IV Magnesium Sulfate in the Treatment of Acute Severe Asthma*

A Multicenter Randomized Controlled Trial

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Background: **Studies of IV magnesium sulfate as a treatment for acute asthma have had mixed results, with some data suggesting a benefit for acute severe asthma, but not for mild-to-moderate asthma. In a multicenter cohort, this study tests the hypothesis that administration of magnesium sulfate improves pulmonary function in patients with acute severe asthma.**

Design: **Placebo-controlled, double-blind, randomized clinical trial.**

Setting: **Emergency departments (EDs) of eight hospitals.**

Patients: **Patients aged 18 to 60 years presenting with acute asthma and $FEV_1 \leq 30\%$ predicted on arrival to the ED.**

Intervention: **All patients received nebulized albuterol at regular intervals and IV methylprednisolone. Two grams of IV magnesium sulfate or placebo were administered 30 min after ED arrival. The primary efficacy end point was FEV_1 at 240 min, and the data analysis was intent to treat.**

Results: **Two hundred forty-eight patients were included, and the mean FEV_1 on ED arrival was 22.9% predicted. At 240 min, patients receiving magnesium had a mean FEV_1 of 48.2% predicted, compared to 43.5% predicted in the placebo-treated group (mean difference, 4.7%; 95% confidence interval [CI], 0.29 to 9.3%; $p = 0.045$). A regression model confirmed the effect of magnesium compared to placebo was greater in patients with a lower initial FEV_1 ($p < 0.05$). If the initial FEV_1 was < 25% predicted, the final FEV_1 was 45.3% predicted in the magnesium-treated group and 35.6% predicted in the placebo-treated group (mean difference, 9.7%; 95% CI, 4.0 to 15.3%; $p = 0.001$). If the initial FEV was ≥ 25% predicted, magnesium administration was not beneficial; the final FEV_1 was 51.1% predicted in the magnesium-treated group and 53.9% predicted in the placebo-treated group (mean difference, − 2.9%, 95% CI, − 9.4 to 3.7; p = not significant). Overall, the use of magnesium sulfate did not improve hospital admission rates.**

Conclusion: **Administration of 2 g of IV magnesium sulfate improves pulmonary function when used as an adjunct to standard therapy in patients with very severe, acute asthma.**

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Key words: acute disease; asthma; magnesium

Abbreviations: CI = confidence interval; ED = emergency department; PEFR = peak expiratory flow rate

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There are an estimated 1.8 million annual emergency department (ED) visits for acute asthma in the United States, and nearly 500,000 patients are hospitalized each year with the primary diagnosis of asthma.[1] The high morbidity associated with asthma focuses attention on methods to improve treatment

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of the acutely ill patient. Presently, the mainstays of therapy in the ED are inhaled β-agonists and systemic steroids.[2] The beneficial effects of β-agonists occur minutes after administration, while steroids may take a number of hours to improve pulmonary function. In the search for additional therapeutic options, IV magnesium sulfate has been proposed as an effective and safe adjunct in the treatment of acute asthma.

Magnesium was first reported as a treatment for acute asthma in 1936.[3] Magnesium has since been shown to be a bronchodilator,[4–7] and case reports[8,9] note clinical benefits in patients with respiratory failure complicating acute asthma. Several pediatric trials[10–12] demonstrated a benefit from IV magnesium. Of the several randomized controlled trials testing IV magnesium in acutely ill adults, results have been mixed, with some studies demonstrating a benefit and others not.[7,13–15]

A study[13] in adults suggested that patients with acute severe asthma, defined as an $FEV_1 \leq 25\%$ predicted on arrival to the ED, had significant improvement in FEV_1 and hospital admission rates when 2 g of IV magnesium was administered as part of a standardized treatment protocol. No benefit from magnesium was found in patients with $FEV_1 > 25\%$ predicted when compared to control subjects. To validate the beneficial findings in patients with severe airway obstruction, we conducted a larger multicenter study. The objective was to determine if 2 g of IV magnesium sulfate when used as an adjunct to standard therapy improves pulmonary function over standard therapy alone in patients presenting to the ED with severe asthma. Although the previous study suggested a beneficial FEV_1 cutoff only when the initial FEV_1 was $\leq 25\%$ predicted, it involved relatively few severely ill patients. We therefore enrolled only asthmatics with severe pulmonary compromise and allowed an initial FEV_1 of up to 30% predicted to avoid excluding patients who may potentially benefit from the intervention.

