Escalation in Therapy Based on Intravenous Magnesium Sulfate Dosing in Pediatric Patients With Asthma Exacerbations

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OBJECTIVE Our objective was to compare doses of intravenous magnesium sulfate and their association with escalations in therapy in children and adolescents presenting to the emergency department with an asthma exacerbation.

METHODS This was a retrospective cohort study among children who received both magnesium sulfate and standard of care therapy for asthma exacerbations. A classification and regression tree (CART) analysis was performed to identify a breakpoint in dose in which a difference in the primary outcome was present. The primary endpoint was need for escalation in therapy within 24 hours of initial magnesium sulfate dose, defined as need for invasive or non-invasive mechanical ventilation or need for adjunctive therapy, that is, epinephrine, terbutaline, aminophylline, theophylline, ketamine, heliox, or additional doses of magnesium sulfate.

RESULTS A total of 210 patients were included in the study. A CART analysis identified that a breakpoint of 27 mg/kg of magnesium was associated with a difference in the primary outcome of escalation in therapy in patients <40 kg. A subgroup analysis of patients <40 kg ($n = 149$) found patients who received magnesium doses >27 mg/kg had a higher incidence of the primary outcome of escalation in therapy, 15 patients (18.3%) versus 3 patients (4.5%) in the ≤ 27 -mg/kg/dose group ($p = 0.011$).

CONCLUSIONS Our results demonstrate larger doses of magnesium sulfate are associated with an increased need for invasive or non-invasive mechanical ventilation or need for adjunctive therapy(ies). Our findings are limited by confounding factors that may have influenced this outcome in our population.

ABBREVIATIONS CART, classification and regression tree; ED, emergency department; EMR, electronic medical record; IV, intravenous; NAEPP, The National Asthma Education and Prevention Program

KEYWORDS asthma; children; exacerbation; magnesium; pediatric; status asthmaticus

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Introduction

Asthma exacerbations present a significant burden to our health care system, affecting more than 7 million children currently living the United States.^{1,2} During an exacerbation, patients experience acute bronchoconstriction in response to a trigger or stimuli, as well as an increased neutrophil predominance and the presence of other inflammatory mediators.¹ Standards of care in the management of pediatric patients presenting to the emergency department (ED) include inhaled short-acting bronchodilators and systemic steroids. Despite these standardized therapies, asthma exacerbations remain a leading cause of hospital admission in the pediatric population, resulting in more than 400,000 hospitalizations annually in the United States.²

The National Asthma Education and Prevention Program (NAEPP) guidelines currently recommend intravenous magnesium sulfate as an adjunctive treatment in

the management of severe asthma exacerbations or in patients unresponsive to first-line therapies.¹ Although magnesium sulfate has been used in the management of patients with asthma for decades, the mechanism of action remains largely unknown.³ Several mechanisms have been proposed. The predominant theory is that magnesium enhances calcium uptake into the sarcoplasmic reticulum, resulting in direct bronchodilation. Other suggested mechanisms include enhancement of beta-agonist activity via regulation of adenylyl cyclase and sodium and potassium ATPase, inhibition of acetylcholine release at motor nerve terminals, and inhibition of histamine release from mast cells.^{3,4}

Magnesium sulfate presents an appealing therapeutic option as a bronchodilator that can be quickly administered in the emergent setting. This therapy has the potential to improve patient outcomes and reduce the burden of asthma on the health care system by reducing the frequency of hospitalization and the need

for intubation. There is little information regarding a preferred dosing regimen, particularly in pediatric patients.^{1,5} The NAEPP guidelines reference literature that supports a 25 to 75 mg/kg dose of magnesium sulfate as adjunctive treatment in the management of severe asthma exacerbations.¹ However, recent pharmacokinetic data suggest that doses at the upper end of that range are necessary to achieve serum concentrations in a proposed target range of 25 to 40 mg/L.⁶

The role of magnesium sulfate in patients with asthma was first described in the late 1980s in a study of 10 adults with mild asthma exacerbations.⁷ In this pilot study, authors found intravenous magnesium sulfate was associated with improved markers of respiratory function and demonstrated a dose-dependent effect on relief of bronchostriction.⁷ Subsequent randomized controlled trials confirmed the clinical benefit of magnesium sulfate in adult patients with asthma exacerbations, demonstrating significant improvement in rates of discharge from the ED and markers of respiratory function.⁸ Pediatric literature has supported these findings, with a statistically significant reduction in hospital admission reported by several meta-analyses performed since 2016.^{5,9,10}

Given the paucity of data regarding a preferred dosing regimen for pediatric patients, the objective of our study was to compare doses of intravenous magnesium sulfate and their association with escalations in therapy in children and adolescents presenting to the ED with an asthma exacerbation.

Methods

Study Design, Study Population, and Data Source.

