthmatic attacks in children.

Methods: A systematic and comprehensive search of literature was performed to identify controlled clinical trials conducted on IV and nebulized $MgSO_4$ in pediatric patients with acute asthma.

Results: Data generated from three randomized clinical trials were included in the final analysis. In this analysis, intravenous $MgSO_4$ did not improve respiratory function (RR=1.09, 95%CI: 0.81–1.45) and not safer than conventional treatment (RR=0.38, 95%CI: 0.08–1.67). Similarly, use of nebulized $MgSO_4$ showed no significant effect on respiratory function (RR=1.05, 95%CI: 0.68–1.64) and more tolerable (RR=0.31, 95%CI: 0.14–0.68).

Conclusion: Intravenous $MgSO_4$ may not be superior to conventional treatment in moderate to severe acute asthma among children and neither have significant adverse effects. Similarly, nebulized $MgSO_4$ showed no significant effect on respiratory function in moderate to severe acute asthma in children under five but it seems a safer alternative.

Keywords: magnesium sulfate, asthma, Ethiopia, systematic review

Introduction

Asthma is a common, chronic inflammatory airway disease that is associated with airway hyper-responsiveness.[1] It is the most common chronic inflammatory diseases in children which affects the airways and is characterized by airflow obstruction. Globally, the prevalence of pediatric asthma varies from 10% to 30%.[2] Its symptoms range from chronic cough to life-threatening bronchospasm.[1,3] The most common triggers of asthma exacerbations in both younger and older children are viral respiratory tract infections, exposure to allergens, tobacco smoke, air pollutants, cold or dry air, and poorly controlled asthma.[1,4] Poorly controlled asthma in children leads to significant morbidity, mortality, and socio-economic problems.[2] During emergency room management, all patients with acute severe asthma may initially receive standard treatment with nebulized β2-agonists, systemic corticosteroids, nebulized anticholinergics and general management with oxygen therapy. However, bronchodilators act within minutes and corticosteroids may require hours.

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Sometimes, these standard treatments and general management in children with moderate to acute severe asthma may not result in adequate response, leading to severe morbidity and mortality.

Rationale

There is an increasing need for a new and effective bronchodilating agents to improve the outcomes of moderate to acute severe asthma. The use of magnesium sulphate ($MgSO_4$) in treating asthma was noted about 60 years ago and several case reports were published on its impact in decreasing admissions and endotracheal intubations.[3] $MgSO_4$ is considered an alternative therapeutic option in patients resisting standard therapies.[2,5,6] It is an intracellular cation and important coenzyme for various enzyme activities with the following important actions in the management of acute severe asthma: blocks intracellular calcium entry, facilitates calcium release and activation of Na+-Ca2+ pumps, promotes muscle relaxation (inhibition of myosin and calcium interaction), reduces inflammatory mediators (inhibition of degranulation of mast cells and T cells stabilization), depresses the irritability of muscle fibers, and inhibits prostacyclin and nitric oxide synthesis. These mechanisms lead to reduction in the symptoms of acute severe asthma.[7]

$MgSO_4$ has been used in its intravenous (IV) and nebulized dosage forms. The nebulized route offers a potential advantage of quick onset of action and reduced incidence of systemic side-effects.[8] Studies indicated that nebulized $MgSO_4$ is not significantly associated with improved respiratory function or hospital admission, further need of treatment and it is equally effective as nebulized salbutamol for managing severe acute asthma in children.[1,2,9] The use of $MgSO_4$ is resulted in improved hospitalization and decreased the need of further treatment among children with severe acute asthma. Intravenous magnesium sulfate is the most effective therapy for children with significant impact on pulmonary function.[6,10,11] However, studies conducted on the clinical impacts of IV and nebulized $MgSO_4$ among asthmatic children under five had already generated inconsistent results.[2]

Objective

This review was aimed to evaluate the safety and effectiveness of $MgSO_4$ in the treatment of acute asthmatic attacks in children under five.

Methods

A systematic and comprehensive literature search was conducted to identify controlled clinical trials of $MgSO_4$ conducted among pediatric patients diagnosed with severe acute asthma. Such trials evaluated the impacts of $MgSO_4$ on hospitalization, short-term pulmonary function, symptom scores, and treatment related adverse effects. Electronic searches were conducted in PubMed, MEDLINE, Google Scholar and Cochrane Library. The key terms used were "magnesium sulphate", and "safety", "effectiveness" and "asthma" and "children." The search strategy "magnesium sulphate" OR "$MgSO_4$" AND "safety" AND "effectiveness" AND "asthma" OR "asthmatic" OR "chronic respiratory disease" AND "Children" AND "under five years old" OR "below five years" was employed to effectively locate appropriate trials.