Materials and Methods

Study Patients

Patients between the ages of 18 years and 60 years presenting with acute asthma to the EDs of eight teaching hospitals were considered for enrollment. Patients were eligible if asthma was diagnosed in the past by a clinician and asthma medication was used during the previous 6 months. Patients were included if they had an $FEV_1 \leq 30\%$ predicted on presentation to the ED, were willing to remain in the ED for 4 h, and were able to give written informed consent. Exclusion criteria were a history of COPD or other chronic lung disease, congestive heart failure, coronary artery disease, diabetes mellitus, renal insufficiency, or hypertension treated with medication. Patients were also ineligible if their temperature was $> 38.9°C$, if they were suspected of having pneumonia, or if they were pregnant. Patients requiring intubation or unable to perform spirometry were also excluded. The study was approved by the human subjects review committee at all participating centers.

Patient Assessment

All patients were evaluated and treated according to the same protocol. Baseline data were obtained on presentation and prior to any ED treatments, and included a brief history and physical examination, vital signs, pulse oximetry, spirometry, and modified Borg dyspnea scale evaluation.[16] The latter is a cued rating scale from 0 through 10 that allows patients to self-assess breathlessness, where 0 indicates no dyspnea and 10 represents the most severe dyspnea.

Each site used the same model spirometer to measure pulmonary function (Spiromate AS600; Riko; Minato, Japan). Since patients with acute severe asthma may not be able to perform spirometry according to accepted standards, we developed criteria to capture the best possible FEV_1. Investigators accepted spirograms in which the forced expiration lasted at least 2 s, back extrapolation volume was $< 5\%$, a sharply defined peak flow was present early in expiration, lack of significant glottic closure was present in the first second, and the patients appeared to be offering their best effort. Patients were encouraged to give at least three acceptable efforts at each time period where the FEV_1 measures from the two best efforts were within 10% of each other. An exception was on ED arrival, when patients in severe distress could be enrolled if only one otherwise acceptable effort was performed. Completed time-volume and flow-volume printouts from all efforts were reviewed blindly by two of the investigators (R.A.S. and S.S.), and comments on technique and adherence to protocol guidelines were forwarded to the site investigators. FEV_1 and peak expiratory flow rate (PEFR) measures were recorded from the spirometer, predicted values were calculated from the Knudson equations, and a 10% correction was made for African-American patients.[17]

Randomization and Treatment Protocol

This was a placebo-controlled, randomized, double-blinded trial. Patients were allocated to the two groups using a 1:1 ratio randomization table unique for each center. The study pharmacist at each site placed drug or placebo in identically appearing vials, with only the study identification number printed on the label.

After the initial ED evaluation, patients received 0.5 mL of 0.5% albuterol (2.5 mg) administered via wet nebulizer with 100% oxygen. Informed consent was then obtained, and 125 mg of IV methylprednisolone was administered. At 20 to 25 min after the initial albuterol treatment, a repeat assessment including spirometry was performed. At 30 min, the patient received either 2 g magnesium sulfate in 50 mL of normal saline solution, or a like-appearing placebo administered IV over 10 to 15 min. Albuterol was readministered 30 min after ED arrival, and again at 60 min, 120 min, and 180 min after ED arrival. Clinical

assessments including spirometry were performed prior to each treatment and again at 240 min. At 240 min, a decision to hospitalize or discharge was made. Hospital admission criteria were standardized: $FEV_1 < 50\%$ predicted, respiratory rate ≥ 26 breaths/min, no improvement in shortness of breath or wheezing, or significant dyspnea on ambulation. If the patient was hospitalized, the protocol ended. All patients discharged from the ED were instructed to continue their regular medications, to use inhaled albuterol every 3 to 4 h as needed, and to take prednisone, 20 mg bid, for 7 days. Telephone follow-ups to inquire about the need for subsequent urgent visits or hospitalization for asthma were done at 1 day and 7 days.

Specimens

Blood was drawn prior to randomization, and serum was frozen to − 20°C within 1 h of collection. Specimens were batched, and total serum magnesium levels were analyzed.

Statistical Analysis

The data analysis was intention to treat, and the primary outcome variable was FEV_1 percent predicted at 240 min. The study objective included determining whether patients with a lower baseline FEV_1 were more likely to benefit from magnesium treatment, as earlier work had suggested.[13] Secondary outcome measures included PEFR, hospital admission rates, changes in pulse, Borg dyspnea ratings, accessory muscle usage, and respiratory rate.

