

Optimizing the Use of Intravenous Magnesium Sulfate for Acute Asthma Treatment in Children

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Summary. Background: Asthma is the most common pediatric chronic disease and currently affects 7.1 million children in the United States. Many children experience acute asthma exacerbations. Many children also require hospitalization despite treatment in an emergency department with current standard therapy (corticosteroids, albuterol, and ipratropium). These hospitalizations may be avoided if effective adjunctive therapies can be developed to adequately treat severe exacerbations. Methods: Publications were searched in the PubMed database using the following keywords: magnesium AND asthma AND children AND randomized controlled trial. A total of 30 publications were returned. References of relevant articles were also screened. We included publications of controlled randomized trials where intravenous magnesium sulfate was studied in children (age < 18 years) with acute asthma (n = 7). We excluded studies in adults or trials with other formulations of magnesium (e.g., nebulized). Results: Previous studies have demonstrated that intravenous magnesium sulfate (IV MgSO₄) significantly improves respiratory function and reduces hospitalization rate in children with moderate to severe asthma exacerbations. Current dosing regimens involve a short infusion of 25–75 mg/kg over 20 min (maximum 2–2.5 g/dose), though no studies have directly compared dosages for relative efficacy. Several studies suggest utilizing a peak plasma concentration of magnesium higher than 4 mg/dL as a surrogate of efficacy. This review summarizes the literature regarding the use of IV MgSO₄ for the treatment of pediatric acute asthma. Conclusions: We suggest that optimized dosing regimens could be developed using a linked pharmacokinetic–pharmacodynamic modeling and simulation approach. We propose the factors that should be considered in future clinical trial design in order to better

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INTRODUCTION

Asthma is a prevalent disease that affects as many as 334 million individuals worldwide, and is a major source of disability and premature death in children.¹ Asthma affects 7.1 million children in the United States² and is the most common pediatric chronic disease.³ In 2013, acute asthma resulted in 679,643 ED visits and 70,429 hospitalizations in children 2–17 years old.⁴ Hospitalization is a primary driver of direct costs in asthma in children,⁵ contributing \$3.4 billion of the \$9.3 billion in total pediatric asthma costs in 2008.⁶

Current management strategies for acute asthma recommend a stepwise approach, with first-line standard therapy followed by additional therapeutic options.⁷ First-line therapy consists of inhaled rapid-acting selective β_2 -agonists, inhaled ipratropium bromide, and oral or intravenous corticosteroids. Response to standard acute asthma therapy is variable, influenced by factors that cannot be assessed or accounted for urgently such as genetic polymorphisms.^{8–11} For patients who do not respond adequately to first-line therapy, further improvement can be seen with additional therapy such as inhaled magnesium sulfate (MgSO₄) or intravenous aminophylline, terbutaline, or magnesium sulfate. Though all available second-line therapeutic agents produce bronchodilatory effects, magnesium produces fewer side effects, is more widely available, and costs less than other second-line therapies.¹² A single infusion of 1.2 or 2 g intravenous MgSO₄ over 15 or 30 min has been shown to reduce hospital admissions, and improve lung functions in adult patients who fail to respond to first-line therapy.¹³ This combination of efficacy, few side effects, wide availability, and low cost suggest that magnesium sulfate is a promising therapeutic agent that deserves further consideration for use in children with acute asthma.

In published trials, MgSO₄ has been delivered either via intravenous or nebulized routes for acute asthma treatment.^{14–21} Differences between the two formulations have been systemically reviewed.²² While both routes have been demonstrated to have minimal side-effects, the efficacy of the nebulized form has insufficient evidence in children.²³ The extensive literature of nebulized MgSO₄ is beyond the scope of this review, which focuses on the intravenous form (IV MgSO₄).