Eligibility Criteria

Randomized controlled trials, published in English language from 2001 to 2021, examined the effectiveness or safety of IV or nebulized $MgSO_4$ among children under-five with acute asthmatic attack were included. Whereas, review articles, cross-sectional, cohort, and case-control studies, clinical protocols, case reports, and randomized controlled trials conducted among patients age >5 years were excluded.

Critical Appraisal and Data Extraction

TAM and HG conducted critical appraisal using JBI critical appraisal tools for systematic reviews. HD managed the disagreements between the above independent reviewers whereas; HH and KL extracted the data using Excel spread sheet. Data were extracted on the following variables: name of the authors, year of publication, type of outcomes, number of events, and total number of participants form experimental and standard treatment groups.

Risk of Bias Assessment and Statistical Analysis

RevMan statistical data analysis software for systematic reviews was used to assess the risk of bias and the report was generated along with the safety or effectiveness data. The risk of bias was reported based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and others. Each potential source of bias was graded as high, low, or unclear risk. The risk of bias was reported along with the study findings.

Data were analyzed using RevMan statistical software. The risk ratio (RR) with its 95% confidence interval (CI) was calculated to describe the effects of $MgSO_4$ on the intended outcomes. Data were presented by forest plot along with its interpretation. Heterogeneity across the trials was assessed and reported using I^2. The assessed outcomes include respiratory distress and hospitalization, as defined by the trials.

Outcomes

Safety of intravenous or nebulized $MgSO_4$ is defined as development of serious adverse events such as hypotension requiring medical intervention or admission to pediatric intensive care unit.

Effectiveness of intravenous or nebulized $MgSO_4$ is defined as reduction in the use of mechanical ventilation and need of supplemental oxygen treatment, medical intervention or admission to pediatric intensive care unit.

Results

Extensive literature search using title and abstract retrieved 639 potential records. After excluding 636 articles based on the eligibility criteria shown in Figure 1, only three (one IV, two nebulized) randomized placebo-controlled trials were included in the meta-analysis. The mean and median age of the participants was less than five years.

The characteristics of the included trials are described in Table 1. The sample size of the studies ranges from 50 to 816. All patients who enrolled in to the clinical trials had similar asthma severity defined by inadequate response to standard treatment; ie, severe acute asthma. Based on the quality assessment, two trials had low risk of bias and one had high risk of bias in the domain of blinding of participants. The dose response relationship was not evaluated and one

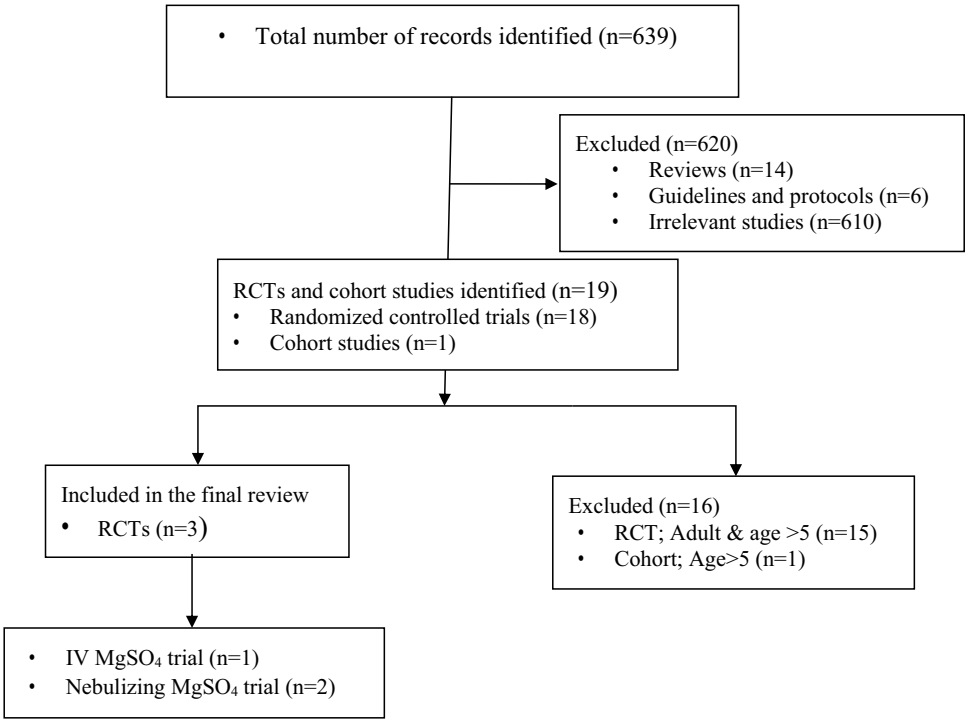

Figure 1 PRISMA flow diagram showing the selection of trials included in the review.