We conducted a retrospective cohort study of pediatric patients admitted to the ED at a large academic hospital between July 1, 2011, and July 1, 2017. We identified children 2 years to 18 years of age who presented to the ED and were given standard of care treatment for an acute asthma exacerbation (i.e., albuterol, ipratropium, and systemic corticosteroids) plus a dose of intravenous magnesium sulfate. In our ED there is no standardized protocol for the management of asthma exacerbations and no standardized dose of magnesium sulfate. Management of patients, including use and dosing of magnesium sulfate, is at the discretion of the treating physician. We excluded patients with a diagnosis of bronchiolitis or croup. Data were collected by using an electronic data collection form via electronic data extraction and manual review of the electronic medical record (EMR).

Exposure. For our primary analysis, classification and regression tree analysis (CART) was used to identify the dose of magnesium sulfate associated with an escalation of therapy. Escalation in therapy was defined as 1) need for adjunct therapy (i.e., epinephrine, terbutaline, aminophylline, theophylline, ketamine, heliox); 2) an additional dose of intravenous magnesium sulfate; 3) need

for high-flow nasal cannula; or 4) need for mechanical ventilation (invasive or non-invasive) within 24 hours of magnesium sulfate administration in the ED. Vital sign measurements including blood pressure, heart rate, respiratory rate, and oxygen saturation were collected at time of admission, immediately prior to, and immediately post magnesium administration.

Outcomes. The presence or absence of escalation in therapy was determined from the criteria defined above. Disposition was collected and categorized into discharge from the ED, admission to a general care unit, and admission to the intensive care unit.

Covariates. Demographic data, such as age, sex, race, and weight, were collected from the EMR. To account for variation in the severity of exacerbation, a modified pediatric asthma score was used based on oxygen requirement and respiratory rate upon admission. Because physical examination data were inconsistently documented in the EMR, we were unable to include additional objective criteria (e.g., the presence of retractions, dyspnea/air movement, or wheezing upon presentation) in the score. The use of continuous albuterol, intravenous steroids, and oxygen saturation upon admission was also collected as potential covariates.

Statistical Analysis. Baseline characteristics of patients with or without subsequent escalation in therapy were compared by using the Wilcoxon rank sum test for continuous variables and the χ^2 tests for categorical variables. Baseline characteristics were also compared across the magnesium therapy groups, based on the CART analysis. We performed multiple logistic regression to test the association between escalation in therapy within 24 hours of magnesium administration in the ED. The association between covariates and escalation in therapy was first evaluated by using univariate analysis. The final multivariable model was constructed, including results from the CART analysis, along with other covariates if p value < 0.2 from the univariate model. A p value < 0.05 was considered significant, and all p values were 2-sided. All analyses were performed by using Stata, version 13.1 (StataCorp LLC, College Station, TX).

Results

During our study period, 211 pediatric patients received intravenous magnesium sulfate, in addition to standard of care therapies, for the management of asthma in the ED. One patient was excluded owing to a diagnosis of bronchiolitis. In patients <40 kg, CART analysis identified that a magnesium sulfate dose larger than 27 mg/kg was associated with an increase in the primary outcome. No association was identified for patients ≥ 40 kg.

Based on the CART analysis findings, a subgroup analysis was performed among patients <40 kg comparing those who received magnesium sulfate doses

Table 1. Baseline Characteristics of Patients <40 kg

Characteristic	Magnesium Dose		p value
	≤27 mg/kg (n = 67)	>27 mg/kg (n = 82)	
Male, n (%)	41 (61.2)	51 (62.2)	0.900
Age, mo, median (IQR)	65 (44–87)	66.5 (45–84)	0.938
Weight, kg, median (IQR)	18.6 (15.1–25.5)	19.2 (15–26.2)	0.994
Race, n (%)			
Caucasian	19 (28.4)	27 (32.9)	0.548
African American	42 (62.7)	48 (58.5)	0.606
Asian	0 (0)	1 (1.2)	1.000
American Indian or Alaskan Native	0 (0)	1 (1.2)	1.000
Other	6 (9.0)	4 (4.9)	0.346
Unknown	0 (0)	1 (1.2)	1.000
Ethnicity, n (%)			
Non-Hispanic or Latino	61 (91.0)	71 (86.6)	0.394
Magnesium dose, mg/kg, median (IQR)	25 (25–25.1)	50 (41.7–50)	<0.001

≤27 mg/kg (IQR, 25–25.1 mg/kg; n = 67) to patients who received doses >27 mg/kg (IQR, 41.7–50 mg/kg; n = 82). Baseline characteristics were similar between the 2 groups (Table 1). Patients who received doses >27 mg/kg had a significantly higher incidence of the primary outcome of escalation in therapy than patients who received smaller doses, 15 patients (18.3%) versus 3 patients (4.5%), respectively, $p = 0.011$. Among patients who received doses >27 mg/kg, escalations in therapy included high-flow nasal cannula (n = 4), non-invasive mechanical ventilation (n = 4), invasive mechanical ventilation (n = 2), and use of adjunctive medications. Among patients who received doses ≤27 mg/kg, escalations in therapy included high-flow nasal cannula (n = 1) and adjunctive medication use (n = 3). The most

common adjunctive medications used in the 24 hours following initial magnesium sulfate administration were terbutaline, epinephrine, and additional doses of magnesium sulfate (Table 2).

