



High-Dose Magnesium Sulfate Infusion for Severe Asthma in the Emergency Department: Efficacy Study*

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Objective: To assess the efficacy of a high-dose prolonged magnesium sulfate infusion in patients with severe, noninfectious-mediated asthma.

Design: Prospective, randomized, open-label study.

Setting: Twenty-nine-bed pediatric emergency department located in a children's hospital in Asuncion, Paraguay.

Patients: All patients of 6–16 years old who failed to improve after 2 hours of standard therapy for asthma.

Interventions: Subjects were randomized to receive magnesium sulfate, 50 mg/kg over 1 hour (bolus) or high-dose prolonged magnesium sulfate infusion of 50 mg/kg/hr for 4 hours (max, 8,000 mg/4 hr). Patients were monitored for cardiorespiratory complications.

Measurements and Main Results: Asthma severity was assessed via asthma scores and peak expiratory flow rates at 0–2–6 hours. The primary outcome was discharge to home at 24 hours. An analysis of the hospital length of stay and costs was a secondary outcome. Thirty-eight patients were enrolled, 19 in each group. The groups were of similar ages, past medical history of asthma, asthma score, and peak expiratory flow rate. There was a significant difference in the patients discharged at 24 hours: 47% in high-dose prolonged magnesium sulfate infusion (9/19) versus 10% (2/21) in the bolus group ($p = 0.032$) with an absolute risk reduction 37% (95% CI, 10–63) and a number needed to treat of 2.7 (95% CI, 1.6–9.5) to facilitate a discharge at or before 24 hours. The length of stay was shorter in the high-dose prolonged magnesium sulfate infusion group (mean $\pm$ sd in hr: high-dose prolonged magnesium sulfate infusion, 34.13 ± 19.54 ; bolus, 48.05 ± 18.72 ; $p = 0.013$; 95% CI, 1.3–26.5). The cost per patient in the high-dose prolonged magnesium sulfate infusion group was one third lower than the bolus group (mean $\pm$ sd: high-dose prolonged magnesium sulfate infusion, $\$603.16 \pm 338.47$; bolus, $\$834.37 \pm 306.73$; $p < 0.016$). There were no interventions or discontinuations of magnesium sulfate due to adverse events.

*See also p. 177.

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Conclusions: The early utilization of high-dose prolonged magnesium sulfate infusion (50 mg/kg/hr/4 hr), for non-infectious mediated asthma, expedites discharges from the emergency department with significant reduction in healthcare cost. (*Pediatr Crit Care Med* 2016; 17:e29–e33)

Key Words: cost-effective; emergency department; high-dose infusion; magnesium sulfate; pediatric; severe asthma

High levels of unbound magnesium in serum (IoMg) act as a smooth muscle relaxant with subsequent bronchodilation (1–3). IV magnesium sulfate (MgSO_4) has been used in the treatment of asthma at various dosing regimens with inconsistent clinical results (4–7). The physiology of the serum magnesium is in great part responsible for these discrepancies. Renal clearance is the major determinant of free serum magnesium, as nearly all levels above normal is rapidly excreted in the urine (8). Therefore, the maximum serum level during therapy depends more on the rate of infusion and not on the total dose or duration of the infusion. We have previously determined the feasibility and safety of a high-dose, prolonged magnesium infusion (HDMI) in the PICU for status asthmaticus, producing sustained levels of IoMg associated with smooth muscle relaxation (9–11).

In pediatrics, asthma is one of the leading causes for hospital admission from the emergency department (ED) (12). The clinical practice in the ED in Asuncion, Paraguay, similar to many underdeveloped countries, demands a judiciously administration of inpatient beds. Patients with mild to severe asthma are treated in the ED unless they require admission to the ICU. In this institution, prior to this study, IV MgSO_4 has not been used for the management of asthma.

This study was intended to evaluate the efficacy of HDMI in the ED. We hypothesize that patients with noninfectious asthma receiving HDMI, instead of IV MgSO_4 bolus, would experience a faster recovery. Our first aim was to assess the rate of patients discharged from the ED at 24 hours, differences in total length of stay (LOS) and healthcare costs. A post hoc analysis was conducted to estimate the economic impact of the differences, if any, among therapies.

METHODS

Patient Population

This prospective, randomized, open-label study was approved by the hospital institutional review committee, and all participating patients underwent a surrogate-signed informed consent. All patients between 6 and 18 years old seeking attention in the ED for severe asthma between October 2012 and June 2014 were assessed for eligibility. Patients were excluded if they had an underlying comorbidity or an infectious etiology that could be suspected through medical history or physical examination, including a temperature more than 38.3°C. Patients were excluded if any antibiotic therapy was administered immediately prior or during the ED visit. Asthma severity was classified according to the 2006 revised Global Initiative for Asthma score (<http://www.ginasthma.org>).

