

The role of magnesium sulfate in the acute and chronic management of asthma

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Purpose of review

Acute asthma is common and severe exacerbations may result in hospitalization, need for endotracheal intubation and, rarely, death. Standard emergency care includes systemic corticosteroids and bronchodilators, but additional treatments may be required in severe cases. We summarize the substantial evidence regarding the role of MgSO₄ in acute asthma and comments on the potential benefit in chronic asthma.

Recent findings

Inhaled and intravenous MgSO₄ agents are used in the treatment of acute asthma, but only the intravenous formulation is effective. In severe asthma exacerbations, a single bolus dose of intravenous MgSO₄ reduces admissions and improves pulmonary functions. Inhaled MgSO₄ is more effective than placebo as a bronchodilator, but performs no better than salbutamol and there is no apparent synergy when the two are combined. Whereas intravenous MgSO₄ treatments appear to be effective, long-term 'replacement' therapy with magnesium does not appear to affect chronic asthma.

Summary

Evidence suggests that intravenous MgSO₄ is beneficial in acute asthma, while the evidence for inhaled MgSO₄ is less convincing. Moreover, the role of replacement therapy with oral magnesium remains to be clarified. The use of intravenous MgSO₄ remains uncommon, with emergency physicians appropriately restricting its use to patients with severe exacerbations.

Keywords

asthma, bronchodilation, emergency medicine, magnesium sulfate, systematic reviews

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Introduction

More than 27 million people in the USA have received a diagnosis of asthma at some point in their lives, and there are approximately 1.8 million emergency department visits in the USA each year [1]. The burden of illness is high, in both children and adults, and the costs associated with asthma are staggering. For example, the annual expenditures for asthma exceeded \$12 billion dollars in the USA [2] and 25% of asthma costs are expended on acute care (emergency department visits; hospitalizations) [3].

The treatment of acute asthma in the emergency department has been the subject of much research and synthesis of asthma trials into systematic reviews is common [4–6]. Although most patients with acute asthma can be stabilized in the emergency department or equivalent setting, there are some patients with more severe presentations, for whom more intensive therapy is required. The initial emergency department treatment management involves inhaled salbutamol either by nebulizer (intermittent or continuous) or metered-dose inhaler and holding chamber devices [7]. In addition, multiple doses of inhaled anti-

cholinergics, and systemic [8] and inhaled [9] corticosteroids have been shown to be effective; data on heliox are limited and provide mixed results [10]. By contrast, there is substantial evidence that aminophylline [11] and antibiotics [12] do not improve outcomes.

In severe acute asthma (e.g. severe bronchoconstriction with lack of response to β -agonists) intravenous MgSO₄ may be helpful. Moreover, there is emerging evidence that inhaled MgSO₄ may also be helpful. This review summarizes the current evidence related to the use of magnesium agents in acute and chronic asthma.

Mechanisms

Magnesium is an important intracellular and extracellular cation which is a cofactor of many intracellular enzymatic reactions [13]. Magnesium may be effective in acute asthma through a variety of mechanisms. For example, magnesium has been shown to relax smooth muscle, and may be involved with inhibition of smooth-muscle contraction. This theory has been proposed as an explanation for the effects of magnesium in acute asthma; however,

this explanation is perhaps overly simplistic. Magnesium is also involved with cellular homeostasis through its role as an enzymic cofactor, as well as being involved in acetylcholine and histamine release, from cholinergic nerve terminals and mast cells, respectively. Moreover, investigators have proposed that the effect of magnesium is related to its ability to block the calcium-ion influx to the smooth muscles of the respiratory system [14]. Finally, the role of magnesium as an anti-inflammatory agent has been identified in adults with asthma [15]. In summary, this cation is ubiquitous within the human body and has clear potential to play an important role in asthma; however, the precise mechanism or the relative importance of the aforementioned mechanisms is unclear at this time.

Despite the widespread interest in magnesium metabolism in asthma, the evidence for decreased levels in asthma patients is conflicting. Since much of the body's magnesium stores are intracellular, the serum magnesium level may be meaningless, or at least misleading. Thus, it would appear that predicting response to magnesium would be difficult based solely on serum magnesium levels.

Searching for evidence

Systematic searches of MEDLINE and EMBASE (covering the period from January 2006 to July 2007) were performed to identify recent full-text, English-language publications evaluating the use of intravenous and nebulized, inhaled, or oral magnesium for the treatment of asthma in humans. Search terms included terms for magnesium (magnesium, magnesium sulfate, Mg, MgSO₄) and asthma. The Cochrane Library is particularly rich in high-quality systematic review evidence on numerous aspects of asthma, especially acute asthma [16]. Due to their methodological rigor and currency, when multiple systematic reviews were identified, the Cochrane review was explored in detail.