Univariate analysis did not find any additional variables to be independently associated with escalation in therapy (Table 3). Thus, a diagnosis of status asthmaticus was included in the multivariate logistic regression owing to its clinical significance as a marker of physician-perceived illness severity. The results of our multivariate logistic regression analysis are included in Table 4. A magnesium sulfate dose >27 mg/kg was associated with an increase in odds of escalation in therapy (OR 4.4; 95% CI, 1.2–16.1; $p = 0.025$) while controlling for a diagnosis of status asthmaticus (OR 1.9; 95% CI, 0.7–5.4; $p = 0.204$).

Table 2. Escalation in Therapy Between Magnesium Groups

Escalation in Therapy	Magnesium Dose		p value
	≤27 mg/kg (n = 67)	>27 mg/kg (n = 82)	
Use of escalation therapy, n (%)	3 (4.5)	15 (18.3)	0.011
Specific therapy, n (%)			
High-flow nasal cannula	1 (1.5)	4 (4.9)	0.379
Mechanical ventilation	0 (0)	4 (4.9)	0.128
Invasive ventilation	0 (0)	2 (2.4)	0.502
Adjunctive therapies			
Epinephrine	0 (0)	3 (3.7)	0.253
Terbutaline	1 (1.5)	8 (9.8)	0.042
Aminophylline/theophylline	0 (0)	0 (0)	—
Ketamine	0 (0)	0 (0)	—
Heliox	0 (0)	0 (0)	—
Additional magnesium	2 (3.0)	6 (7.3)	0.296

Table 3. Univariate Analysis of Variables Associated With Escalation in Therapy

Variable	Escalation in Therapy (n = 18)	No Escalation in Therapy (n = 130)	OR (95% CI)	p value
Diagnosis of status asthmaticus, n (%)	9 (50.0)	40 (30.5)	2.3 (0.8–6.2)	0.106
Male sex, n (%)	14 (77.8)	78 (59.5)	0.4 (0.1–1.4)	0.145
Continuous albuterol, n (%)	11 (61.1)	86 (65.7)	0.8 (0.3–2.3)	0.705
Intravenous steroid administration, n (%)	17 (94.4)	91 (69.5)	7.5 (0.9–58.1)	0.055
Oxygen saturation, %, median (IQR)	95.5 (90–100)	95 (90–97)	0.9 (0.9–1.1)	0.878
Pediatric Asthma Score, n (%)				
O ₂ saturation,* n (%)				
1	11 (61.1)	96 (73.3)	Reference [†]	—
2	4 (22.2)	27 (20.6)	1.3 (0.4–4.4)	0.680
3	3 (16.7)	8 (6.1)	3.3 (0.8–14.2)	0.113
RR, [‡] bpm, n (%)				
1	3 (16.7)	35 (26.7)	Reference [†]	—
2	5 (27.8)	14 (10.7)	4.2 (0.9–19.8)	0.073
3	10 (55.6)	82 (62.6)	1.4 (0.4–5.5)	0.609

bpm, breaths per minute; RR, respiratory rate

* Oxygen saturation categorized as 1 for >90% in room air; 2 for 85% to 90% in room air, and 3 for <85% in room air.

[†] The score of 1 served as a reference for the O₂ saturation and respiratory rate, the OR for scores of 2 or 3 are compared to the reference.

[‡] RR categorized as 1 for patients 2 to 3 years of age with RR ≤34, 4 to 5 years of age with RR ≤30, 6 to 12 years of age with RR ≤26, and >12 years of age with ≤23; RR categorized as 2 for patients 2 to 3 years of age with RR of 35–39, 4 to 5 years of age with RR 31–35, 6 to 12 years of age with RR 27–30, and >12 years of age with RR 24–27; RR categorized as 3 for patients 2 to 3 years of age with RR ≥40, 4 to 5 years of age with RR ≥36, 6 to 12 years of age with RR ≥31, and >12 years of age with RR ≥28.

In our study population, 61.7% of patients were admitted to the intensive care unit, 34.2% of patients were admitted to a general care unit, and 4% of patients were discharged from the ED. No significant differences in disposition were found between groups ($p = 0.696$). The median length of stay was 2 days in both groups.