Spirometric assessments that did not meet study criteria were excluded from analysis only for the time point when the inadequate technique was noted. When the 240-min pulmonary function test was unavailable (for example if the patient left the ED early or was too ill to complete the protocol), the last recorded FEV_1 was used in the analysis.

Differences between groups with regard to baseline characteristics and final outcome were tested for significance using a *t* test or analysis of variance for independent samples or a Wilcoxon rank-sum test. Differences for categorical variables were tested using a χ^2 test, with an exact p value calculation for small frequencies where required. Significance was considered at an α level of 0.05.

Regression models were developed to determine whether the response to magnesium was influenced by the FEV_1 on ED arrival, prerandomization response to albuterol, age, gender, cigarette smoking, or baseline serum magnesium levels. To account for any differences in response to the initial β-agonist between the two groups, the model adjusted for improvement from time 0 to 30 min (prerandomization response to β-agonist therapy). The final model included treatment, initial FEV_1, prerandomization response to albuterol, and the interaction between initial FEV_1 and treatment.

Results

Study Population

A total of 254 patient visits were randomized. Six patients were inadvertently enrolled twice, having appeared in different hospitals participating in the study, and only the first entry was included in the data analysis. The 248 remaining patients formed the intent-to-treat population. A number of patients randomized had protocol violations and were retained in the intent-to-treat data set. These included three patients whose initial FEV_1 was $> 30\%$ predicted, three patients with chronic lung disease in addition to asthma, one patient who subsequently received a diagnosis of *Pneumocystis carinii* pneumonia, and one patient with congestive heart failure. Six additional patients had medication protocol violations that included adding or omitting a β-agonist treatment at a single time interval (magnesium treatment [n = 1], placebo treatment [n = 3]), one patient received oral rather than IV steroids (placebo), and one patient received a second dose of steroids at 2 h (placebo). Sixteen patients did not have a 240-min assessment for the following reasons: 7 patients decided to leave the ED before study completion (magnesium [n = 5], placebo [n = 2]), 2 patients missed readings due to investigator error (magnesium [n = 2]), and one reading was not obtained due to spirometer malfunction (placebo). Six patients were withdrawn from the protocol by the investigator before the 240-min end point due to illness severity (magnesium [n = 4], placebo [n = 2]); of these six patients, one patient required endotracheal intubation in the ED (magnesium).

Performance of spirometry did not meet study acceptability criteria for 20 patients on ED arrival (magnesium [n = 12], placebo [n = 8]) and for 12 patients (magnesium [n = 6], placebo [n = 6]) at 30 min. Spirometry acceptability criteria were not met at the final reading for two patients (magnesium [n = 1], placebo [n = 1]).

The mean age for the 248 patients was 36 years, the patients had a history of asthma for an average of 20 years, and 52% were female. A history of endotracheal intubation for asthma was reported by 21% of patients. The mean FEV_1 on ED arrival was 22.9% predicted, the mean peak flow was 142 L/min, and 68% of patients were using accessory muscles to breath. Baseline historical and clinical variables were similar in both groups (Tables 1, 2).

Improvement in Pulmonary Function for the Entire Data Set

The 240-min mean FEV_1 in the magnesium-treated group was 48.2% predicted compared to 43.5% of predicted in the placebo-treated group (mean difference between treatments, 4.7%; 95% confidence interval [CI], 0.29 to 9.3%; $p = 0.045$; Fig 1). Greater improvements in PEFR were also noted in patients receiving magnesium with the 240-min flow rate of 272 L/min, compared to 236 L/min in the placebo group (mean difference between treatments, 36 L/min; 95% CI, 8 to 64 L/min; $p < 0.01$; Table 2). Results did not

Table 1—*Characteristics of the Study Patients According to Treatment Group

Characteristics	Placebo (n = 126)	Magnesium (n = 122)
Age, yr	36.5 (11.4)	36.4 (11.1)
Female gender	49	55
Race		
Black	38	39
Hispanic	43	43
White	11	14
Other	8	4
Years with asthma	21 (14.1)	19 (12.4)
Duration of dyspnea for current episode, h	24 (11–72)	35 (13–87)
Asthma ED visits past year, No.	2 (1–5)	2 (1–6)
Asthma hospitalizations past 5 yr, No.	1 (0–3.75)	1 (0–5)
Past intubation for asthma	22	19
Smoking status		
Never	39	44
Current	30	32
Quit	30	24
Pack-years for current/past smokers, No.	14.8 (21.1)	14.4 (20.5)
Oral steroids past 24 h	17	14
Theophylline use past 24 h	31	36
Inhaled steroids past 24 h	29	36
Baseline serum magnesium, mg/dL†	1.92 (0.27)	1.91 (0.25)

*Data are presented as mean (SD), %, or median (IQR). There were no significant differences between the two groups. Duration of dyspnea and past visits expressed as median because of outlying values.