Evidence on intravenous MgSO₄

The value of intravenous MgSO₄ in acute asthma can be explored by examining effectiveness (in children and adults) as well as safety and dosing issues.

Effectiveness

Intravenous MgSO₄ is a treatment option for a variety of acute diseases such as eclampsia [17], cardiac arrhythmia [18^{••}], and severe hypomagnesemia. The use of intravenous and, to a lesser extent, inhaled MgSO₄ in unresponsive acute asthma has gained support over the past decade. There have been a number of systematic reviews which all conclude that intravenous magnesium is not only safe but effective in those patients with severe exacerbations [19–21]. The original Cochrane review examined the

addition of intravenous MgSO₄ to β -agonists and systemic corticosteroids and identified seven trials (five adult, two pediatric) involving a total of 668 patients [19]. Recent additional trial evidence has been published and when combined with the original review, there are now 13 studies (eight adult, five pediatric) involving 965 patients included in this review. It is important to recognize that these patients were largely enrolled after the standard treatment had been initiated. In addition, standard care in these cases included systemic corticosteroids and inhaled β -agonists.

When all studies were considered, the addition of MgSO₄ reduced hospitalization; however, significant heterogeneity was identified (I^2 , 47.6%; Fig. 1). When the analysis was restricted to only adults, the treatment did not appear to reduce admissions [relative risk (RR), 0.91; 95% confidence interval (95% CI), 0.77–1.09]. In the subgroup with severe exacerbations, MgSO₄ did reduce hospitalization when all studies were considered (RR, 0.60; 95% CI, 0.48–0.74), and also improved pulmonary function [peak expiratory flow (PEF): 26.8 l/min; 95% CI, 7.3–45] [21].

