A Randomized Trial of Magnesium in the Emergency Department Treatment of Children With Asthma

Study objective: Magnesium sulfate has been shown to benefit asthmatic children and adults with poor responses to initial β₂-agonist therapy in the emergency department. We sought to determine whether the routine early administration of high-dose magnesium would benefit moderate to severely ill children with acute asthma.

Methods: This was a randomized, double-blind, placebo-controlled trial of 54 children 1 to 18 years of age who presented to the ED of a tertiary care children’s hospital with a moderate to severe asthma exacerbation. After receiving a nebulized albuterol treatment (0.15 mg/kg) and methylprednisolone (1 mg/kg), patients were randomly assigned to receive either 75 mg/kg of magnesium sulfate (maximum 2.5 g) or placebo. Thereafter, all patients were treated with frequent nebulized albuterol following a structured protocol. The main outcome was degree of improvement as assessed by Pulmonary Index scores over 120 minutes. Secondary outcomes included hospitalization rates and time required to meet discharge criteria.

Results: The mean change in Pulmonary Index score from baseline to 120 minutes was 2.83 for the magnesium group compared with 2.66 for the placebo group (95% confidence interval –1.24 to 1.60). Eleven (46%) of 24 magnesium-treated patients were hospitalized compared with 16 (53%) of 30 in the placebo group (95% confidence interval –19% to 34%). There were no statistically significant differences between the groups with respect to time required to meet discharge criteria.

Conclusion: The routine administration of high-dose magnesium to moderate to severely ill children with asthma, as an adjunct to initial treatment with albuterol and corticosteroids, was not efficacious.

INTRODUCTION

In the United States, 4.8 million children have asthma, the most prevalent chronic disease of childhood. The self-reported prevalence rate for asthma increased 75% from 1980 to 1994, with an increase of 160% among children from birth to 4 years. This increased prevalence has been accompanied by increasing morbidity and mortality. From 1980 to 1994, the national hospitalization rate for asthmatic children from birth to 4 years increased 47%, while the national death rate for asthma among children and adults has more than doubled from 1975 to 1995.

For patients in the emergency department with a moderate to severe asthma exacerbation, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health recommends aggressive use of β2-agonists and systemic corticosteroids. However, several clinical trials have shown that patients with this degree of illness treated with β2-agonists and corticosteroids alone typically have an incomplete response and frequently (19% to 50%) require hospitalization. In each of 2 separate trials, 31% of children in the ED with moderate to severe exacerbations treated with prednisone and frequent, intermittently nebulized albuterol for 4 hours required hospitalization. Therefore, it would seem that many patients with a moderate to severe exacerbation might benefit from therapy with additional medications.

Reports of the use of magnesium sulfate to treat acute asthma first appeared in the literature more than 60 years ago. However, there are no specific recommendations provided by the NHLBI guidelines for the use of magnesium to treat status asthmaticus, and although it has been shown to be effective for asthmatic patients with the most severe disease, it has not been well studied among those with more moderate illness. The early literature reports on magnesium therapy consisted mostly of small case series. To date, there have been few prospective, randomized studies assessing the efficacy of magnesium for acutely ill asthmatic patients in the ED. Ciarallo et al found that the administration of 25 mg/kg of magnesium to asthmatic children with poor response to initial β2-agonist therapy resulted in significant improvements. Skobeloff et al found similar effects among very ill, β2-agonist–unresponsive adults, and Bloch et al demonstrated a magnesium benefit among a small subset of severely ill adults. However, Green and Rothrock found that the routine early administration of magnesium to a more mildly ill population of adults with acute asthma did not alter outcome.

We hypothesized that the routine early administration of high-dose magnesium would benefit moderate to severely ill children with asthma, irrespective of the response to initial β2-agonist therapy. The primary study outcome in this randomized, double-blind, placebo-controlled clinical trial was the change in a clinical asthma score over time. Secondary outcome measures included hospitalization rates and time required to meet discharge criteria.