†Magnesium: mg/dL × 0.4114 = mmol/L.

differ when time points for patients with unacceptable spirometry results were included in the analysis or when the analysis was per protocol.

Impact of Other Variables on Improvement in FEV_1

The study objective included the hypothesis that illness severity influenced the response to magnesium, and specifically that patients with a lower initial FEV_1 would have the greatest improvement in pulmonary function. The data were reanalyzed by comparing patients with an $FEV_1 < 25\%$ predicted on ED arrival to patients with an $FEV_1 \geq 25\%$ predicted using a similar cutoff from a previous study.[13] Patients with an initial $FEV_1 < 25\%$ predicted who received magnesium had a final FEV_1 of 45.3% predicted compared to 35.6% predicted for those who received placebo (mean difference, 9.7%; 95% CI, 4.0 to 15.3%; $p = 0.001$). If the initial FEV_1 was $\geq 25\%$ predicted, the final FEV_1 was 51.1% predicted in the magnesium group and 53.9% predicted in the placebo group (mean difference, − 2.9%; 95% CI, − 9.4 to 3.7%; p = not significant).

A regression model confirmed that the effect of magnesium on pulmonary function compared to placebo was greater in patients with a lower FEV_1 ($p < 0.05$). The unadjusted data were classified into three groups by baseline FEV_1 to highlight the relationship between baseline illness severity and response to magnesium (Table 3). Although there were some differences between response to the initial prerandomization β-agonist, the overall results did not substantially change after adjusting for these differences. The adjusted improvement in response to magnesium is illustrated by taking the improvements in FEV_1 from the time of study drug infusion to final assessment (Fig 2). All of the analyses demonstrate that patients with the lowest initial FEV_1 had the greatest improvements in pulmonary function after receiving magnesium, and the higher the initial FEV_1 the less the benefit. No apparent benefit was obtained in patients whose initial FEV_1 was closer to 30% predicted. Additional models found the influence of magnesium on improvement in pulmonary function to be independent of age, gender, history of cigarette smoking, initial ED serum magnesium level, and the magnitude of the response to initial albuterol treatment.

Hospital Admission

The overall hospital admission rate at 4 h was identical in patients receiving magnesium (39 of 122 patients) or placebo (41 of 126 patients), 32% in each group.

Other Clinical Response Variables

The 240-min pulse rate was lower in the magnesium-treated group as compared to control treatment, while other clinical variables including respiratory rate, use of accessory muscles, and Borg dyspnea index did not significantly differ (Table 2).

Relapse

A total of 168 patients were discharged from the ED, including those who refused hospital admission. Patients were contacted by telephone 7 days after ED discharge to determine whether subsequent urgent visits or hospitalizations for asthma were needed. Of the 103 patients (61%) contacted, 15 patients (15%) required urgent medical attention, 9 patients in the placebo group and 6 patients who received magnesium. Five of the 15 patients required hospitalization, including 4 patients in the placebo group and 1 patient who received magnesium.

Table 2—*Clinical Measure According to Study Group on ED Arrival, 30 min After Arrival, and 240 min After Arrival