Severe asthma was defined as failure to improve after 2 hours of treatment. The standardized initial ED treatment was dexamethasone 0.2 mg/kg IV and 5 mg of nebulized salbutamol (max, 5 mg) every 20 minutes. Failure to improve with the above-mentioned regimen was defined as persistent signs of asthma upon clinical examination, including respiratory distress and a Woods-Downes asthma score (AS) greater than 4.

Study Design

IV MgSO_4 was administered to all patients as a bolus or as HDMI. Patients were randomized by previously prepared sealed envelopes to receive MgSO_4 50 mg/kg bolus (> 1 hr) or HDMI group (50 mg/kg/hr for 4 hr; max 8.000 mg/4 hr) diluted in 0.9% saline at a concentration of 10 mg/mL. Peak expiratory flow rates (PEFRs) were recorded as the best of three attempts (Micro Peak;

CareFusion, San Diego, CA), and AS were performed immediately before initiation of the protocol, at 2 and 6 hours post MgSO_4 administration. The primary outcome was discharge at 24 hours, secondary variables were total LOS and cost implications.

Subsequent Management

Oxygen was delivered via Venturi or rebreathing mask for oxygen requirements more than 40% (goal saturations > 90%), albuterol was nebulized every 2 hours and IV dexamethasone 0.2 mg/kg given every 6 hours. Once oxygen requirement decreased, the patient were switched to nasal cannula, oral prednisone 2 mg/kg/8hr (max, 60 mg), and albuterol puff every 4 hours.

The physicians in charge of the patient disposition, after the initial 8 hours, were not a part of the study group and blinded to the treatment that the patients received. A secondary analysis of discharges was conducted for 12 and 36 hours to explore whether these differences in discharge were consistent with the 24-hour threshold.

Hospital Costs

Cost of LOS was calculated using a 12-hour shift model; if the patient stayed longer than the shift, then the cost was estimated as an additional 12 hours. Hospital costs, \$191 per day, were estimated by the cost of the daily inpatient operation and consumables calculated in a previous study (13). The costs reported in the study do not represent “charges.” The pharmacy expenses for the MgSO_4 equaled 1 ampule (\$1.00) per child, regardless of the treatment group as there was no fractioning of the ampules. The Children’s hospital is a government-subsidized institution, with 100 inpatient beds, 29 ED beds, 80,000 ED visit per year, 30% of level I, II, or III on triage, which primarily serves an indigent population.

Power Calculation and Statistical Analysis

Power calculations were performed for the primary outcome, discharge at 24 hours. On the basis of our clinical experience, we estimated the rate of discharge would be about 5% in the bolus group and 40% in the HDMI group. Using a *p* value of less than 0.05 significance level and at least 80% power, the projected sample was 22 per group; 44 randomized envelopes were placed into a box. An interim analysis was done after about 80% of each group’s sample was completed. The interim analysis produced significant results with an *n* = 19 per group.

Continuous and ordinal variables are described using means and sds. Categorical variables are described using frequencies. Nonparametric analyses were used (Mann-Whitney *U* tests, chi-square, and Spearman ρ) to test for group differences and relationships between variables. Bonferroni correction for multiple comparisons was used when indicated. A *p* value of less than 0.05 was considered significant.

RESULTS

Demographics and Admission Data

Fifty-one patients with noninfectious-mediated asthma were admitted to the ED during the study period, six refused to

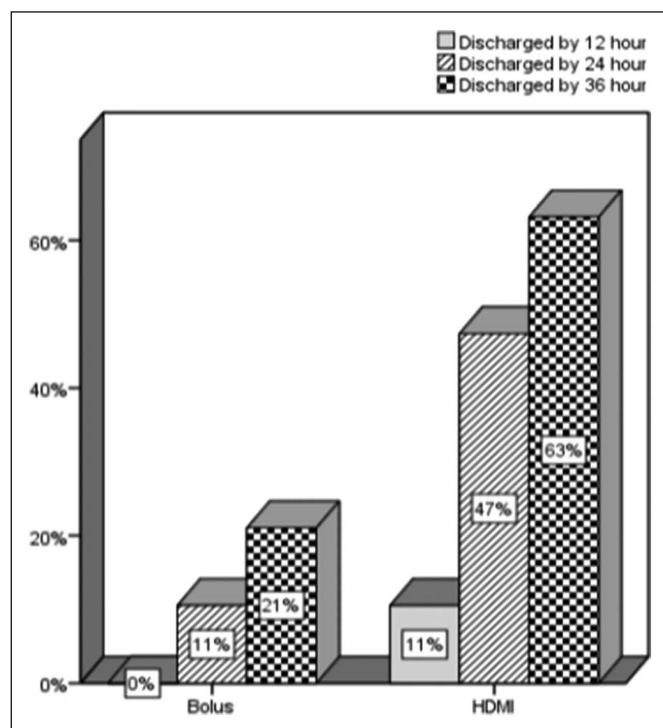


Figure 1. Time to discharge home. Columns represent patients discharged home by group. HDMI = high-dose magnesium infusion.

participate and seven patients were not adequately assessed for eligibility. A total of 38 were enrolled, 19 in each group. There were no protocol violations. All patients remained in the ED except for one who was admitted to the hospital general ward, contrary to the traditional management of such patients in the institution. This patient was discharged home at 72 hours from time of arrival to the ED and was included in the statistical analysis.

