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Early versus delayed administration of intravenous magnesium sulfate for pediatric asthma

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ABSTRACT

Objective: This study aims to describe and examine the factors associated with the early administration of intravenous magnesium sulfate (IV Mg) in children presenting to the pediatric emergency department (ED) for an asthma exacerbation.

Methods: Retrospective cohort study of children aged 5–11 years who received IV Mg in the pediatric ED between September 1, 2018 and August 31, 2019 for management of an asthma exacerbation. Primary outcome was administration of IV Mg in ≤60 min from ED triage ('early administration'). Comparison of clinical management and therapies in children who received early versus delayed IV Mg and the factors associated with early administration of IV Mg were examined.

Results: Early (n = 90; 31.6%) IV Mg was associated with more timely bronchodilators (47 versus 68 min; $p \leq 0.001$) and systemic corticosteroids (36 versus 46.5 min; $p \leq 0.001$). There was no difference between the two cohorts in returns to the ED within 72 h (1.1% versus 2.1%; p = .99) or readmissions within 1 week one week (2.2% versus 0.5%; p = .2). Hypoxia (aOR = 3.76; 95% CI = 2.02–7.1), respiratory rate (aOR = 1.04; 95% CI = 1.02–1.07), retractions (aOR = 2.21; 95% CI = 1.25–3.94), and prior hospital use for asthma-related complaints (aOR = 2.1; 95% CI = 1.16–3.84) were significantly associated with early IV Mg.

Conclusions: Early administration of IV Mg was associated with more timely delivery of first-line asthma therapies, was safe, and improved ED throughput without increasing return ED visits or hospitalizations for asthma.

1. Introduction

Asthma affects approximately seven million children under the age of eighteen in the United States [1]. Over one-half of children in the United States with asthma experience one or more asthma exacerbations annually [1]; thus, asthma is a common reason for unscheduled health care visits. At a substantial cost to the healthcare system, over 750,000 children seek emergency department (ED) care, and approximately 70,000 children are hospitalized each year for asthma [2-4].

Inhaled bronchodilators and systemic corticosteroids are the cornerstones of acute asthma therapy [5]. Standard therapies may be insufficient, and adjuvant therapies such as intravenous magnesium sulfate (IV Mg) may be administered in the ED. [6] Prior work suggests that administering IV Mg in the ED is safe, cost-effective, improves pulmonary function, and reduces the need for hospitalization in pediatric patients with a moderate-to-severe asthma exacerbation [7-15]. Despite the proposed benefits, few pediatric patients receive IV Mg in the ED, and only 7% of clinicians report prescribing this therapy [15-17]. As ED visits and hospitalizations for asthma remain stable with a continued burden on families and the healthcare system [2,3], an improved approach to ED asthma management is needed to mitigate the morbidity and mortality associated with acute exacerbations [1].

Asthma management in the ED is time-sensitive, with quality care defined as providing standard therapies within 60 min of ED triage [5,18]. Triage systems, clinical respiratory scores, and oxygen saturation measures are commonly used to identify and prioritize high-acuity

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; ESI, emergency severity index; IQR, interquartile range; IV Mg, intravenous magnesium sulfate; PEM, pediatric emergency medicine; PICU, pediatric intensive care unit.

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patients who are at risk for clinical decompensation and may require immediate intervention [5]. Abnormalities in these metrics denote a moderate-to-severe asthma exacerbation and provide valuable information to support decision-making related to ED management and disposition [5]. IV MG is commonly reserved until initial therapies have proven to be ineffective [5-15]. However, ED disposition decisions are often reached within four hours of triage [5]. Early administration of IV Mg in conjunction with first-line asthma therapies may therefore help to quickly optimize the patient's respiratory status and prevent hospitalizations. However, few clinicians prescribe IV Mg as a first-line therapy, with a nationally reported median time-to-administration of over two hours post-triage [15].

This study aims to describe and examine the factors associated with the early administration of IV Mg (≤ 60 min) in children presenting to the pediatric ED for an asthma exacerbation. Secondary aims were to examine administrative and clinical outcomes between patients prescribed 'early' versus 'delayed' IV Mg, including ED and hospital length of stay, critical care admissions, and the provision of respiratory support and adjuvant medical therapies.