MATERIALS AND METHODS

Candidates eligible for the study were patients between 1 and 18 years with a past history of at least 1 episode of wheezing who presented to the ED with a moderate to severe asthma exacerbation (defined as a Pulmonary Index [PI] score of 8 to 13, Table 1). More mildly (PI score

<table>
<thead>
<tr>
<th>Score</th>
<th>Respiratory Rate (breaths/min)*</th>
<th>Wheezing†</th>
<th>Inspiratory/Expiratory Ratio</th>
<th>Accessory Muscle Use</th>
<th>Oxygen Saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤30</td>
<td>None</td>
<td>2:1</td>
<td>None</td>
<td>99–100</td>
</tr>
<tr>
<td>1</td>
<td>31–45</td>
<td>End expiration</td>
<td>1:1</td>
<td>+</td>
<td>96–98</td>
</tr>
<tr>
<td>2</td>
<td>46–80</td>
<td>Entire expiration</td>
<td>1:2</td>
<td>++</td>
<td>93–95</td>
</tr>
<tr>
<td>3</td>
<td>&gt;80</td>
<td>Inspiration and expiration without stethoscope</td>
<td>1:3</td>
<td>+++</td>
<td>&lt;93</td>
</tr>
</tbody>
</table>

*For patients ≥6 years: through 20, score 0; 21 through 35, score 1; 36 through 50, score 2; >50, score 3.
†If no wheezing due to minimal air entry, score 3.
≤7) or severely (PI score ≥14) ill children were excluded. Also excluded were patients who had used corticosteroids within the preceding 72 hours, had concurrent bronchiolitis, lobar pneumonia, group or suspected foreign body aspiration, a history of cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, liver or renal disease, sickle cell anemia, or who were pregnant. To avoid enrolling young children with bronchiolitis, the lower age limit for study inclusion was raised to 2 years from November 15 through March 30. The ordering of chest radiographs was at the discretion of the emergency physicians, independent of study investigators. Lobar pneumonia was defined by the results of chest radiographs interpreted by staff radiologists unaware of the study. The presence of interstitial disease or atelectasis on a chest radiograph was not cause for exclusion. The protocol was approved by the hospital's institutional review board.

On arrival to the ED, eligible patients were identified by a nurse or resident physician, who then notified the investigator on call. The investigator examined the patient and assigned a PI score. Patients with a clinical score of 8 to 13 and who met all other eligibility criteria were invited to participate. All children were treated initially with inhaled albuterol (0.15 mg/kg) by facemask or mouthpiece from a nebulizer driven by 100% oxygen at a flow of 6 L/min. While the first albuterol treatment was administered, informed consent was obtained. On completion of this treatment, intravenous access was established and all study children were given a second albuterol treatment and 1.0 mg/kg (maximum 125 mg) of intravenous methylprednisolone followed immediately by 75 mg/kg (maximum 2.5 g) of intravenous magnesium sulfate or intravenous placebo (normal saline solution) over 20 minutes, in a randomized manner. This was time zero for the study. The magnesium or placebo were identical in appearance and prepared by hospital pharmacists who also created and concealed the allocation schedule, broken only at study's end. In the absence of the study investigator, either study drug was administered by a nurse not involved with study measurements. Supplemental oxygen was provided for patients with an oxygen saturation of 92% or less as determined by pulse oximetry.

Patients in each arm of the study received albuterol by an identical regimen, 30 minutes apart (allowing 10 minutes for nebulization time). Thus, the third, fourth, and fifth albuterol treatments were administered to all children at times 40, 80, and 120 minutes, respectively. Clinical assessments (assigning a PI score and assessing oxygen saturation), as well as pulse and blood pressure measurements, were obtained at times 20, 30, 40, 60, 80, and 120 minutes. Any adverse effects, such as vomiting or flushing, were noted as well. Also recorded were deviations from the protocol such as delays in scheduled albuterol treatments or clinical deteriorations mandating more frequent β2-agonist therapy than that allowed by the study protocol.

Patients remained in the study for 150 minutes, at which time the blinded investigator decided patient disposition, independent of the emergency physician’s disposition. An oxygen saturation less than or equal to 92% was an absolute indication for admission; relative indications included significant work of breathing or poor aeration by auscultation. Although all patients were treated for the entire 150 minutes, for discharged patients, investigators recorded the time that they met discharge criteria. Discharge criteria included sustained good aeration, absent or minimal wheezing, minimal work of breathing, and oxygen saturation greater than 95% in room air.

All patients discharged to home, whether they were initially randomly assigned to receive magnesium or placebo, were prescribed inhaled albuterol every 3 to 4 hours and 2 mg/kg per day of prednisone in 2 divided doses, for 5 days. Parents were encouraged to return to the ED if worsening respiratory distress developed, and all received a follow-up telephone call 48 hours after the ED visit to determine the need for a revisit to the ED or a private physician.

Before the study’s onset, in a pilot phase, intraclass correlation coefficients were used to assess reliability of the PI. They were calculated for subsets of investigators who examined patients simultaneously. The coefficients ranged from 0.79 to 0.94. Mean differences between investigators never exceeded 1 point and did not substantially affect the estimated reliabilities.