Table 1 Characteristics of the Included Trials for the Safety and Efficacy Analysis of $MgSO_4$

Study	Location	Sample Size	Age (Years)	Asthma Severity	Total $MgSO_4$ Dose	Outcome
Schuh et al 2020[1]	Canada	816	Median 4	Severe acute	Nebulized: 600 mg	Hospitalization
Powell et al 2013[12]	United Kingdom	505	Mean 4	Severe acute	Nebulized: 250 mmol/L	Hospitalization
Santana. et al 2001[13]	Brazil	50	Mean 4.5	Severe acute	IV: 50 mg/kg IV	Respiratory acidosis

study concluded that nebulizing $MgSO_4$ was not superior to standard treatment among children with severe acute asthma with no significant adverse effects.[1] Another study found that nebulizing $MgSO_4$ has a greater clinical effect in children with more severe asthma exacerbation. It has shortened symptom duration and no significant adverse events.[12] A study on IV $MgSO_4$ also reported that early administration of intravenous $MgSO_4$ achieved a rapid clinical response with excellent prognosis and no significant adverse effects among children with acute severe asthma which is refractory to standard treatment[13] (Table 1).

Effectiveness and Safety of IV $MgSO_4$

A study reported the outcome of 33 patients (17 IV $MgSO_4$ group and 16 standard treatment group). In this study, five patients (two from $MgSO_4$ and three from the standard treatment group) required mechanical ventilation. The pooled result indicated, treatment with IV $MgSO_4$ was not associated with improved respiratory function (RR=1.09, 95%CI: 0.81–1.45) (Figure 2).

According to the study by Santana et al,[13] tachycardia was reported among eight patients (three from $MgSO_4$ and five from standard treatment group). The meta-analysis result indicated that safety of IV $MgSO_4$ was not statistically different from standard treatment (RR=0.38, 95%CI: 0.08−1.67) (Figure 3). Two studies; involving the data of 1321 patients (660 from $MgSO_4$ and 661 from standard treatment group), were used for analyzing the efficacy of nebulized $MgSO_4$. In the studies, 409 (200 from $MgSO_4$ and 209 from standard treatment group) of 1321 participants were hospitalized for persistent respiratory distress or needed supplemental oxygen therapy within 24 h of randomization. According to the meta-analysis, nebulized $MgSO_4$ did not significantly improve respiratory function (RR=1.05, 95%CI: 0.71–1.19) (Figure 4) with an acceptable degree of heterogeneity (I^2=55%).

The data of 1323 participants were included in the analysis for the safety of nebulized $MgSO_4$. The studies reported that serious adverse events; defined as hypotension requiring medical intervention or admission to pediatric intensive care unit, were reported among 34 participants (eight from $MgSO_4$ and 26 from standard treatment group). The meta-analysis analysis result indicated that nebulized $MgSO_4$ was safer than placebo. It resulted in 69% lower risk of adverse effects (RR=0.31, 95%CI: 0.14–0.68) (Figure 5) compared to the standard treatment.

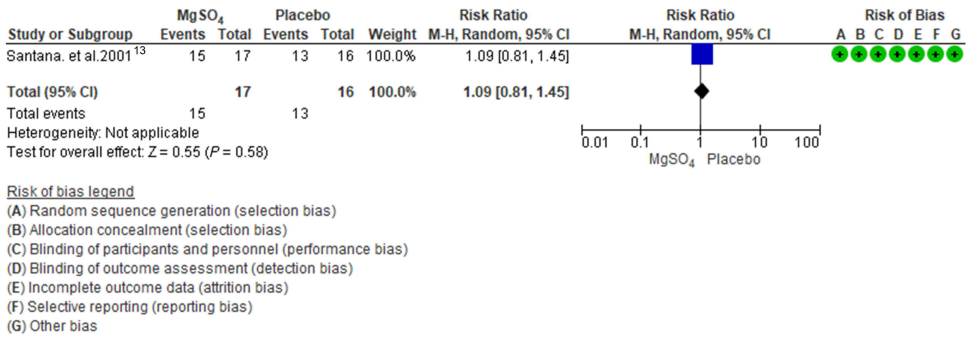

Figure 2 The effectiveness of IV $MgSO_4$ for managing acute severe asthma among children under five.