2. Methods

2.1. Study design, sample and setting

Following ethics approval from our institutional review board, this retrospective cohort study was conducted at an academic, urban, free-standing children's hospital. Our children's hospital sees approximately 85,000 pediatric ED visits and 10,000 inpatient admissions annually. Data were extracted from the electronic medical record on patients identified through a pharmacy billing query who received IV Mg in the pediatric ED between September 1, 2018 and August 31, 2019.

Children between five and eleven years of age who presented to the ED for an asthma exacerbation and received IV Mg were eligible for study inclusion. This age range was selected to (1) exclude preschool-aged children in whom viral-induced wheeze is common, yet IV Mg is ineffective [19], and (2) reflect the pediatric population where asthma morbidity is greatest but reluctance to start an IV might exist [1]. An asthma exacerbation was determined based on the presence of two criteria. First, bronchodilator therapy needed to be administered in the pediatric ED for a respiratory-related chief complaint (i.e., cough, wheeze, difficulty breathing). Second, the final disposition diagnosis by the ED provider needed to be consistent with an acute asthma exacerbation (i.e., asthma exacerbation, status asthmaticus).

Patients were excluded from our study if they had a co-morbid systemic disease (e.g. congenital heart disease), they were transferred from an outside facility, or they were discharged home from the pediatric ED. The decision to exclude patients discharged from the ED was based on our prior retrospective work related to ED asthma therapy, where it was noted during data collection that IV Mg was not administered to any patients discharged home following ED management for acute asthma [20].

2.2. Variables and outcome measurement

Data from the electronic medical record of eligible patients were reviewed and abstracted by trained medical research assistants. Data were collected using a standardized electronic tool and managed using REDCap [21]. In addition to patient characteristics we collected data on asthma specific interventions and clinical management during the index pediatric ED visit. To parallel the reporting of asthma related quality metrics in the United States, all time-sensitive therapies were documented from the time of ED triage [18].

Our primary outcome was the administration of IV Mg in ≤60 min for children in the pediatric ED after triage. Cases where IV Mg was administered within one hour of ED triage were classified as 'early administration', and cases that exceeded the one-hour mark were classified as 'delayed administration'. Predictors of early IV Mg administration, and potential confounders, were selected based on the prior literature and the clinical expertise of the research team [5,15-17]. Predictors of interest included age, oxygen saturation, respiratory rate, retractions, albuterol use prior to presenting to the pediatric ED, and previous asthma-related acute care use (defined as an ED visit or hospitalization in the year prior to the index ED visit). Both oxygen saturation and respiratory rate were measured during the triage process, with oxygen saturation measured as a percentage and respiratory rate measured as breaths per minute. Triage acuity was measured using the five-item Emergency Severity Index (ESI) [22]. We elected to trichotomize this variable for lack of variance (i.e., most patients received an ESI of two or three), and classified patients as emergent (ESI 1 or 2), urgent (ESI 3), or non-urgent (ESI 4 or 5). Finally, we defined 'intensive ED therapy' in keeping with prior work as three bronchodilator treatments with albuterol and ipratropium bromide and a systemic corticosteroid administered within 60 min of ED triage [16].

2.3. Data analysis

Descriptive statistics were reported using general measures of frequency and central tendency. A series of chi-square, Fisher's exact and Mann-Whitney *U* tests were conducted to provide an unadjusted comparison of clinical management and therapies in children who received early versus delayed IV Mg. Binary logistic regression was conducted to examine the factors associated with early administration of IV Mg in the pediatric ED while adjusting for relevant patient and clinical factors. Model fit was examined using the Hosmer-Lemeshow Goodness-of-Fit test. Data were screened for the presence and pattern of missingness; no missing data were found. Analyses were performed using the *'stats'* package in R version 4.0.

3. Results

A total of 285 children visited our pediatric ED for an asthma exacerbation and were treated with IV Mg. The median age of the sample was seven years (interquartile range [IQR] = 3). The majority of children were male (63.9%) and African-American (84.9%). An emergent triage score was given to 87.7% of children, though only 10.2% required a critical care admission. In the prior year, 51.2% of children visited an ED for an asthma-related complaint and 35.8% required hospitalization. Table 1 displays a comprehensive overview of patient and visit characteristics.