While the pharmacology of magnesium in asthma treatment has been previously reviewed,^{12,24} it deserves a

brief introduction. The physiologically active molecule of MgSO₄ is the magnesium cation. Magnesium causes smooth muscle relaxation by blocking calcium release from endoplasmic reticulum, and by activating sodium-calcium pumps. Consequent inhibition of calcium's interaction with myosin leads to muscle cell relaxation. Magnesium also acts through other mechanisms including T cell stabilization, mast cell degranulation inhibition, acetylcholine release inhibition, and stimulation of nitric oxide and prostacyclin synthesis. Overall, these effects depress muscle fiber excitability, reducing the airflow obstruction characteristic of acute asthma.

In this review, the overall rationale for magnesium use in pediatric acute asthma will be discussed by reviewing the results of published clinical trials of magnesium in pediatric acute asthma. The challenges and considerations of trial design are also discussed with suggestions for future investigation.

METHODS

Publications were searched in the PubMed database using the following keywords: magnesium AND asthma, AND children AND randomized controlled trial. A total of 30 publications were returned. References of relevant articles were also screened. We included publications of controlled randomized trials where intravenous magnesium sulfate was studied in children (age < 18 years) with acute asthma (n = 7).^{14–19} We excluded studies in adults or trials with other formulations of magnesium (e.g., nebulized). Although some published trials of IV MgSO₄ included both children and adults, we excluded trials, where pediatric data were not reported separately from adult data. This resulted in seven trials for inclusion.

Evidence of Efficacy

Since the first case reports of use of IV MgSO₄ in children with asthma in 1994,²⁵ evidence has accumulated of magnesium's efficacy in treating pediatric acute asthma, including a number of trials, and meta-analyses (Table 1).

The most convincing and dramatic evidence of the efficacy of IV MgSO₄ in pediatric asthma came from two small, double-blind, randomized, placebo-controlled trials published by Ciarallo et al. in children who could perform spirometry, and had insufficient improvement

TABLE 1—Summary of Randomized Controlled Trials of MgSO₄ in Children With Acute Asthma

Study	Year	Sample size	Age range (years)	Indication	Treatment arm	Dosing form	Standard therapy				Primary outcome
							Control arm	Inhaled β_2 -agonist	Inhaled anticholinergics	Systemic corticosteroid	
Singhi	2014	100	1–12	Severe	50 mg/kg over 20 min	IV	IV terbutaline, IV	Albuterol 0.15 mg/kg/dose at 0, 20, 40 min	Ipratropium	Budesonide 800 ug/dose at 0, 20, 40 min; hydrocortisone 10 mg/kg	Treatment success (reduction in the CAS of four points or more)
Torres	2012	143	2–15	Severe	25 mg/kg over 20 min (max 2 g)	IV	None	Albuterol 0.15 mg/kg/dose (min 2.5 mg, max 10 mg every 20 min) at 0, 20, 40 min	None	MP 1 mg/kg	Mechanical ventilation requirement
Scarfone	2000	54	1–18	Moderate to severe	75 mg/kg over 20 min (max 2.5 g)	IV	Saline	Albuterol 0.15 mg/kg/dose at 0, 40, 80, 120 min	None	MP 1 mg/kg (max 125 mg)	Hospital admissions and PI score
Ciarallo	2000	30	6–18	Moderate to severe	40 mg/kg over 20 min (max 2 g)	IV	Saline	Albuterol	Ipratropium	MP 2 mg/kg (max 100 mg)	PEFR, FEV ₁ , FVC, and discharge ratio
Gurkan	1999	20	6–16	Moderate to severe	40 mg/kg over 20 min (max 2 g)	IV	Saline	Albuterol 0.15 mg/kg/dose, three doses at 20 min intervals	None	MP 2 mg/kg (max 100 mg)	PEFR and clinical asthma scores
Devi	1997	47	1–12	Severe	100 mg/kg over 35 min	IV	Saline	Albuterol 0.15 mg/kg/dose, three doses at 20 min intervals	None	Hydrocortisone	PEFR and SaO ₂
Ciarallo	1996	31	6–18	Moderate to severe	25 mg/kg over 20 min (max 2 g)	IV	Saline	Albuterol 0.15 mg/kg	None	MP 2 mg/kg	PEFR and hospital admissions