The groups did not have a significant difference in age, sex, past medical history of asthma, initial AS, or PEFR (Table 1). Of note, none of the patients suffered from obesity. The clinical tools of severity used at admission had a strong correlation (initial AS and PEFR = $r^s = -0.547$; $p = 0.0004$).

Discharges, LOS, and Costs

The HDMI group was significantly more likely to be discharged from the ED within 24 hours, HDMI 47% versus bolus 10% ($p = 0.032$) with an absolute risk reduction (ARR) 37% (95% CI, 10–63), and a number needed to treat of 2.7 (95% CI, 1.6–9.5) (Table 2).

The total LOS for the entire population ranged from 12 to 88 hours with no significant relationship to age, sex, or past medical history of asthma. In analyzing LOS, the HDMI group experienced a lower LOS than the bolus group (mean $\pm$ SD for HDMI 34.13 ± 19.54 ; bolus, 48.05 ± 18.72 ; $p = 0.013$; 95% CI, 1.3–26.5).

To observe whether the findings were confined to the primary clinical outcome threshold (24 hr), a secondary analysis 12 hours before and after was performed. At 12 hours, there were no significant differences, but at 36 hours, the same trend noted at 24 hours continued ($p = 0.021$) with two third of the HDMI patients being discharged home at 36 hours (Fig. 1). The hospital cost per patient was significantly different with a potential savings representing 28% of the hospitalization; mean $\pm$ SD for HDMI $\$603.16 \pm 338.47$, bolus $\$834.37 \pm 306.73$ ($p < 0.016$).

No patient in either group required discontinuation or intervention related to adverse events, and there were no reports of clinical hypotension. None of the patients required admission to the PICU or mechanical ventilatory support. None of the patients returned to the ED in the following week post discharge.

DISCUSSION

Among children with severe asthma who did not initially respond to standard therapies, those treated with a 4-hour infusion of $MgSO_4$, compared with a single bolus dose, were over four times more likely to be discharged from the ED and avoid hospital admission. Furthermore, among those admitted to the hospital, LOS and costs were significantly lower in the high-dose infusion group. Improvements in the ED management of asthma, a leading diagnosis for admission to hospitals, could have a significant economic impact (14), in particular, for areas with low resources. Incorporating HDMI to the ED management of asthma, in this institution, is cost-effective.

The primary mechanism of action of $MgSO_4$ is thought to be smooth muscle relaxation (1–3). Supraphysiologic unbound magnesium, directly related to IoMg when used IV, produces a proportional and only transient block of the N-methyl-D-aspartate receptor-gated calcium channels with subsequent muscle relaxation (3). Although other mechanisms have putative beneficial effects, their degree of contribution in the therapeutic management is less clear (15). IV $MgSO_4$ onset of action and renal elimination are rapid (16, 17). Achieving sustained smooth muscle relaxation is challenging, as renal tubular reabsorption is at maximal capacity with normal serum levels and renal clearance rises linearly with higher concentrations (17).

Since its original description, the optimal regimen of $MgSO_4$ in severe asthma has not been established, leading to the utilization of a wide dosing range, route of administration, and

TABLE 1. Data Obtained Upon Entering the Study Did Not Demonstrate a Significant Clinical Difference Between Groups

Patients	Bolus (n = 19)	HDMI (n = 19)	p
Age (yr)	9.0 $\pm$ 2.9	11.1 $\pm$ 3.8	0.079 ^a
Gender (M/F) (%)	M = 9 (47) F = 10 (53)	M = 7 (37) F = 10 (63)	0.742 ^b
Initial peak expiratory flow rate (%)	42.7 $\pm$ 17.4	38.3 $\pm$ 16.6	0.389 ^a
Initial asthma score	7.0 $\pm$ 1.7	6.6 $\pm$ 1.5	0.554 ^a
Severity of asthma (Global Initiative for Asthma)			0.382 ^c
Intermittent	9	5	
Mild	5	6	
Moderate	4	8	

M = male, F = female.

^aMann-Whitney U test.

^bChi-square with continuity correction.

^cChi-square.