3.1. Unadjusted analyses

Table 2 provides the unadjusted comparison of clinical management and therapies between children who received early ($n = 90$; 31.6%) versus delayed ($n = 195$; 68.4%) IV Mg. The median time to IV Mg administration in the early administration group was 37 min versus 130 min for the delayed group. Children in the early administration group received three bronchodilator treatments in fewer minutes than children who received a delayed dose (47 versus 68; $p \leq 0.001$). Children who received an early dose of IV Mg also waited fewer minutes to receive a systemic corticosteroid (36 versus 46.5; $p \leq 0.001$) and were more likely to receive intensive ED therapy (66.7% versus 32.8%; $p \leq 0.001$). Children who received a delayed dose of IV Mg were less likely to receive adjuvant asthma medications (3.1% versus 28.9%; $p \leq 0.001$) or respiratory support in the ED (39.0% versus 53.3%; $p = .03$).

During hospitalization, children who received an early dose of IV Mg were more likely to require respiratory support during inpatient care (62.2% versus 44.1%; $p = .005$) and require transfer to the pediatric intensive care unit (14.4% versus 5.1%; $p = .01$). There was no difference in the proportion of children returning to the ED within 72 h (1.1% versus 2.1%; $p = .99$) or being readmitted within one week of discharge for asthma between the two cohorts (2.2% versus 0.5%; $p = .2$).

Table 1
Patient and visit characteristics ($N = 285$).

Variable	N (%)
Age[a]	7(3)
Sex (Male)	182 (63.9)
Race	
African-American	243 (85.3)
Caucasian	6 (2.1)
Other	36 (12.6)
Asthma History	
Home bronchodilator	242 (84.9)
Home inhaled corticosteroid	114 (40)
Home oral corticosteroid	8 (2.8)
ED visit in the past year for asthma	146 (51.2)
Hospitalized in the past year for asthma	102 (35.8)
Previous PICU admission for asthma	74 (26)
Triage Acuity[b]	
Emergent	250 (87.7)
Urgent	34 (11.9)
Non-urgent	1 (0.4)
Primary Emergency Provider	
PEM Physician	253 (88.8)
Pediatrician	26 (9.1)
Advanced practice provider[c]	6 (2.1)
Triage Oxygen Saturation[a]	94 (5)
Triage Respiratory Rate[a]	36 (10)
Severe Presentation[d]	250 (87.7)
ED Disposition	
Observation unit	100 (35.1)
Inpatient floor	156 (54.7)
PICU	29 (10.2)

ED = emergency department; PEM = pediatric emergency medicine; PICU = pediatric intensive care unit.
[a] Data reported as median and interquartile range.
[b] Triage acuity was measured using the Emergency Severity Index (ESI) [22]. Emergent = 1 or 2; Urgent = 3; Non-Urgent = 4 or 5.
[c] Advanced practice provider included nurse practitioners and physician assistants.
[d] Severe presentation defined as presenting to triage with an oxygen saturation of < 90% or the assignment of an emergent ESI score [15].

3.2. Adjusted analyses

Table 3 displays the results of the binary logistic regression model. Our multivariable model determined that hypoxia, respiratory rate, retractions, and prior hospital use for asthma-related complaints were significantly associated with the provision of IV Mg within one hour of triage. Children with a pulse oximetry reading of less than 92% had approximately four times the odds of receiving an early dose of IV Mg (aOR = 3.76; 95% CI = 2.02–7.1). For every increase in breath per minute, there was a 4% increase in the odds of receiving an early dose of IV Mg (aOR = 1.04; 95% CI = 1.02–1.07). Children who presented to ED triage with retractions (aOR = 2.21; 95% CI = 1.25–3.94) and those with prior asthma-related hospital use (aOR = 2.1; 95% CI = 1.16–3.84) had approximately twice the odds of receiving an early dose of IV Mg. Our multivariable model had a good fit per the Hosmer-Lemeshow goodness-of-fit test ($p > .05$), and our event-per-variable was greater than 10, increasing the reliability of findings [23].

4. Discussion

To our knowledge, this is the first study to evaluate the timing of IV Mg in the ED management of pediatric asthma. Approximately one-third of patients received IV Mg within 60 min of triage, and early administration was associated with clinical and historical markers of a severe asthma exacerbation. Notably, early administration of IV Mg was associated with more timely delivery of first-line asthma therapies. Concurrent administration of IV Mg with bronchodilators and systemic corticosteroids was safe, and improved ED throughput without increasing return ED visits or hospitalizations for asthma.

Prior reviews and meta-analyses have demonstrated that IV Mg is safe and effective in the ED management of pediatric asthma [7-15]. Consequently, previous authors have commented that IV Mg should be standard in patients who fail to respond to initial therapy [10,12].