MP, methylprednisolone; PEFR, peak expiratory flow rate; SaO₂, oxygen saturation; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; PI score, pulmonary index score; CAS, clinical asthma severity score.

after initial treatment.^{16,17} In the first trial in 1996, a 20 min infusion of magnesium (20 mg/kg, 2 g maximum) improved peak expiratory flow rate (PEFR) by 46% (16% in controls; $P = 0.05$), forced expiratory volume in 1 sec (FEV₁) by 34% (no improvement in controls; $P = 0.05$), and reduced hospitalization by 27% (11/15 receiving IV MgSO₄ hospitalized vs. 16/16 controls; $P = 0.02$). No adverse events were reported. Four years later in a second study of 30 patients using a similar design, a higher dose of IV MgSO₄ (40 mg/kg, 2 g maximum) improved PEFR by 80% (<10% improvement in controls; $P < 0.001$), and reduced hospitalization by 50% (8/16 receiving IV MgSO₄ hospitalized vs. 14/14 controls; $P = 0.002$).

In 2000, Scarfone et al. reported a trial of 54 children with an initial pulmonary index (PI) score of 8–13 (0–15 scale) prior to initial asthma treatment, randomized to IV MgSO₄ (75 mg/kg, 2.5 g maximum), or placebo.¹⁵ By using a respiratory score as inclusion criteria, they evaluated the effect of earlier use of IV MgSO₄ in a more broad severity range of acute asthma and avoided the potentially confounding effect of spirometry-based trial inclusion. Respiratory scores were no different in children treated with IV MgSO₄ compared to controls. No significant improvement in hospitalization rate was found (11/24 receiving IV MgSO₄ hospitalized vs. 16/30 controls), though the study was not powered for this outcome. Later meta-analyses of these three trials suggests that IV MgSO₄ may decrease hospitalization with a relative risk of 0.7 (95% CI 0.54–0.90), and a number needed to treat (NNT) of 4.^{24,26–28} However, reduction in hospitalization may be limited to the more severe subgroup.²⁸

Other studies have also provided evidence of IV MgSO₄ as an effective adjuvant agent to conventional therapy for pediatric acute asthma, though not directly assessing the effect of IV MgSO₄ on hospitalization. In 1997, Devi et al. reported that in 47 children in India who did not respond to initial β_2 -agonist therapy, those that received IV MgSO₄ (100 mg/kg) had significantly improved PEFR and oxygen saturation one hour after infusion compared to those that received placebo.¹⁹ Improvement in lung physiology with IV MgSO₄ was also found by Gurkan et al., who in 1999 reported a trial involving 20 children in Turkey with PEFR less than 60% after initial β_2 -agonist therapy. Intravenous magnesium sulfate (40 mg/kg) resulted in improved PEFR by 43% (14% in controls) and clinical asthma scores by 1.8 (on a 10-point scale²⁹).¹⁸ In a randomized trial of 143 children in Argentina reported in 2012, children given 25 mg/kg IV MgSO₄ versus placebo had an absolute risk reduction in mechanical ventilation of 28% (4/76 receiving IV MgSO₄ receiving mechanical ventilation vs. 22/67 controls) in addition to inhaled β_2 -agonist and an IV steroid.¹⁴ In a randomized trial of 100 children in India reported in 2014, patients receiving a single dose of IV MgSO₄ (50 mg/kg)

as adjuvant therapy in addition to inhaled β_2 -agonist and corticosteroids had higher rates of treatment success (33/34), defined as improvement of 4 or more points on a 15-point clinical asthma score, compared to those receiving terbutaline or aminophylline as adjuvant therapy (23/33; $P = 0.006$).³⁰

There have been no US trials studying the efficacy of IV MgSO₄ in pediatric acute asthma in the past 15 years. Intravenous magnesium sulfate is recommended as an adjunctive treatment for severe acute asthma in children,^{31,32} though the range of recommended doses is wide, from 25 to 75 mg/kg. This dose recommendation reflects the wide range in studied dosages without evidence to guide dosage choice, supporting the need for further pharmacokinetic/pharmacodynamics studies to generate the evidence needed to guide optimal clinical use of IV MgSO₄.