Before the study and based on the study investigator’s extensive experience with the PI, a clinically significant improvement in the PI was defined as an increase of 2 or more units over time, as was a difference of 2 or more units between groups at any point in time. To calculate sample size then, 2 units was considered to be the minimum relevant difference. Based on the standard deviation for change in PI score found in a previous study of asthmatic children with a similar degree of illness (pooled SD=1.97) and setting α at .05, 34 children were needed for 80% power. Because this was a gross power estimate, additional children were studied in anticipation that the observed SDs might be greater than those found in the previous study. Simple comparisons between the groups on categorical variables were made with χ2 or Fisher’s exact test. A 2-tailed unpaired t test was used to compare
the mean changes in PI from time 0 to time 120 minutes. Two-way analysis of variance with repeated measures on the time factor was used to analyze the change in PI over time since this variable was normally distributed. Normality of the PI and changes in PI were confirmed using the skewness measure provided by SPSS software (version 8; SPSS Inc, Chicago, IL). Other assumptions of the analysis of variance were also tested by SPSS, and corrected for as needed.

Other data were analyzed using Epi Info statistical software (version 6.04b; Centers for Disease Control and Prevention, Atlanta, GA).

**RESULTS**

Sixty-two children were examined by investigators and met eligibility criteria. Of these, 8 refused to participate, leaving 54 study subjects. Twenty-four children were treated with magnesium and 30 with placebo. At entry, there were no significant differences between the 2 treatment groups with respect to sex or race, although subjects treated with magnesium were older ($P = .04$, Table 2). Duration of wheezing and recent asthma medication use was also similar between the groups. Children in each group had equivalent degrees of illness at initial presentation as reflected by the initial mean PI score and oxygen saturation in room air. Eighteen (75%) of 24 children treated with magnesium used a facemask to receive albuterol treatments compared with 26 (87%) of 30 in the placebo group ($P = .46$). The mean delay from the administration of the first albuterol treatment to the administration of the second albuterol treatment and the study drug (time zero), reflecting the time needed for intravenous access, was 41 minutes for each group ($P = .59$).

Mean PI scores for each of the 7 assessment times are shown in the Figure. Within each group, children experienced a significant improvement in mean PI scores from baseline to 120 minutes ($P<.001$). However, 2-way analysis of variance found no evidence for a magnesium benefit. Neither the group main effect (a comparison of the overall means, $P = .37$) nor the interaction between group and time (a comparison of the pattern of changes over time between the groups, $P = .39$) was significant. The mean change in PI from baseline to 120 minutes was 2.83 (SD±2.44) for magnesium-treated patients compared with 2.66 (SD±2.65) for placebo-treated patients (95% confidence interval [CI] on the difference –1.24 to 1.60.) There was 80% power to detect a difference between these 2 mean changes of 2.0 (2-tailed).

The mean differences in PI scores and the 95% CIs for those treated with magnesium compared with controls at each time point (T, in minutes) are as follows: T0=0.41 (95% CI –0.59 to 1.40); T20=–0.33 (95% CI –1.45 to

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**Table 2.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Magnesium</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Mean age, mo (±SD)</td>
<td>81 (44)</td>
<td>58 (39)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>14 (58)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Black, No. (%)</td>
<td>14 (58)</td>
<td>19 (63)</td>
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<tr>
<td>Mean hours of wheezing (±SD)</td>
<td>28 (25)</td>
<td>23 (22)</td>
</tr>
<tr>
<td>Theophylline use, No. (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
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<tr>
<td>β2-Agonists, No. (%)</td>
<td>3 (13)</td>
<td>2 (7)</td>
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<tr>
<td>1 hour before</td>
<td>13 (54)</td>
<td>21 (70)</td>
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<tr>
<td>24 hours before</td>
<td>16 (67)</td>
<td>18 (80)</td>
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<tr>
<td>Corticosteroids, No. (%)</td>
<td>4 (17)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>In the past</td>
<td>9.8 (1.4)</td>
<td>9.9 (1.3)</td>
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<tr>
<td>Mean PI score (±SD), at entry</td>
<td>93.9 (2.2)</td>
<td>94.1 (2.4)</td>
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<tr>
<td>Mean oxygen saturation, % (±SD)</td>
<td>8.2±1.6</td>
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<tr>
<td></td>
<td>6.8±2.0</td>
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0.80); T30=0.30 (95% CI –0.89 to 1.49); T40=0.65 (95% CI –0.56 to 1.86); T60=0.85 (–0.54 to 2.24); T80=0.80 (95% CI –0.62 to 2.22); and T120=0.74 (95% CI –0.83 to 2.31).