Table 2
Bivariable analysis of clinical management between early and delayed administration of intravenous magnesium sulfate (IV Mg).

Variable	Early Dose of IV Mg (n = 90)	Delayed Dose of IV Mg ($n = 195$)	p
Pre-hospital bronchodilator administered	73 (81.1)	152 (77.9)	0.65
Number of bronchodilator treatments			0.63
< 2	4 (4.4)	10 (5.1)	
≥ 3	86 (95.6)	185 (94.9)	
Time to administration of three bronchodilator treatments (minutes)[a]	47 (15.8)	68 (42.5)	< 0.001
Time to IV Mg Administration (minutes)[a]	37 (18.6)	130 (98)	< 0.001
Hypotension Experienced	3 (3.3)	3 (1.5)	0.38
Normal Saline Bolus Administered	79 (87.8)	165 (84.6)	0.6
Administration of systemic corticosteroid			< 0.001
Oral	71 (78.9)	183 (93.8)	
Intravenous	19 (21.1)	4 (2.1)	
No Steroid Given	0 (0)	8 (4.1)	
Time to Administration of Systemic Corticosteroid (minutes)[a]	36 (51)	46.5 (23.5)	< 0.001
Intensive ED therapy[b]	60 (66.7)	64 (32.8)	< 0.001
Adjuvant asthma medications administered in the ED			
Epinephrine	24 (26.7)	6 (3.1)	< 0.001
Intravenous Bronchodilator	2 (2.2)	0 (0)	0.32
None	64 (71.1)	189 (96.9)	< 0.001
Respiratory support in the ED	48 (53.3)	76 (39)	0.03
Adjuvant asthma medications administered during hospitalization			
None	68 (75.6)	164 (84.1)	0.06
Epinephrine	1 (1.1)	4 (2)	0.94
Additional IV Mg	14 (15.6)	20 (10.3)	0.24
Other	7 (7.7)	7 (3.6)	0.04
Respiratory support needed during hospitalization	56 (62.2)	86 (44.1)	0.005
Transfer to the PICU during hospitalization	13 (14.4)	10 (5.1)	0.01
ED Length of Stay (minutes)[a]	218 (121)	260 (117.5)	< 0.001
Hospital Length of Stay (hours)[a]	13.5 (10.6)	13.3 (10.2)	0.52

ED = emergency department; IV Mg = intravenous magnesium sulfate; PICU = pediatric intensive care unit.
[a] Data reported as median and interquartile range.
[b] Intensive ED therapy defined as three bronchodilator treatments with albuterol and ipratropium bromide and a systemic corticosteroid administered within 60 min of ED triage [16].

Table 3
Multivariable analysis of associations with early administration of intravenous magnesium sulphate.

Variable	Early Administration of Intravenous Magnesium Sulfate aOR (95% CI)
Intercept	0.02 (0.001–0.07)
Age (> 6 years)	1.33 (0.95–1.27)
Hypoxia (pulse oximetry <92%)	3.76 (2.02–7.1)
Respiratory rate	1.04 (1.02–1.07)
Retractions	2.21 (1.25–3.94)
Albuterol administered prior to ED visit	1.34 (0.65–2.87)
Prior asthma-related hospital use	2.1 (1.16–3.84)
Hosmer & Lemeshow Goodness of Fit	$X^2 = 11.8$; $p = .16$

ED = emergency department; aOR = Adjusted Odds Ratio; CI = Confidence Interval.

However, this is not common practice, as only 10.5% of children received IV Mg during their pediatric ED visit for asthma [15]. Despite its infrequent use, most emergency providers agree that IV Mg is beneficial in severe asthma, generally prescribed to prevent an intensive care admission [17]. As a result, the use of IV Mg is predicted by the severity of disease exacerbation upon ED presentation and historical markers of asthma severity, including hospitalization within the past 12 months, previous intensive care unit admission, and current oral corticosteroid use [17]. The benefit of IV Mg, however, is not in preventing the need for critical care but in reducing hospitalizations by 30% [10].