Among all patients included in our study, 19 patients experienced a decrease in systolic blood pressure (>20%) following magnesium administration, and 63 patients experienced a decrease in diastolic blood pressure (>20%). No blood pressure readings meeting the criteria for clinically significant hypotension were documented following magnesium administration in our population.

Discussion

Our study results demonstrate that patients who received larger doses of magnesium sulfate required more aggressive subsequent management as evidenced by the increased incidence of escalation in therapy. Given the retrospective nature of our study and lack of randomization, we suspect that patients with more severe exacerbations were preferentially prescribed larger doses of magnesium sulfate and required more robust escalations in therapy, based on their overall acuity. Our ability to account for this potential confounder was limited by the lack of standardized asthma scoring in our ED. We attempted to account for

this in the univariate analysis, assessing the effect of several surrogate markers of exacerbation severity, but did not find any factor to be independently associated with our primary outcome (Table 3).

Rower et al⁶ recently performed a retrospective pharmacokinetic analysis of intravenous magnesium sulfate in 54 children treated for asthma exacerbations. They hypothesized a therapeutic target serum concentration of 25 to 40 mg/L for the management of asthma. This target was determined on the basis of a reference physiologic concentration of 16 to 23 mg/L at their institution, and previously published toxicity associated with concentrations greater than 48 mg/L. Results of the analysis demonstrated doses between 50 and 75 mg/kg are required to achieve concentration-time profiles within the proposed therapeutic range.

The benefit of a high-dose magnesium sulfate regimen in pediatric asthma exacerbations was further supported by Irazuzta et al¹¹ in a randomized controlled trial. Authors compared a standard dose regimen of 50 mg/kg IV bolus administered over a 60-minute period to a high-dose regimen of 200 mg/kg IV administered over 4 hours by continuous infusion in 38 children with non-infectious asthma exacerbations. Results demonstrated a statistically significant improvement in rates of discharge from the ED in the high-dose group, 9/19 patients (47%), versus 2/21 patients (10%) in the bolus group, $p = 0.032$.

Table 4. Multivariate Logistic Regression of Escalation in Therapy

Variable	Adjusted OR	OR (95% CI)	p value
>27 mg/kg as determined by CART analysis	4.4	(1.2–6.1)	0.025
Diagnosis of status asthmaticus in ED	1.9	(0.7–5.4)	0.204

CART, classification and regression tree; ED, emergency department

Weight-based doses of intravenous magnesium sulfate varied significantly in our population. However, doses prescribed were within the previously studied range referenced in the NAEPP guidelines and Pediatric and Neonatal Dosage Handbook.^{1,12} A retrospective review of magnesium sulfate use in 4 US pediatric hospitals demonstrated similar variability.³ While the rationale for prescribed doses could not be deduced in our retrospective analysis, prescriber practice, severity of illness, and patient specific factors are all likely to contribute. At our institution, clinical support systems integrated into the EMR include suggested dosing buttons when an order for intravenous magnesium sulfate is initiated for a pediatric patient, which vary by age-based contexts. Previously published literature has demonstrated a significant impact of dose selection menus on prescribing patterns, suggesting this may have further influenced prescribing practices in our population.¹³

In our population, adjunctive medications used in the first 24 hours following initial magnesium sulfate administration included terbutaline and epinephrine. It is notable that 2 patients (3%) in the lower dosing group and 8 patients (9.8%) in the higher dosing group received additional doses of magnesium sulfate in the first 24 hours. Owing to the retrospective nature of this study, we cannot deduce what specific factors influenced the decision to prescribe additional magnesium sulfate; our results suggest prescribers expected added clinical benefit from additional doses. This raises the question of whether patients with severe exacerbations could have benefited from larger initial doses.

Previous studies have evaluated the safety of magnesium sulfate in pediatric patients with asthma, with hypermagnesemia and hypotension as the primary safety concerns. Use for this indication has proven to have a favorable safety profile, with no reports of clinically significant hypermagnesemia to our knowledge at doses discussed in this article, and the very rare occurrence of clinically significant hypotension.^{3,14,15} In our population, a number of patients experienced a decrease in systolic or diastolic blood pressure greater than 20% following magnesium administration. No patients were found to have a blood pressure reading defined as clinically significant hypotension.

Additional limitations to the findings of our study include the small, retrospective nature of our study design and limited number of doses at the upper limit of the recommended range prescribed at our institution.

Conclusions

Our results demonstrate that patients who received weight-based magnesium doses >27 mg/kg had a higher incidence of escalation in therapy, likely due to preferential prescribing of larger doses to patients with more severe exacerbations. While there was a large range of doses prescribed to patients in our population, recent literature has supported the necessity of larger doses to achieve therapeutic efficacy.^{6,11} Larger, prospective trials are needed to determine the optimal dosing regimen of intravenous magnesium sulfate in pediatric patients with asthma exacerbations.

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