Among the patients treated with magnesium, 11 (46%) of 24 were determined by investigators to require hospitalization after 150 minutes compared with 16 (53%) of 30 in the placebo group (95% CI on the difference –19% to 34%). No child was admitted for reasons other than respiratory distress, and no parent refused to allow a child to be hospitalized.

Twenty-seven children met discharge criteria before the end of the study protocol; all continued in the study for 150 minutes. The 12 children treated with magnesium and discharged to home met criteria at a mean time of 101 minutes compared with 96 minutes for the 15 discharged placebo-treated patients (P= .75). Among all the children discharged to home, 1 placebo-treated child returned to the ED within 48 hours. This child was treated for asthma and discharged to home.

Emergency physicians ordered chest radiographs for 4 patients. All had been randomly assigned to the magnesium group and all had interstitial disease only. There were no instances of clinically significant hypotension or any differences between the groups in degree of tachycardia. No children reported facial flushing, and just one in the placebo group experienced emesis.

Two patients experienced deviations from the study protocol. One child in the placebo group required more aggressive asthma therapy than allowed for by the protocol after 95 minutes. Another child in the magnesium group was mistakenly given an inadequate dose of magnesium. Importantly, there were no changes in outcome measures when a secondary analysis was performed excluding these 2 children.

DISCUSSION

This study found that the routine administration of high-dose magnesium to moderate to severely ill asthmatic children, early in the course of their ED care and irrespective of their response to albuterol, did not result in additional clinical improvement. There were no significant differences found between the magnesium and control groups with respect to change in PI score from baseline, and the study had adequate power to minimize the risk of a type II error. Similarly, there were no significant differences in the hospitalization rates of the 2 groups, although the study lacked adequate power for this secondary outcome measure.

Others have assessed the use of magnesium in the ED setting.20,24 In a prospective study, Ciarallo et al20 evaluated the use of 25 mg/kg of magnesium among 31 children. Magnesium-treated children had a significant improvement from baseline pulmonary function studies 50 to 80 minutes after drug administration. In a separate study of similar design using 40 mg/kg of magnesium, Ciarallo et al24 once again found a benefit from magnesium treatment. Further, at the higher dose, the improvement in pulmonary function occurred sooner and lasted longer. Importantly, though, only children whose conditions did not improve after 3 β2-agonist nebulizations were enrolled in each study.

In contrast, we sought to determine whether magnesium has a role in the initial therapy of all moderate to severely ill asthmatic children, as opposed to a subset of β2-agonist unresponsive children. That is, should magnesium as well as β2-agonists and corticosteroids be a component of the armamentarium for such children soon after ED arrival? We chose to institute magnesium therapy early in the clinical course because it is not possible to preselect which children will be unresponsive to β2-agonists. Also, we chose a dose near the top of the dose response curve to minimize the possibility that a lack of efficacy might be secondary to underdosing.

Bloch et al22 found that among adults randomly assigned to receive 2 g of magnesium or placebo intravenously, there were no significant differences overall in hospitalizations rates or FEV1 recordings. However, among the 35 severely ill patients (FEV1 <25% predicted), those receiving magnesium had a significantly lower hospitalization rate and greater improvement in FEV1. We excluded the most severely ill children because many would not be able to comply with the standardized schedule of albuterol nebulizations.

Two other randomized and prospective studies among adults have had conflicting results.21,23 In one, 38 patients were treated with 2 β2-agonist nebulizations, corticosteroids, and theophylline.21 Those whose peak expiratory flow rates (PEFRs) did not double were randomly assigned to receive 1.2 g of magnesium sulfate or placebo. Magnesium-treated patients demonstrated a significant increase in PEFR and a significantly lower hospitalization rate. The high (79%) admission rate among the placebo group attests to the degree of illness of these adults. This is yet another study showing a magnesium benefit among very ill patients with poor responses to conventional therapy. However, there are no data provided on the number of β2-agonist treatments received by patients in each group.
Green and Rothrock\textsuperscript{23} assessed the routine administration of magnesium to a less selected group of adults who were not well enough to be discharged home after a single albuterol treatment. Patients were randomly assigned to receive 2.0 g of magnesium or placebo in an unblinded protocol. There were no significant differences between the 2 groups in any outcome measure. Potential magnesium benefits may have been overshadowed by the inclusion of some mildly ill patients, a group more likely to show response to \( \beta \text{-agonist} \) treatment. We theorized that perhaps the relatively low dose of magnesium used in this study contributed to its lack of efficacy and so used a threefold higher dose. We also studied a sicker group of children in whom magnesium benefits were more likely to be discernible.