Variables	0 min (Arrival)		30 min		240 min		240 min
	Placebo	Magnesium	Placebo	Magnesium	Placebo	Magnesium	Mean Difference Between Group (95% CI)
Respiratory rate, breaths/min	25.0 (5.9)	24.9 (5.7)	22.5 (5.0)	22.8 (5.4)	20.0 (4.1)	20.0 (4.1)	0.03 (1.10 to − 1.05)
Pulse rate, beats/min	104 (17)	100 (17)	98 (16)	97 (19)	102 (15)	96 (15)†	− 5.9 (− 10 to − 2.0)
Systolic BP, mm Hg	130 (20)	132 (21.5)	126 (19)	126 (17)	121 (15)	123 (18)	2.2 (− 2.6 to 7.1)
Borg scale	7.8 (1.8)	7.5 (1.8)	5.9 (2.1)	5.5 (2.2)	2.0 (2.1)	1.9 (2.1)	− 0.1 (− 3.3 to 4.5)
Accessory muscle usage, %	65	71	44	52	10	6	3.4 (− 3 to 10)
FEV_1, L	0.75 (0.24)	0.76 (0.23)	0.96 (0.39)	1.0 (0.40)	1.42 (0.66)	1.60 (0.69)†	0.17 (0.02 to 0.34)
FEV_1, % predicted	22.7 (5.7)	23.1 (4.9)	29.0 (10.4)	30.8 (10.0)	43.5 (18.7)	48.2 (18.1)†	4.7 (0.29 to 9.3)
PEFR, L/min	144 (73)	141 (74)	162 (67)	171 (70)	236 (123)	272 (144)‡	36.0 (8 to 64)
PEFR, % predicted	32.0 (14.0)	32.2 (18.0)	36.4 (13.4)	38.6 (13.6)	53.1 (20.9)	62.7 (24.3)§	9.6 (3.7 to 15.4)

*Data are presented as mean (SD) unless otherwise indicated. Borg dyspnea index scaled from 0 (no symptoms) to 10 (most severe symptoms). Accessory muscles evaluated were the sternocleidomastoid group. For patients who did not complete the 240-min protocol, the last observation was carried forward. Placebo or magnesium were administered immediately after the 30-min assessment. Magnesium was administered 2 g IV.
†$p < 0.05$.
‡$p < 0.01$.
§$p < 0.001$.

Discussion

This multicenter trial demonstrates that 2 g of IV magnesium sulfate when administered as an adjunct to standard therapy improves pulmonary function in patients presenting to the ED with severe asthma. Overall, patients receiving magnesium had a final FEV_1 of 48.2% predicted, compared to 43.5% predicted for patients receiving placebo. Patients with the most severe airway compromise on ED arrival had the greatest response to magnesium, and patients with an FEV_1 on ED arrival closer to 30% predicted had no apparent benefit. These results support the use of magnesium to improve pulmonary function in severely ill patients, and also help to define its limitations. These results also suggest that illness severity as represented by pulmonary function can be an important determinant of response to therapeutic interventions, and this factor should be considered when evaluating new treatment regimens.

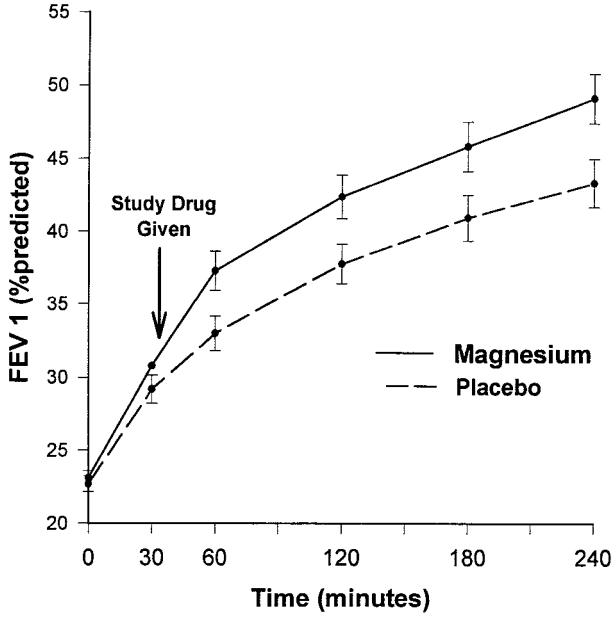

Figure 1. FEV_1 percent predicted expressed as mean ± SEM. Spirometry was performed at 0 min (ED arrival), 30 min, 60 min, 120 min, and 180 min, and albuterol was administered immediately after each measurement. Magnesium or placebo was administered after the 30-min measurement. At 240 min, the final spirometry was performed and the treatment protocol ended. The last observation was carried forward for missing data.

