JAMA | Original Investigation

Effect of Nebulized Magnesium vs Placebo Added to Albuterol on Hospitalization Among Children With Refractory Acute Asthma Treated in the Emergency Department
A Randomized Clinical Trial

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IMPORTANCE While intravenous magnesium decreases hospitalizations in refractory pediatric acute asthma, it is variably used because of invasiveness and safety concerns. The benefit of nebulized magnesium to prevent hospitalization is unknown.

OBJECTIVE To evaluate the effectiveness of nebulized magnesium in children with acute asthma remaining in moderate or severe respiratory distress after initial therapy.

DESIGN, SETTING, AND PARTICIPANTS A randomized double-blind parallel-group clinical trial from September 26, 2011, to November 19, 2019, in 7 tertiary-care pediatric emergency departments in Canada. The participants were otherwise healthy children aged 2 to 17 years with moderate to severe asthma defined by a Pediatric Respiratory Assessment Measure (PRAM) score of 5 or greater (on a 12-point scale) after a 1-hour treatment with an oral corticosteroid and 3 inhaled albuterol and ipratropium treatments. Of 5846 screened patients, 4332 were excluded for criteria, 273 declined participation, 423 otherwise excluded, 818 randomized, and 816 analyzed.

INTERVENTIONS Participants were randomized to 3 nebulized albuterol treatments with either magnesium sulfate (n = 410) or 5.5% saline placebo (n = 408).

MAIN OUTCOMES AND MEASURES The primary outcome was hospitalization for asthma within 24 hours. Secondary outcomes included PRAM score; respiratory rate; oxygen saturation at 60, 120, 180, and 240 minutes; blood pressure at 20, 40, 60, 120, 180, and 240 minutes; and albuterol treatments within 240 minutes.

RESULTS Among 818 randomized patients (median age, 5 years; 63% males), 816 completed the trial (409 received magnesium; 407, placebo). A total of 178 of the 409 children who received magnesium (43.5%) were hospitalized vs 194 of the 407 who received placebo (47.7%) (difference, −4.2%; absolute risk difference 95% [exact] CI, −11% to 2.8%]; $P = .26$). There were no significant between-group differences in changes from baseline to 240 minutes in PRAM score (difference of changes, 0.14 points [95% CI, −0.23 to 0.50]; $P = .46$); respiratory rate (0.17 breaths/min [95% CI, −1.32 to 1.67]; $P = .82$); oxygen saturation (−0.04% [95% CI, −0.53% to 0.46%]; $P = .88$); systolic blood pressure (0.78 mm Hg [95% CI, −1.48 to 3.03]; $P = .50$); or mean number of additional albuterol treatments (magnesium: 1.49, placebo: 1.59; risk ratio, 0.94 [95% CI, 0.79 to 1.11]; $P = .47$). Nausea/vomiting or sore throat/nose occurred in 17 of the 409 children who received magnesium (4%) and 5 of the 407 who received placebo (1%).

CONCLUSIONS AND RELEVANCE Among children with refractory acute asthma in the emergency department, nebulized magnesium with albuterol, compared with placebo with albuterol, did not significantly decrease the hospitalization rate for asthma within 24 hours. The findings do not support use of nebulized magnesium with albuterol among children with refractory acute asthma.

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Visual Abstract

Supplemental content

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Acute asthma is a leading cause of pediatric hospitalizations.[1] While inhaled β_2 agonists, anticholinergics, and systemic corticosteroids are widely recommended to reduce hospitalizations in severe asthma exacerbations,[2-4] some children have a limited response to β_2 agonists and corticosteroids.[5]

When administered intravenously (IV) to children with severe acute asthma, magnesium has been shown to decrease hospitalizations from the emergency department (ED).[6-9] However, children are rarely discharged home after receiving IV magnesium, and IV magnesium is often given with the intent to prevent intensive care admission.[10,11] Clinician reluctance to use IV magnesium may be in part because of the pain associated with IV insertion and because of its well-known association with hypotension.[10,11] In contrast, administration of magnesium by nebulization is noninvasive, and potentially more efficient, because this treatment mode targets the lower airway and reduces systemic exposure.

Previously published pediatric asthma studies of nebulized magnesium were small,[12,13] and had methodological limitations such as lack of focus on health care utilization outcomes[13-15] and not limiting participants to those not responsive to initial optimized care.[12,13,15] Therefore, the Magnesium Nebulization Utilization Management in Pediatric Asthma (MAGNUM PA) Trial was designed to evaluate the effectiveness of inhaled magnesium in children who presented to EDs with an acute asthma exacerbation and remained in moderate or severe respiratory distress after evidence-based standardized initial therapy. The study hypothesis was that the administration of 3 magnesium sulfate nebulization treatments added to ongoing albuterol treatment would result in a lower 24-hour hospitalization rate compared with albuterol nebulization with placebo.