The mechanisms of action by which magnesium benefits some asthmatic patients can only be speculated on at this time. Magnesium impairs the movement of calcium across cell membranes. A decreased uptake of calcium by bronchial smooth muscle cells may, in turn, lead to bronchodilation.\textsuperscript{23} Magnesium also has a role in inhibiting degranulation of mast cells, an important initial step in the asthmatic response resulting in the production and recruitment of inflammatory mediators such as thromboxanes and leukotrienes. The principal trigger for their release is an increase in intracellular calcium, an action antagonized by magnesium.\textsuperscript{25}

In our small sample, magnesium therapy was well tolerated, although clearly the sample size was too small to assess infrequent adverse events. Side effects of magnesium infusion are mild; they include transient facial warmth, flushing, dry mouth, or malaise. Significant adverse effects at therapeutic doses have not been reported.\textsuperscript{26} Transient hypotension may be seen with rapid infusion. Abnormalities in cardiac conduction, absent reflexes, muscle weakness, and respiratory depression can occur if total serum magnesium levels in excess of 12.0 mg/dL are achieved.\textsuperscript{26} However, to achieve this level, a dose of more than 150 mg/kg is required.\textsuperscript{26}

Despite randomization, the mean age of the magnesium-treated children was about 7 years versus about 5 years for those in the control group \( (P=.04) \). However, because the drug was delivered intravenously, there should not be enhanced delivery to older children (as might occur with nebulized medications). Similarly, there is no indication from existing literature that children with this age disparity would respond differently to magnesium therapy.

It was not the intent of this study to correlate clinical effectiveness of magnesium with serum magnesium levels. There is a poor correlation between serum and tissue magnesium levels, making their interpretation difficult.\textsuperscript{27} Although the dose used was higher than that of most previous studies, it was not high enough to produce significant adverse effects. Although early signs of magnesium toxicity do not appear until levels exceed 8 mg/dL,\textsuperscript{26} a serum magnesium level greater than 4 mg/dL seems to be needed for significant bronchodilating effects.\textsuperscript{11} Okayama et al\textsuperscript{11} administered 2.5 g of magnesium sulfate to 10 asthmatic adults and found that mean levels rose from 2.1 to 5.1 mg/dL. Noppen et al\textsuperscript{14} administered a dose of 3 g of magnesium sulfate intravenously to 12 asthmatic adults and found that the level increased from 2.1 to 4.7 mg/dL. Monem et al\textsuperscript{26} gave 50 mg/kg to 10 asthmatic children and levels increased from 2 mg/dL to a peak of 3.3 mg/dL. As a result, those investigators increased their standard dose to 75 mg/kg. Based on these data and because of inconsistent results using lower doses, we selected 75 mg/kg as a dose that would decrease safely within this wide therapeutic window and avoid the costs and difficulties inherent in obtaining serial magnesium levels. The use of high-dose magnesium also minimized underdosing as a reason for the lack of magnesium benefit in this study. However, the optimal magnesium dosing and frequency of administration (bolus versus continuous intravenous infusion) should be determined by future studies.

This is the first study to report the use of magnesium in children younger than 6 years, necessitating that an asthma score be used as the primary outcome measure. The PI is a clinical asthma score, and changes in the score after \( \beta \text{-agonist} \) therapy have been shown to correlate significantly with pulmonary function studies and the need for hospitalization among children in the ED with acute asthma.\textsuperscript{28} A subsequent study found that children treated in the ED for asthma with intramuscular corticosteroids had a significantly lower score compared with a placebo group.\textsuperscript{9} In a previous study using the modified version of the score used in this trial, children requiring hospitalization had a significantly lower PI score compared with those discharged home.\textsuperscript{4} The PI score is simple, easily derived from clinical assessment, in common use at our institution, and each investigator has had extensive experience with it with excellent interobserver reliability.

We have found that among a cohort of moderate to severely ill asthmatic children treated with aggressive \( \beta \text{-agonist} \) therapy and intravenous corticosteroids, high-dose magnesium conferred no additional benefit when administered early in the course of treatment. Magnesium has widespread availability, low cost, and minimal adverse effects; others have found that magnesium does
benefit adults and children with poor response to β₂-agonists or who have more severe disease. However, at this time, there are no data to support the use of magnesium as part of the routine initial treatment of moderate to severely ill children.

**REFERENCES**