Pharmacokinetics/Pharmacodynamics

To achieve therapeutic effect, MgSO₄ is usually administered with the intent to raise the serum magnesium level. Previous studies in acute asthma suggest that the serum magnesium level must be above 4.0 mg/dl to produce beneficial results,^{25,33,34} similar to the range associated with therapeutic effects for the treatment of preeclampsia.³⁵ In a kinetic study, eight children from 4 months to 18 years of age received 17–60 mg/kg MgSO₄ over 20 min while simultaneously receiving intravenous methylprednisolone, oxygen, and continuous inhaled albuterol.³⁶ Magnesium concentrations at baseline, 20 min, and 60 min after the start of infusion were 2.03 ± 0.29 , 3.35 ± 0.43 , and 2.54 ± 0.27 mg/dl (mean $\pm$ SD), respectively. A trend toward PEFR improvement was observed at peak serum magnesium concentration (20 min), although this concentration did not reach 4 mg/dl. It was noted that an initial bolus loading dose of 66–83 mg/kg should achieve peak serum magnesium levels of 4–4.5 mg/dl. Addition of a continuous infusion after an initial loading bolus was shown to maintain plasma magnesium concentration near 4.0 mg/dl in a retrospective review of children with refractory wheezing in an ICU.³⁷ Patients with weights less than 30 kg required significantly higher loading and/or infusion doses than those who weigh more than 30 kg.^{37,38} However, the mathematical relationship between MgSO₄ pharmacokinetics and patient weight was not examined. Relationships between important pharmacokinetic parameters of IV MgSO₄ (clearance, volume of distribution, AUC, and trough concentrations, etc.) and patient demographic characteristics (weight, age, sex, ethnicity, etc.) have not been defined.

Ionized magnesium is the active form of magnesium that penetrates cells and executes its physiological function. Reduced intracellular magnesium levels have

been observed in patients with acute asthma.³⁹ Intravenous magnesium sulfate treatment is able to increase both total and ionized plasma magnesium in patients with asthma.⁴⁰ A prospective cohort study by Egelund et al., evaluated the relationship between total and ionized magnesium concentrations in 19 admitted patients (1–16 years) who had acute asthma exacerbation, and were refractory to conventional therapy.⁴¹ Patients received a bolus dose of MgSO₄ at 50 mg/kg (for patients weighing >30 kg) or 75 mg/kg (for those weighing ≤30 kg), followed by a continuous infusion of 40 mg/kg/hour for 4 hr. Serum magnesium concentrations (total) were 4.4 ± 0.98 mg/dl (mean $\pm$ SD) at the end of infusion, which achieved theoretical therapeutic level and agreed well with the previous retrospective study results.³⁸ Ionized magnesium concentration was 2.3 ± 0.5 mg/dl (mean $\pm$ SD), which was strongly correlated with serum magnesium concentration ($R^2 = 0.924$).⁴¹

Pharmacodynamic information used to assess the effect of MgSO₄ therapy usually includes respiratory responses (respiratory rate, PEFR, SaO₂, FEV₁, and FVC) and cardiovascular effects (blood pressure) during treatment.^{16,17} Egelund's study compared the cardio-respiratory effects between children in the treatment group and those in the control group.⁴¹ No differences in blood pressure or oxygen saturation were observed, whereas, the heart rate and respiratory rate were statistically lower in the treatment group (heart rate 5.95 beats per min, $P = 0.03$; respiratory rate 4.69 breaths per min, $P = 0.01$) than the control group.⁴¹ However, the dose–response relationship of IV MgSO₄ and cardio-respiratory effects in children is still poorly understood.⁴²

Considerations of Future Trial Design

Published trials have showed promising efficacy of IV MgSO₄ in treating pediatric acute asthma. However, limitations in published trials should be addressed in future investigations to better understand the use of this agent in clinical practice.