While several studies[10–12] in children demonstrate magnesium to be beneficial is severe asthma, the published literature on adult asthmatics has yielded conflicting results. A number of case reports indicate magnesium is beneficial for treating acute severe asthma,[3,8,9,18,19] while results of controlled clinical trials evaluating the effect of magnesium in acutely ill ED patients widely differ. When 1.2 g of magnesium or placebo was administered to 38 patients with moderate-to-severe airway compromise, significant improvements occurred in peak flow and hospital admission rates.[7] In another study, 2 g of magnesium or placebo was administered to 120 patients with wide ranges of asthma severity, and there was no improvement in hospital admission or peak flow rates.[14] In 48 patients with moderate-to-severe asthma, no significant benefit was noted from 2 g of magnesium,[15] although there was a trend among the more severely ill patients who received magnesium to have greater improvement in pulmonary function

Table 3—*Improvement in Pulmonary Function Analyzed by FEV_1 Percent Predicted on ED Arrival

Variables	FEV_1 Percent Predicted			Mean Difference Between Treatment Groups at Final Assessment (95% CI)
	0 min (Arrival)	30 min	240 min	
Initial FEV_1 25 to 30% predicted				
Placebo (n = 48)	28.1 (3.6)	36.1 (9.3)	53.9 (16)	− 2.9 (− 9.4 to 3.7)
Magnesium (n = 52)	27.3 (2.2)	35.2 (9.8)	51.1 (16.6)	
Initial FEV_1 20 to 24.9% predicted				
Placebo (n = 32)	21.9 (1.6)	27.2 (8.2)	37.9 (12)	5.9 (− 1.2 to 13.1)
Magnesium (n = 33)	22.0 (1.2)	29.5 (7.4)	43.8 (16.4)	
Initial FEV_1 < 20% predicted				
Placebo (n = 38)	16.3 (2.4)	21.0 (5.8)	33.7 (15.4)	13.6 (4.3 to 22.8)
Magnesium (n = 25)	15.9 (2.5)	24.0 (9.0)	47.3 (20.9)	

*Data are presented as mean (SD). Data are reported for patients with an adequate initial FEV_1 measure (n = 228). The last observation is carried forward for patients not completing the 240-min protocol. Placebo or magnesium were administered immediately after the 30-min assessment.

than those receiving placebo (Brian Tiffany, MD, PhD; personal communication; 2000).

Taking into consideration potential differences in response to treatment based on illness severity, Bloch et al[13] administered 2 g of magnesium or placebo to 145 patients with varying degrees of airflow obstruction, and the data were analyzed by stratifying pulmonary function on ED presentation. When the presenting FEV_1 was > 25% predicted, there was no improvement in pulmonary function. Of the 35 randomized patients whose initial FEV_1 was ≤ 25% predicted, hospital admission rates decreased and pulmonary function improved in patients receiving magnesium.

In a larger, multicenter trial, the present study also found magnesium treatment to improve pulmonary function in severely ill patients. This supports previous observations that the response to magnesium is related to the initial FEV_1, and helps to explain the conflicting results reported in the literature. It appears that for acutely ill patients, 2 g of IV magnesium may be a useful adjunct to β-agonists only when there is severe airway compromise. Even among this group of severely ill patients, magnesium caused the greatest improvements in pulmonary function when the initial FEV_1 was lowest.

This study found that magnesium did not decrease hospitalization rates. The hospital admission analysis draws attention to some of the complexities faced in using hospitalization as a study end point, and it is unclear whether the results simply reflect the therapeutic limitations of magnesium in this population

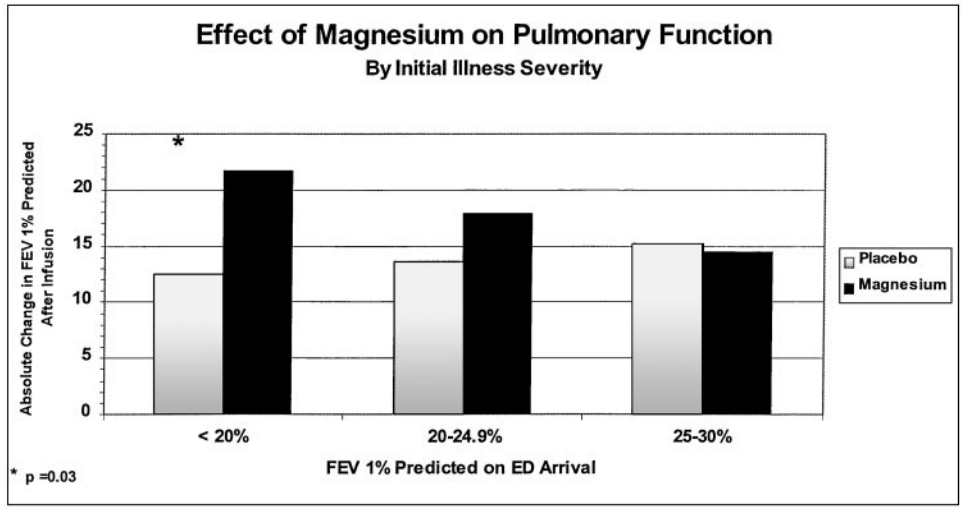

FIGURE 2. Patients were categorized by pulmonary function on ED arrival (horizontal axis) to demonstrate the influence of illness severity on response to magnesium. The vertical axis represents absolute change in pulmonary function from the time magnesium or placebo was administered to the last recorded study value (final FEV_1 percent predicted − 30-min FEV_1 percent predicted). The values are adjusted for the response to the initial albuterol treatment.