To this end, early administration of IV Mg in conjunction with first-line asthma therapies may mitigate the risk of hospitalization by expediting the time to clinical improvement and safe discharge home. Nationally, only 18.6% of patients were given IV Mg within 60 min of triage, suggesting that discharge home is however not the primary endpoint [15]. In our cohort, all patients were hospitalized but those who received IV Mg early in their ED management pathway also not features of a severe asthma exacerbation. Moreover, the variables associated with the early use of IV Mg in our analysis are also associated with hospitalization; thus, early administration of IV Mg to patients in our cohort was likely directed by disease severity and not the anticipated discharge disposition.

Pediatric patients with severe asthma are most likely to benefit from early and aggressive clinical intervention in the ED setting [5]. In our cohort, patients who received IV Mg early during their ED course were also more likely to receive timely intensive ED therapy. Intensive therapy, previously defined as including albuterol, ipratropium bromide, and systemic corticosteroids within 60 min of triage, was used in 20% to 63% of patients in a multicenter study of Canadian EDs [16]. In our cohort, only 44% of patients received intensive therapy in conjunction with IV Mg. Yet, early IV Mg administration had the unintended benefit of providing 68.9% of patients in this group other evidence-based asthma interventions in a timely manner. Suboptimal use of evidence-based asthma therapies limits our conclusions regarding the role of IV Mg as a concurrent or adjunctive therapy, both in our study and the published literature, where ipratropium bromide is infrequently included as a co-intervention [15]. Thus, future prospective studies examining the utility of IV Mg should consider including intensive therapies as the standard of care to facilitate valid estimates and replicable findings.

The body of literature related to the use of IV Mg in pediatric asthma continues to evolve, and there is currently only low certainty evidence for IV Mg dosing, side effects, and clinical outcomes. A dose between 25 and 75 mg/kg is often used clinically, but the optimal dose remains unknown [5,15]. In a small prospective study of children treated with IV Mg for acute asthma, 50 mg/kg was noted to be safe, though a higher dose may be needed to mitigate the risk of hospitalization [13]. As the median dose in our overall cohort aligned with this study, the clinical impact of the timing of IV Mg administration may be underestimated.

Hypotension, apnea, and heart block are IV Mg related side effects, though at 50 mg/kg, few adverse effects were noted [13]. Hypotension is the most commonly reported side effect of IV Mg, noted in 7.6% of ED encounters where IV Mg was administered [15]. In our cohort, hypotension was uncommon and did not differ with the timing of IV Mg administration, though this may be related to low statistical power. The majority of patients in our cohort also received a normal saline fluid bolus in conjunction with the IV Mg as prophylactic therapy for anticipated blood pressure instability. The need for this practice is still unclear, as it is not yet well understood whether or not hypotension associated with IV Mg is transient or clinically significant [15]. Finally, patients receiving early IV Mg required additional adjuvant medications and respiratory support in the ED, and a greater proportion of these patients needed intensive care. These clinical outcomes are likely reflective of the severity of the exacerbation. What remains unknown is whether early administration of IV Mg for this subset of patients positively influenced their clinical course, for example, by reducing the degree of respiratory support required or the length of stay in the intensive care unit.

Our findings need to be considered in light of several limitations. First, the retrospective design of our study may undermine data accuracy. However, medical chart abstraction was performed by trained assistants to mitigate errors associated with data collection. Second, we were unable to categorize asthma severity upon presentation to the ED as our institution does not routinely document a standardized asthma score in the electronic medical record. Thus, it is difficult to accurately ascertain whether patients warranted intensive therapy. However, IV Mg is intended to be provided once initial therapies fail, which implies that all patients receiving IV Mg should have first received intensive therapy. Failure to provide intensive therapy undermines any conclusions regarding the role of IV Mg in ED asthma management. Third, this is a single-center study, and the majority of patients in our cohort were cared for by a fellowship-trained physician. Practice patterns may not translate to other settings, such as community EDs, where the use of IV MG in pediatric asthma is less uncommon [15]. In addition, our medical record is not integrated with that of neighboring hospitals; thus, we can only account for clinical care that occurred within our institution. Finally, triage time was used to calculate the timing of all subsequent therapies, but the use of triage time may over or underestimate the timing of care delivery as external factors such as ED census influence clinical care and ED wait times [24].

5. Conclusion

IV Mg was given early in the ED course to one-third of pediatric patients, the majority of whom presented with severe asthma. The use of IV MG as a concurrent co-intervention to bronchodilators and systemic steroids is safe and associated with more timely delivery of first-line asthma therapies. Future research is needed to determine optimal dosing and standardize asthma management pathways to incorporate IV Mg.

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Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose.

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