First, more specific attention should be paid to the effects of IV MgSO₄ in reducing hospital admission. To date, a total of 425 children have been enrolled in studies that have addressed various efficacy outcomes including respiratory function measurements, PI scores, mechanical ventilation requirement, and hospital admission rate. While measures of respiratory function help demonstrate the physiologic impact of IV MgSO₄, hospital admission is a much more determinant outcome than other intermediate measurements. It is also a significant and meaningful outcome for patients, parents, hospitals, payers, and clinicians. However, only 115 children have been enrolled in trials examining the effect of IV MgSO₄ on the need for hospital admission. The results of these small trials are promising, but far from conclusive in

evaluating the effect of IV MgSO₄ to decrease hospitalization. Future trials should be designed and powered to examine IV MgSO₄ effects on reducing hospitalization with greater confidence.

Second, and similarly, larger trials with strong statistical power are needed. Published trials have reached varying conclusions regarding the efficacy of IV MgSO₄. For example, the conclusions from Scarfone's study suggest limited efficacy, while Ciarallo's studies suggest dramatic efficacy. This difference may be accounted for by difference in study design, such as dramatic effects found in trials that include only patients with inadequate improvement after initial therapy. Nonetheless, these varying conclusions are not surprising from a statistical perspective, considering the relative small size (with fewer than 60 patients) in each study. This increases the risk that the intervention's effect in the population may not be accurately represented in published trial results. Cautions about interpreting treatment effects based on small study results have been widely discussed.^{43–46} This does not cast doubt on the methods or findings of the published studies. Rather, it demands that a conclusive answer to the efficacy of IV MgSO₄ in preventing hospitalization in pediatric asthma will depend on larger trials with more statistical power.

Third, the efficacy of IV MgSO₄ should be examined in younger children. Most children hospitalized with asthma are less than 4 years old.⁴⁷ It is commonly accepted that distinguishing asthma from age-related bronchospasm (such as bronchiolitis) is challenging in young children, especially children younger than 2 years old. To avoid confounding asthma with bronchiolitis, most studies exclude patients younger than 2 years old. When adequate spirometry measurement is required for inclusion, children of 2–6 years old are also often excluded by design,^{16–18} due to insufficient coordination with breathing that is needed for spirometry. Inability to perform spirometry also occurs due to respiratory distress.^{48,49} In children with respiratory distress, even those older than 6 years, only 30% can perform spirometry in the emergency department.^{48,49} Few trials have included patients based on severity classification using a clinical severity score which can be applied in young patients with respiratory distress.^{15,19} However, characterization of illness severity is challenging due to insufficient validation of such scores, thus, preventing comparison and application of results from such studies.⁵⁰

Fourth, IV MgSO₄ should be studied in the context of current standard therapy. The evidence supporting the treatment of acute asthma has evolved significantly in the 19 years since Ciarallo's initial study. At the time, inhaled β -agonists and IV, or oral corticosteroids were known to improve acute asthma and were used as the standard of care.^{51,52} Inhaled ipratropium was being intensely studied at the time and is now known to be valuable in preventing

admission.⁵³ Ciarallo's second study is the only trial to include ipratropium as a co-intervention. Ipratropium is now considered standard of care in moderate and severe asthma.⁷ Devi and Singhi included aminophylline as a co-intervention, which is now considered ineffective and prone to significant side effects.⁵⁴ No study since 2000 has tested the effect of IV MgSO₄, when given in addition to current standard therapy of steroids, inhaled beta agonists, and inhaled ipratropium.