or whether other factors also play a role. In this study, the majority of patients who were advised hospital admission refused, making it more difficult to identify potential differences between treatment groups. It is possible that the relatively low final FEV_1 percent predicted represented an improvement that brought patients close to their usual baseline levels, which would explain why so many refused hospital admission. For those patients, it would have been helpful to know their usual or best percent predicted FEV_1 when evaluating for disposition, although different cutoff values for hospital admission may be needed when the patient's usual FEV_1 is very low. Regardless, these values would not be available to the investigator at the time of discharge; therefore, uniform disposition criteria were written into the protocol.

Had hospitalization been based strictly on the study disposition guidelines, then the hospital admission rates would largely be functions of the initial ED FEV_1, the improvement in FEV_1 with treatment, and the FEV_1 hospital admission threshold. Using study and National Asthma Education and Prevention Program spirometry guidelines to identify patients who "should" have been admitted (final $FEV_1 < 50\%$ predicted as cutoff), there would be a trend toward decreased hospital admissions in the magnesium group (81 of 122 patients [66%] vs 96 of 126 patients [76%], respectively). Magnesium would also appear more beneficial when the initial FEV_1 is lower (Fig 2), and also if the FEV_1 disposition threshold is lowered. *Post hoc* analysis did reveal actual hospital admission rates to be lower in magnesium-treated patients with the lowest ED arrival FEV_1, consistent with the greater improvements in FEV_1 found in these patients. For unexplained reasons, however, hospital admission rates for magnesium-treated patients were higher when the initial FEV_1 was closer to 30% predicted as compared to placebo-treated patients, results not consistent with the improvements in FEV_1 found in the same patients. Interpreting any subgroup hospital admission analysis becomes even more problematic because of the observations that other factors such as gender, race, asthma history, and recent medication usage can independently influence hospitalization rates.[20]

In contrast, pulmonary function testing performed by spirometry provided more uniform and reproducible measures. Much emphasis was placed on investigator training and quality assurance, the instrument was modified to facilitate ease of use, and acceptability criteria for spirometric efforts were developed and tracings reviewed promptly by the monitoring center. Even in this severely ill population, the quality of spirometry was consistently good at all the sites, and relatively few efforts did not meet protocol acceptability criteria. The use of spirometry in this study helped define the population most likely to have improvements in FEV_1 in response to magnesium treatment. This end point is relevant, however, only to the extent that FEV_1 measurements reflect illness severity, a concept that for acutely ill patients merits further study.

The mechanism for a beneficial effect of magnesium on pulmonary function is not clear. Magnesium is required for a wide variety of cellular activities and biological processes, and therefore can potentially exert an effect on any number of pathways. Based on the present literature, a number of mechanisms can possibly explain the effects on patients with acute asthma. The immediate improvement noted after administration of magnesium in this study points to an acute bronchodilator effect; *in vitro*, magnesium causes relaxation of bronchial smooth muscle.[21] This may occur by modulation of calcium ion movement both within the cell and through transmembrane calcium channels.[22] Magnesium is also known to decrease the amount of neurotransmitter released at motor nerve terminals, diminish depolarizing action of acetylcholine at the neuromuscular end plate, and depress excitability of smooth-muscle membranes.[23] There is evidence that prostaglandin-mediated vascular smooth-muscle relaxation is magnesium dependent.[24] Magnesium is necessary for steps involving the interaction of the β-agonist receptor complex, G protein and guanosine triphosphate, leading to activation of adenylyl cyclase.[25,26] It has also been reported *in vitro* that magnesium decreases superoxide production in neutrophils obtained from adult asthmatics, therefore providing some evidence that magnesium has an antiinflammatory effect.[27] This is a possible explanation for the sustained improvement in pulmonary function even several hours after magnesium was administered.