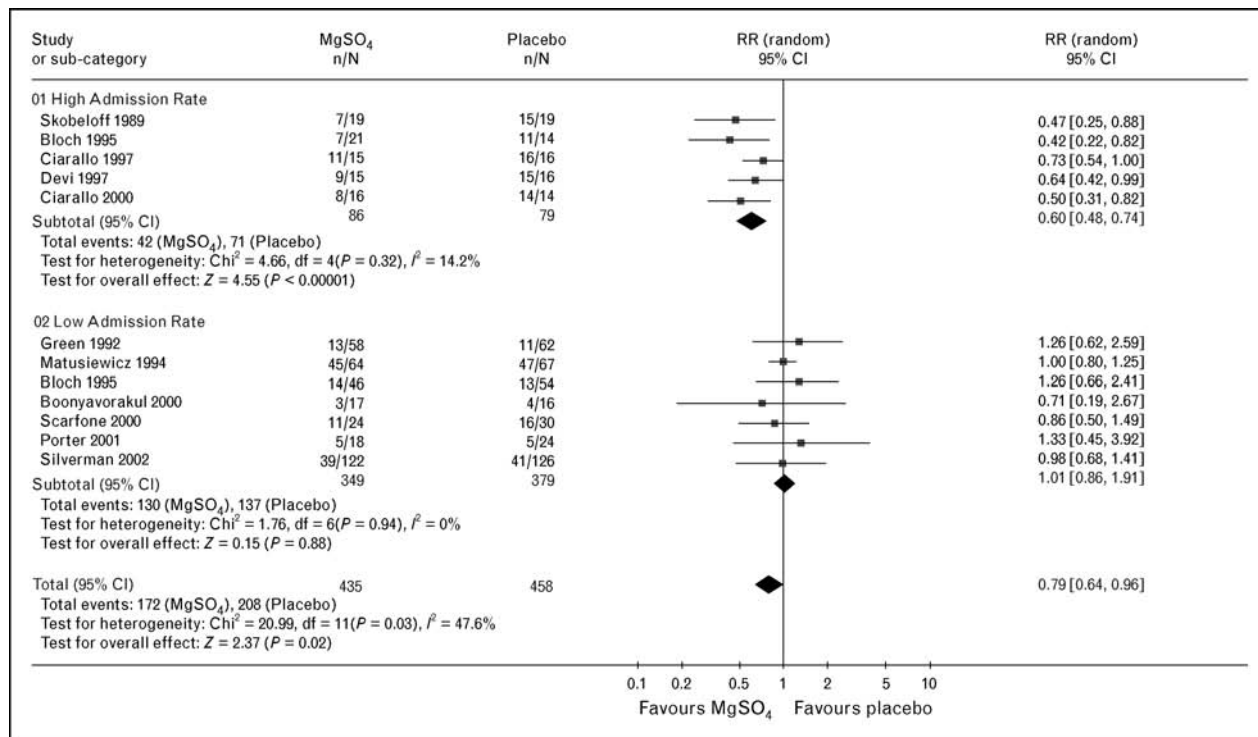
Children

The sub-group analysis in the Cochrane review suggested that children benefit from the use of intravenous MgSO₄ [21]. A separate systematic review that focused strictly on children shows a clear benefit in this age group [22]. In the latter review, which included five placebo-controlled trials involving a total of 182 patients, the authors concluded that the use of intravenous MgSO₄ reduced hospitalization (odds ratio, 0.29; 95% CI, 0.14–0.59) with congruent results in the pulmonary function outcomes. These results translate into a number needed to treat of four (95% CI, 3–8).

Do these results imply a different mechanism or more effectiveness for MgSO₄ in children than adults? While superficially this might be a conclusion, when examined closely, the pediatric studies all enrolled children with severe exacerbations, whereas the adult studies enrolled a more heterogeneous population of patients with mixed acute asthma severity [21]. In fact, the difference between the studies of adults with severe acute asthma and those of asthmatic children failed to reach statistical significance in the Cochrane review sub-group analysis.

Safety profile

Overall, adverse effects and side effects with this treatment were rare or minor, although these outcomes are poorly reported in most clinical trials. For example, in the Cochrane review, the agent did not significantly increase the incidence of hypotension, change pulse or respiratory rate or result in serious adverse events [21].

Figure 1 Reduction in hospital admissions with early administration of intravenous MgSO₄ compared with placebo in acute asthma

See [21] for details of the studies listed on the figure. 95% CI, 95% confidence interval; df, degrees of freedom; RR, relative risk. Adapted from [21].

Minor side effects, which appear to be self-limited, include flushing, pain at the intravenous site and fatigue. To illustrate the safety of this agent, higher doses have been administered for other diseases and in medical error and infrequently result in serious adverse effects.

While serious adverse effects are rare, they can occur, and magnesium supplementation can be problematic in some patients. As pointed out by Onishi and Yoshino [23^{*}], hypermagnesemia is a serious disorder that is difficult to diagnose. Hypermagnesemia is somewhat predictably observed in patients with abnormal renal function or small-bowel hypomotility. It should also be considered, however, in elderly patients presenting with a constellation of symptoms that mimic sepsis, cardiac ischemia, and/or other severe illnesses (e.g. hypotension, arrhythmia, hypo-reflexia, or respiratory depression); magnesium-containing cathartics or antacids should be used extremely carefully in elderly patients.

Dosing

Finally, this agent has been shown to be readily available, easy to use, and inexpensive. Overall, adult patients with clinically severe asthma, pulmonary function testing less than 30% predicted, and/or who exhibit a poor response to initial bronchodilator therapy appear to benefit most from intravenous MgSO₄ treatment. Currently, the recommended dose is 2 g administered intravenously over

20 min in adults, or 25–75 mg/kg up to 2 g in children. While continuous-drip MgSO₄ is not currently recommended, the evidence for its lack of benefit is restricted to a sub-group comparison in one trial [24].

Evidence on inhaled MgSO₄

The value of inhaled MgSO₄ in acute asthma can be explored by examining the effectiveness of this agent in comparison with traditional bronchodilators and also in addition to traditional bronchodilators.

Inhaled MgSO₄ compared with salbutamol

The Cochrane review on inhaled MgSO₄ included six trials involving 296 patients; four studies compared nebulized MgSO₄ with β_2 -agonist to nebulized β_2 -agonist alone, and two studies compared nebulized MgSO₄ with nebulized β_2 -agonist alone [25,26]. Three studies enrolled only adults and two enrolled children exclusively; three of the studies enrolled patients with severe exacerbations. There was no evidence of a significant advantage for MgSO₄ alone compared with β_2 -agonist alone with respect to pulmonary functions (standardized mean difference, 0.17; 95% CI, -0.51 to 0.86) in this review. Admission to hospital was only reported in one trial, and did not provide sufficient evidence to identify any benefit. Overall, the evidence accumulated here was not conclusive.