Fifth, future studies should include direct comparison on the effectiveness of differing IV MgSO₄ dosages. All studies to date randomized patients to placebo or a single dose of IV MgSO₄. Higher doses in the Devi (100 mg/kg) and Scarfone (75 mg/kg) studies did not result in increase in effect compared to the smaller dosages in Ciarallo's two studies, though the two differing dosages (20 vs. 40 mg/kg) appeared to have a significant dosage-dependent effect. However, all these studies were separated in time and performed in different settings of co-interventions, limiting direct comparisons of dose effect. This suggests that the enhanced effect in Ciarallo's higher-dose study may be random effect rather than a dose-response. In order to determine an effective dosing regimen and the dose-response relationship of IV MgSO₄ in pediatric patients, randomizing subjects to different dosages with identical co-interventions settings is critical.

Determining the dose-response relationship of IV MgSO₄ can partially be accomplished via pharmacokinetics and pharmacodynamics studies with greater emphasis on pharmacometric approaches. Published studies have reported some PK measurements (clearance, volume of distribution, AUC, and trough concentrations, etc.) with different dosing regimens regarding or regardless of weight. Given the results by Egelund et al., in which increased doses were required for efficacy in smaller children,⁴¹ it is highly likely that patient weight may impact the success of IV MgSO₄ therapy, as may other sources of variability. However, no population modeling/simulation attempt has been reported to describe the kinetics of MgSO₄ and its potential variation within the pediatric population. Defining inter-individual sources of variability which impact the disposition of MgSO₄ is a critical next step towards developing a robust dosing recommendation for children. More studies with surveillance of serum magnesium levels are needed in order to determine the PK of MgSO₄ within this population.

In addition, neither the dose-response relationship nor the pharmacodynamics of MgSO₄ has been assessed with definite mathematical approaches. Specifically, more work is needed to establish changes in respiratory function corresponding to "successful" therapy with MgSO₄. Furthermore, these studies must correlate improvements in respiratory function metrics with decreases in hospitalization rates, so as to prove the

benefit of MgSO₄ therapy. These efficacy endpoints should also be incorporated into pharmacokinetic studies of IV MgSO₄ to quantitatively examine the linked-effects of pharmacokinetics and pharmacodynamic. Such information will guide optimization of the IV MgSO₄ dose regimen for pediatric acute asthma.

Finally, studies of severely ill children with asthma in the ICU suggest that a brief infusion and a weight-based dosage with a maximum dosage, such as has been used in most studies, may not have pharmacologic rationale. Rather, strict body-weight-normalized dosage without a maximum and more prolonged infusion may better match the actual physiology of children with acute asthma.⁴¹ Future studies that attempt to examine dose-response must utilize pharmacologic rationale that does not exclude potentially valuable dosage regimens.

Future prospective studies should be powered to detect differences in hospitalization rates between MgSO₄ treated and untreated patients. In addition to collecting data describing changes in hospitalizations, physiologic markers, such as serum magnesium concentrations and respiratory function scores, should be collected to develop a robust link between MgSO₄ administration, improved respiratory function, and decreased need for hospitalization. Studies should examine multiple weight-based dosing strategies to investigate the potential for a dose-response relationship. Studies should also evaluate the benefits of adding MgSO₄ as a first-line therapy, as well as impact on disease severity in relation to inter-individual patient's response to therapy. A trial of this nature would bring great clarity to the clinical use of IV MgSO₄ as an alternative treatment for children experiencing acute asthma attacks.

CONCLUSIONS

Early small trials showed dramatic results of IV MgSO₄ treatment in pediatric acute asthma, which is now included in guidelines as a consideration for children who do not respond to inhaled β_2 -agonists, steroids, and inhaled ipratropium. However, the effects of IV MgSO₄ have been studied in very few children. Trials published to date have been small in size and only one study has examined IV MgSO₄ as an adjunct to therapy currently considered to be of the best evidence. The pharmacodynamic relationships between IV MgSO₄ treatment and pulmonary physiology in children with acute asthma have been inadequately studied. More work is demanded in order to determine the most efficacious dosage and validate its effectiveness in decreasing hospital admission, in addition to improving other outcomes such as respiratory function. Future trials should include larger populations, identical trial design, universal outcome assessment, and rational dosage and dosing regimens.

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