It is not known whether the effect of magnesium is primarily due to replacement of an underlying deficiency or through a direct pharmacologic effect. Although response to magnesium in this study was independent of baseline serum magnesium levels, the serum measures may not reflect intracellular concentrations or total body stores; therefore, some patients with normal serum levels may have had a deficiency of magnesium.[28] Also, frequent β-agonist therapy causes acute decreases in serum magnesium levels, although the influence on biological availability of magnesium is not known.[29]

Magnesium is relatively inexpensive, readily available, and easy to administer. Minor side effects can include transient flushing, lightheadedness, lethargy, nausea, or burning at the IV site. Transient urticaria resolving with discontinuation of magnesium has been reported.[30] No major side effects were noted in

this study. Serious side effects at the infusion rate and dose administered in this study are extremely uncommon in patients with adequate renal function.

An important question that this study does not answer is whether magnesium prevents the need for endotracheal intubation in patients with extremely severe asthma episodes. Although the population studied had severely compromised pulmonary function, enrollment was not possible if the patient was too sick to sign consent or unable to perform baseline spirometry. Since magnesium appears to be most beneficial in patients with the lowest FEV_1, we recommend that future studies address whether those in extremis and too ill to perform spirometry would also benefit.

Based on previous data, we chose severely diminished airflow on ED arrival as a marker for response to magnesium. Additional study in adults is needed to determine if other clinical parameters (for example, the lack of response after several albuterol treatments) could better identify patients who would benefit from IV magnesium. Future study should also be directed toward determining the optimal dose and infusion rate for magnesium, as well as whether different doses may benefit patients with less severe airway compromise. Study is also needed to determine if repeat doses or continuous infusions of magnesium benefits ED or hospitalized patients with asthma.

Another consideration is whether protocol bronchodilator therapy provided optimal management for this population. In support of the regimen, 7.5 mg of nebulized albuterol (2.5 mg every 20 min) was shown to be as effective as 22.5 mg (7.5 mg every 20 min)[31]; a small subgroup of severely ill patients did not significantly benefit from higher dosing. In another report,[32] 5.0 to 7.5 mg of nebulized albuterol administered over the first hour provided optimal ED treatment. Intermittent nebulization of β-agonists was found to be as effective as continuous therapy in adults,[33–35] although subgroup observations from the continuous-treated arm suggest severely ill patients benefit from higher doses of β-agonists.[34,35] In addition, another report[36] indicates that repetitive high dosing with inhaled ipratropium bromide is beneficial in more severely ill patients. Whether the magnitude of the response to magnesium would differ if these additional interventions were used is not known, and future studies should consider this in protocol design.

Additional limitations of this study include the possibility that some patients (and investigators) were aware magnesium was administered because of discomfort from the infusion. The measurement of changes of pulmonary function with spirometry and the use of standardized acceptability criteria to evaluate the efforts minimizes but may not completely eliminate the potential for bias.

In summary, 2 g of magnesium sulfate administered as an adjunct to standard therapy to patients presenting to the ED with severe asthma causes improvement in pulmonary function. The improvements were restricted to patients with the most severe airway obstruction, and the lower the initial FEV_1 the greater the improvement in FEV_1. The hospital admission rates, however, did not improve after treatment with magnesium. The use of magnesium to improve pulmonary function should be considered when treating acutely ill asthmatics who present to the ED with severe airway obstruction.

Appendix

The following investigators also participated in the trial: Thomas Kwiatkowski, Pamela Arsove, Helen Bloch, Boris Gabinskiy, Barbara Kirrane, Ruth Paiano, Scott Wolfson, and Adam Green, Long Island Jewish Medical Center; Mark Sprague, Jason Ganz, Robert Malin, Philip Hanline, and Bradley Spiegel, Lincoln Hospital Medical Center; Janet Carter and Marlow Price, Carolinas Medical Center; David Iacometta, Daniel Katzman, John Muratori, Dominick Fratello, Brian Blaufeux, and David Held, Jacobi Hospital Medical Center; Mark Kindshuh and Hector Fuentes, Bellevue Hospital Medical Center; Susan Fish and Herb Kayne, Boston City Medical Center; Elliot Melendez, Douglas Luxenberg, Mark Tang, and Lawrence Shevlin, St. Barnabus Medical Center; Robert Schwartz and Donna Rescorl, Hartford Hospital Medical Center; Manuel Chinchilla, Columbia University School of Public Health; Polly Bijur, Albert Einstein College of Medicine; and James Abberton and Abby Rosen (pharmacy consultants), Long Island Jewish Medical Center.

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