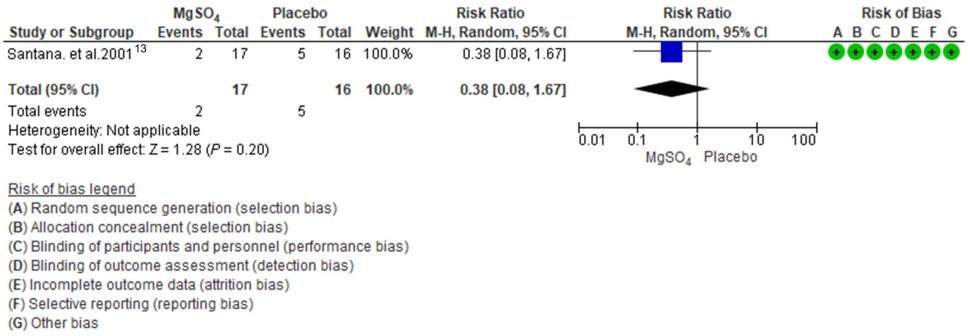

Figure 3 The safety of IV $MgSO_4$ for managing acute severe asthma among children under five.

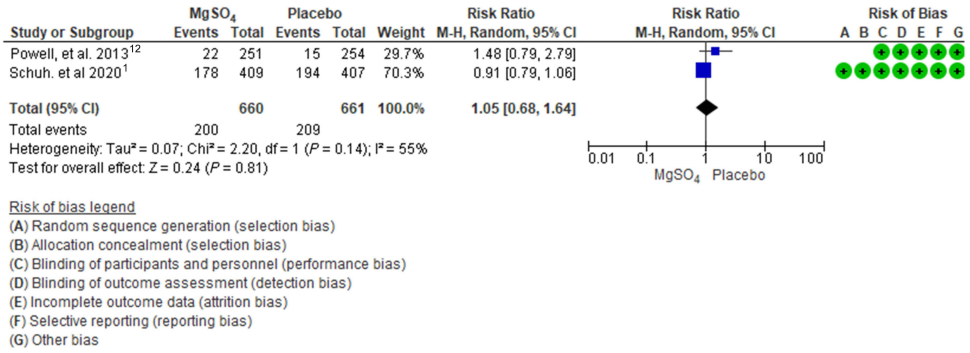

Figure 4 The effectiveness of nebulized $MgSO_4$ for managing acute severe asthma among children under five.

Figure 5 The safety of nebulized $MgSO_4$ for managing acute severe asthma among children under five.

Discussion

In this systematic review and meta-analysis, the authors attempted to synthesize the most comprehensive evidence for the safety and effectiveness of magnesium sulfate among children under five with severe acute asthma. According to this study, IV $MgSO_4$ was not superior to standard treatment (bronchodilators and steroids) among children under five hospitalized with severe acute asthma. It was neither safe nor effective than the standard treatment. In clinical practice, IV $MgSO_4$ is often used in combination with other IV bronchodilators (salbutamol and aminophylline).[14] Another systematic review and meta-analyses confirmed that supplementing IV $MgSO_4$ among children with severe acute asthma was not more effective than the standard therapy.[14] Similarly, nebulized $MgSO_4$ did not show significant effect on respiratory function or hospitalization.[1] This result is consistent with previous studies.[1,2,9]

According to the current study, nebulized $MgSO_4$ is safer than standard treatment. A recent double-blind, randomized, controlled study demonstrated that there was no serious adverse reaction associated with nebulized $MgSO_4$ among Thai

children with moderate asthma exacerbation.[16] However, Tassalpa D et al found that the use of nebulizing and IV $MgSO_4$ has no statistically significant impact on the safety and efficacy of the treatment.[15] Other studies confirmed that, $MgSO_4$ has a low risk of serious adverse effects, minor side effects, such as epigastric or facial warmth, flushing, pain and numbness at infusion site, dry mouth, and malaise.[2,10,12,13] Santana, et al[13] concluded that IV $MgSO_4$ is associated with low risk of tachycardia than salbutamol. This could be due to the variation in mechanism action, as $MgSO_4$ is one of the vasodilating agents.