Inhaled MgSO₄ added to salbutamol

The Cochrane review found insufficient evidence to conclude that the addition of MgSO₄ to routine bronchodilator treatments improved outcomes in acute asthma. For example, nebulized MgSO₄ in combination with a β_2 -agonist failed to demonstrate a clear reduction in admission compared with β_2 -agonist alone (RR, 0.69; 95% CI, 0.42–1.12). Pulmonary function was improved when MgSO₄ with β_2 -agonist was compared with β_2 -agonist alone (standardized mean difference, 0.23; 95% CI, –0.03 to 0.50); however, there was considerable heterogeneity identified (I^2 , 53%). When a random effects model was used to pool these studies, the confidence intervals were considerably wider and nonsignificant (standardized mean difference, 0.27; 95% CI, –0.12 to 0.66).

A recent study by Aggarwal *et al.* [27**] has added new insight into the debate. This randomized controlled trial compared nebulized MgSO₄ and salbutamol with nebulized salbutamol alone in 100 patients presenting to the emergency department with acute asthma. All patients were classified as having severe or life-threatening asthma exacerbations and received up to three doses of MgSO₄; however, intravenous corticosteroids were not administered to all enrolled patients. This study failed to identify any spirometric [e.g. peak expiratory flow (PEF), percentage of predicted PEF], clinical (e.g. vital signs, admission) or laboratory (e.g. PCO₂, MgSO₄ levels) benefit of adding MgSO₄ to salbutamol nebulization in the treatment of patients with severe acute asthma. Combined with current evidence from the systematic review, most clinicians should continue to use the traditional approach of selecting the β_2 -agonist they are familiar with and not add MgSO₄ to this approach.

Dosing and safety

Why inhaled MgSO₄ failed to demonstrate effectiveness is unclear; however, it certainly does not appear to be related to dose of treatment, since a dose–response relationship does not appear to exist [28]. In addition, the role of adjunctive therapy may further limit the role of inhaled MgSO₄. For example, since almost all patients received aggressive management with systemic corticosteroids, it is unlikely these results were biased. Finally, considering the effectiveness of other inhaled agents in acute asthma, such as ipratropium bromide, the role of inhaled MgSO₄ in clinical management is likely even less important.

Oral MgSO₄ supplementation

Previous evidence suggested that supplemental magnesium as part of the chronic (long-term) management of asthma offers no improvement in asthma control [29]. This theory has recently been challenged in a randomized controlled trial of oral magnesium (300 mg/day) in

37 pediatric patients aged 7–19 years old. In addition to the magnesium supplementation, all children were treated with inhaled fluticasone and followed for 2 months [30**]. The authors concluded that oral magnesium supplementation reduced bronchial reactivity to methacholine, diminished allergen-induced skin responses, provided better symptom control and reduced exacerbations in pediatric patients with moderate persistent asthma.

In another study conducted in adults, this effect was not corroborated [31]. A randomized, placebo-controlled, double-blind parallel-group 16-week trial compared supplementation with 1 g/day vitamin C, 450 mg/day magnesium or matched placebo. Overall, 300 adults (18–60 years) with asthma controlled with daily inhaled corticosteroid were recruited from primary care practices in the UK. There was no evidence of any beneficial effect of either supplement on any outcome measure of asthma control (lung-function measures, airway responsiveness to methacholine, symptom scores and bronchodilator use) in the primary analysis, or when restricted to participants who completed the study.

The pediatric results appear robust and this trial certainly suggests that supplemental oral magnesium, or at least increased dietary intake of magnesium food sources (such as whole seeds, grains, nuts and vegetables), may prove an effective adjunctive therapy in asthma. Further research is required in different pediatric populations to confirm this finding and also larger studies in adults may be needed to determine whether this intervention has any merit.

Clinical applications

Only one large prospective cohort study has examined the use of intravenous MgSO₄ in clinical practice [32**]. From 9745 emergency department asthma visits across Canadian and US emergency departments, only 240 (2.5%; 95% CI, 2.2–2.8%) received intravenous MgSO₄. A logistic regression model identified several factors associated with MgSO₄ use (all $P < 0.05$): patient demographics (increasing age; female gender), US (as opposed to Canadian) site, past history (ever intubated; duration of symptoms < 24 h), asthma severity (higher initial respiratory rate; initial predicted PEF $< 50\%$; or PEF missing) and treatment (higher number of β -agonists during emergency department; corticosteroid use). Almost all of the factors would suggest that intravenous MgSO₄ is given to patients with more severe exacerbations.