Data presented as absolute number of patients, $\pm$ representing the mean $\pm$ SD. Global Initiative for Asthma classification is the number of patients with intermittent, mild persistent, or moderate persistent (GINA classification).

TABLE 2. Primary and Secondary Outcomes Demonstrates the Superiority of High-Dose Prolonged Magnesium Sulfate Infusion and Its Consequent Reduction in Hospitalization Costs

Main Outcomes	Bolus	High-Dose Prolonged Magnesium Sulfate Infusion	<i>p</i>
LOS (hr) (mean ± sd)	48 ± 19	34 ± 19	0.013 ^a
Cost (US\$) (mean ± sd)	834.37 ± 306.73	603.16 ± 338.47	0.016 ^a
LOS ≤ 24 hr, <i>n</i> (%)	2 (10.5)	9 (47.4)	0.032 ^b
			Absolute risk reduction, 37%; 95% CI, 10–63; number needed to treat, 3

LOS = length of stay.

^aMann-Whitney *U* test.^bChi-square with continuity correction.

scenarios (18–24). Studies involving young children suggest a superior effect than aminophylline and terbutaline but not to salbutamol and that an early administration is associated with fewer patients requiring mechanical ventilatory support (invasive or noninvasive) (23–25). However, several authors suggest a need of higher dose regimens (9, 20, 21, 23), and multicenter studies have failed to show a consistent decrease in hospital admissions or early discharge (4, 21, 22).

We found superiority of HDMI over MgSO₄ bolus in inducing a shorter LOS when used as an early ED adjunctive therapy in older children and adolescents with severe noninfectious asthma. Some confounding variables were decreased by examining this pediatric age group where there is a more cooperation, a clinical assessment less influenced by apprehension, and where infectious process are more readily excluded by history or physical examination. Many potential patients were excluded because they have received antibiotics prior to the ED visit. Of note, the studied group did not suffer from obesity. HDMI pharmacokinetic have shown magnesium serum levels associated with smooth muscle relaxation but a need of adjustment in patients with obesity (9, 10, 26–29).

We emphasize the roles of MgSO₄ as an adjunctive therapy, whereas corticosteroids and β agonists remain the primary therapeutic agents. It is possible that the inconsistent results from previous studies were due to a failure to achieve sustained serum magnesium and smooth muscle relaxation for the inhaled β agonist to reach the site of action. It is also plausible that MgSO₄ may not exhibit consistent smooth muscle relaxation effects in the setting of infectious-induced asthma exacerbation.

We believe that stabilization and discharge home, to continue chronic management, is a clear outcome for the asthma management in the ED. Not having experienced a secondary ED encounter in the following week implies the appropriateness of the initial discharge. Expenses were calculated in a post hoc analysis, utilizing data for the institution. Although it may not have widespread applicability, it indicates a reduction in cost for an area with limited resources. We were unable to document a difference in the time-progress of scores of severity. This is not unexpected as the outpatient metrics to follow asthma severity in pediatrics

are a significant challenge fraught with limitations on its discriminatory powers. The Woods-Downes score is a group of categorical variables, some of them subjective, with a numerical expression. It is a practical tool to group patients but has coarse granularity as a metric to follow changes in airway resistance. PEFs are effort dependent and not reliable on children unfamiliar with the technique or those experiencing respiratory distress. Peak flow meters are expensive in underdeveloped countries; patients did not have prior experience with its use as they were made available exclusively for the patients enrolled during the study.

We believe that the study did not have a selection bias as patients' asthma severity were classified by the international Global Initiative for Asthma score and underwent appropriate randomization. The major limitations of our findings are related to being a single center, a relative low number of patients and an open-label study. A slow enrolment of patients was, in part, due to excluding patients who exhibited any clinical suspicion of an infectious process or have received antibiotics prior to the ED visit, a common practice throughout Latino America where antibiotics could be dispensed without a medical prescription. We attempted to compensate with a rater-blinded study; the treatment group was concealed from the treating physicians, not involved in the study, making discharge decisions. Cointervention bias could have resulted from both groups receiving standard asthmatic therapies that may have resulted in recovery, despite the addition of magnesium. This was minimized because both groups received the same standard of care resulting in a better comparison. Ipratropium bromide was not available in Paraguay during our study, and we cannot speculate about how its coadministration would have altered our findings. Although safety concerns were not a primary endpoint in this study, HDMI was not associated with clinically significant safety concerns, consistent with previous reports (9, 10). Furthermore, this experience may not be generalizable to a population suffering from obesity as a comorbidity, a situation that may require adjustment of HDMI dosing. The safety and efficacy of HDMI in patients with elevated body mass index remain to be explored.

CONCLUSIONS

In this small study, the utilization of HDMI (50 mg/kg/hr/4 hr) as adjunctive therapy for noninfectious-mediated asthma expedites discharges from the ED.

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