Our meta-analysis has several limitations that must be taken into consideration. Firstly, inclusion of small number of studies, as only few trials with the target population are retrieved. Secondly, only RCTs are included in this study, which may undermine the actual scenario of the clinical practice. Thirdly, as the studies are nearly all from high income nations, the finding cannot be generalized to the all children with severe acute asthma. Hence, we suggest the need for further investigation with appropriate and adequate properly designed studies to identify the true impact and factors affecting the safety and effectiveness of $MgSO_4$ in this population.

Conclusion

This study revealed that intravenous and nebulized $MgSO_4$ were not more effective than the standard treatment among children with severe acute asthma. Besides, both formulations had statistically insignificant effect in reducing the risk of hospitalization and clinical symptoms of severe acute asthma among children under five. However, this study indicated that nebulized $MgSO_4$ was safer than the standard treatment among children under five with severe acute asthma. This finding indeed contradicts the earlier results; therefore the authors suggest the need of further investigation with properly designed trials and adequate sample size.

Data Sharing Statement

All relevant data are within the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Schuh S, Sweeney J, Rumantir M, et al. Effect of nebulized magnesium vs placebo added to albuterol on hospitalization among children with refractory acute asthma treated in the emergency department. *JAMA*. 2020;324(20):2038–2047. doi:10.1001/jama.2020.19839
2. Zhantao S, Rui L, Gai Z. Intravenous and nebulized magnesium sulfate for treating acute asthma in children. *Pediatr Emer Care*. 2016;34 (6):390–395.
3. Yu YY, Ng MHO. Review of the role of magnesium sulphate in the management of asthma patient. *Hong Kong J Emerg Med*. 2003;10(1):37–42. doi:10.1177/102490790301000107
4. Ortiz-Alvarez O, Mikrogianakis A. Managing the pediatric patient with an acute asthma exacerbation. *Paediatr Child Health*. 2012;17(5):251–256. doi:10.1093/pch/17.5.251
5. Goodacre S, Mohmmed, S. Intravenous and nebulized magnesium sulphate for acute asthma. *Emerg Med J*. 2007;24 (12) :823–30.
6. Özdemir A, Doğruel D. Efficacy of magnesium sulfate treatment in children with acute asthma. *Med Princ Pract*. 2020;29(3):292–298. doi:10.1159/000506595
7. Panahi Y, Mojtahedzadeh M, Najafi A, et al. The role of magnesium sulfate in the intensive care unit. *EXCLI J*. 2017;16:464–482. doi:10.17179/excli2017-182
8. Goodacre S, Cohen J, Bradburn M, et al. Intravenous or nebulized magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial). *Lancet Respir Med*. 2013;1:293–300. doi:10.1016/S2213-2600(13)70070-5
9. Sarmin ZU, Anwar S, Khan TH, Mollah MA, Khanam R, Al BSA. Efficacy of nebulized magnesium sulphate in the treatment of acute bronchial asthma compared to nebulized salbutamol. *Bangladesh J Child Health*. 2020;44(1):24–29. doi:10.3329/bjch.v44i1.49683

10. Cheuk DKL, Chau TCH, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child*. 2005;90:74–90. doi:10.1136/adc.2004.050005
11. Irazuztaa JE, Nicolas Chiribogaa B. Magnesium sulfate infusion for acute asthma in the emergency department. *J Pediatr*. 2017;93(Suppl 1):19–25. doi:10.1016/j.jped.2017.06.002
12. Powell CVE, Boland A, Khan K, et al. Magnesium Trial in Children (MAGNETIC) a randomized, placebo-controlled trial and economic evaluation of nebulized magnesium sulphate in acute severe asthma in children. *Health Technol Assess*. 2013;17(45):1–216.
13. Santana JC, Sérgio Saldanha Menna B, Piva JP, et al. Controlled study on intravenous magnesium sulfate or salbutamol in early treatment of severe acute asthma attack in children. *Pediatr*. 2001;77(4):279–287. doi:10.2223/JPED.235
14. Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2016;4(4):1–32. doi:10.1002/14651858.CD011050.pub2
15. Daengsuwan T, Watanatham S. A comparative pilot study of the efficacy and safety of nebulized magnesium sulfate and intravenous magnesium sulfate in children with severe acute asthma. *Asian Pac J Allergy Immunol*. 2017;35(2):108–112. doi:10.12932/AP0780
16. Wongwaree S, Daengsuwan T. Comparison efficacy of randomized nebulized magnesium sulfate and ipratropium bromide/fenoterol in children with moderate to severe asthma exacerbation. *Asian Pac J Allergy Immunol*. 2022;40:31–38. doi:10.12932/AP-190717-0118