In the same study, 87% of investigators from 119 different sites responded to a brief survey on asthma treatment with either intravenous or inhaled MgSO₄. Overall, 92% of respondents stated their emergency departments had MgSO₄ and used it for acute asthma; 64% had personally prescribed it in the preceding 6 months;

however, respondents reported that fewer intensive care units (39%) used MgSO₄ for acute asthma. Few emergency departments (4%) reported using this agent in a nebulized solution in acute asthma.

Most emergency department respondents appropriately listed severity (96%) and failure to respond to initial β -agonists (87%) as factors which would prompt their use of MgSO₄. Other factors such as age (11%), gender (1%) and duration of exacerbation (21%) were less commonly cited as factors influencing MgSO₄ use. Overall, 72% of respondents agreed or strongly agreed with the statement that MgSO₄ is beneficial in severe acute asthma.

Conclusion

A single dose of intravenous MgSO₄ administered to patients with severe acute asthma has been shown to be effective. According to several systematic reviews, this agent is most effective in the subpopulation of patients with severe exacerbations (defined as severe airflow limitation, a relative failure to respond to inhaled bronchodilators, and high risk of admission).

The role of nebulized MgSO₄ is less clear, with pooled analysis failing to provide clear evidence of benefit. Accumulating evidence indicates that adding nebulized MgSO₄ to salbutamol is ineffective in reducing admission

and achieving improved bronchodilation. In contrast with these findings for acute asthma, where magnesium treatments appear to be effective, long-term 'replacement' therapy with magnesium does not appear to be uniformly effective in chronic asthma.

The availability, cost and safety of magnesium treatment deserve emphasis. In brief, this agent is safe (no life-threatening side effects noted in any of the trials), inexpensive, and familiar to most physicians, at least in the intravenous format. Survey evidence suggests that many emergency physicians are familiar with this form of treatment and use it appropriately; that is, in the subset of patients with truly severe exacerbations. The use of inhaled MgSO₄ by any providers appears to be uncommon, at least in North America. The use of oral magnesium supplements is unknown.

Despite this evidence, national and international guidelines provide variable advice regarding the use of magnesium in acute asthma (Table 1 [4–6,33–36,37•]). The Global Initiative for Asthma [34], Canadian [4], and British [35] asthma guidelines do not recommend MgSO₄ for routine treatment; however, they do endorse its use in patients with severe asthma exacerbation not responding to treatment. The earlier National Asthma Education and Prevention Program (NAEPP) guidelines [6,36] did not provide clear recommendations regarding MgSO₄

Table 1 Current and previous asthma guideline recommendations for inhaled and intravenous MgSO₄ (as of August 2007)

Asthma guideline, year	Single-dose intravenous MgSO ₄		Inhaled MgSO ₄
	Adults	Children	
Canadian Thoracic Society (1999) [4] and (2001; updates) [5]	Intravenous MgSO ₄ (level I) may be useful in addition to usual therapy for refractory asthma	No mention	No mention
Canadian Thoracic Society (1996; original) [33]	No mention	No mention	No mention
GINA (2006 update) [34]	Intravenous MgSO ₄ is not recommended for routine use in asthma exacerbations, but can help reduce hospital admission rates in certain groups	Intravenous MgSO ₄ is recommended in children who fail to respond to initial treatment, and children whose FEV ₁ fails to improve above 60% predicted after 1 h of care. Intravenous MgSO ₄ has not been studied in children 5 years and younger	Nebulized salbutamol administered in isotonic MgSO ₄ provides greater benefit than if it is delivered in normal saline (Evidence A)
British Thoracic Society (2004; update) [35]	A single dose of intravenous MgSO ₄ has been shown to be effective in patients with acute severe asthma who have not had a good initial response to treatment	No mention	No mention
NAEPP (1997; original) [6] and (2003; update) [36]	No mention	No mention	No mention
NAEPP (2007) [37••]	Consider intravenous MgSO ₄ in patients who have life-threatening exacerbations and in those whose exacerbations remain in the severe category after 1 h of intensive conventional therapy (Evidence B)	Consider intravenous MgSO ₄ in patients who have life-threatening exacerbations and in those whose exacerbations remain in the severe category after 1 h of intensive conventional therapy (Evidence B)	Mentioned in the text; however, not recommended. Suggested further research is needed

FEV₁, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program.

administration; however, revisions to these guidelines were published in 2007 and reflect this new evidence [37^{••}]. Clearly, guidelines need to be updated to remain valid and physicians need to continue to receive education and review updates to remain current.

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References and recommended reading

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 85–86).

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This is an update of the US guidelines on the diagnosis and management of asthma.