Key Points

Question What is the effectiveness of nebulized magnesium in children and adolescents with acute asthma in the emergency department who remain in moderate or severe respiratory distress after evidence-based standardized initial therapy?

Findings In this randomized clinical trial that included 816 patients, nebulized magnesium with albuterol, compared with placebo with albuterol, did not significantly decrease the rate of hospitalization for asthma within 24 hours (43.5% vs 47.7%, respectively).

Meaning The findings do not support use of nebulized magnesium with albuterol among children with refractory acute asthma.

Methods

Design

This was a randomized, double-blind, parallel-group, placebo-controlled trial comparing the effect of nebulized magnesium sulfate with albuterol vs placebo with albuterol in children with refractory acute asthma. Written informed consent was obtained from all caregivers and participants, along with assent, as appropriate. The research ethics boards of all institutions approved the trial. The trial was registered at ClinicalTrials.gov and the protocol has been published[16] (and is available in Supplement 1) and the statistical analysis plan and its amendments are summarized in Supplement 2, Supplement 3, and Supplement 4. In this trial, we enrolled children with acute asthma in 7 Canadian tertiary-care pediatric EDs belonging to the Pediatric Emergency Research Canada Network (eTable 1 in Supplement 5).

Trial Participants

Children 2 to 17 years of age were eligible if they had a diagnosis of asthma made by a physician, had a previous episode of acute wheeze treated with an inhaled bronchodilator or a systemic corticosteroid, and had persistent moderate to severe asthma after the completion of a 1-hour initial asthma treatment period. The latter was designed to optimize routine management and included an oral corticosteroid (ie, dexamethasone, 0.3-0.6 mg/kg/dose, maximum, 20 mg; or prednisolone, 1-2 mg/kg/dose, maximum, 60 mg) with 3 consecutive inhaled albuterol (500-1000 µg/treatment) and ipratropium bromide (80 µg/treatment) treatments via a metered dose inhaler or a nebulizer (albuterol, 5 mg/treatment; ipratropium bromide, 500 µg/treatment). We excluded children requiring immediate airway management; children who received IV magnesium prior to enrollment; children with comorbidities such as chronic lung, cardiovascular, kidney, neurologic, or other systemic disease; and children with a known hypersensitivity to magnesium. Families without adequate command of the English or French language, without telephone or e-mail contact information, and those previously enrolled were also excluded.

Persistent moderate to severe asthma after the aforementioned initial therapy was defined by a Pediatric Respiratory Assessment Measure (PRAM) score of 5 points or greater (**Table 1**; eAppendix 2 in Supplement 3).[19] This cutoff was chosen based on the high proportion of asthma hospitalizations with PRAM scores of 5 or greater after initial therapy (eTables 2 and 3 in Supplement 5). The PRAM score represents a 12-point pediatric acute asthma measurement tool (higher PRAM scores indicate higher asthma severity), which has been fully validated in the ED setting for use in children 12 months of age or older.[17,20,21]

Randomization and Blinding

Using random number-generating software at https://www.randomizer.org/, the research pharmacist (D.N.) at the coordinating center produced master randomization tables, stratified by site and age (≤5 years vs ≥6 years). Permuted block randomization with block sizes of 6 and 8 with a 1:1 allocation ratio of magnesium to placebo was used. The randomization sequence was restricted to the coordinating research pharmacy until the study database was locked. Consecutively numbered kits containing either magnesium sulfate or 5.5% saline placebo (to match tonicity of magnesium sulfate) were prepared by each pharmacy according to the procedure manual supplied by the coordinating center.

Table 1. Pediatric Respiratory Assessment Measure Score[a]

Sign	Points 0	1	2	3
Suprasternal retractions	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
Oxygen saturation	≥95%	92%-94%	≤91%	
Oxygen saturation in Calgary[b]	≥93%	90%-92%	≤89%	

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[a] PRAM score represents the sum of the individual components (range, 0-12). PRAM scores of 0-3, 4-7, and 8-12 points represent mild, moderate, and severe asthma, respectively.[17]

[b] Because Calgary, Alberta, Canada, is 1000 m above sea level, the saturation cutoffs have been adjusted accordingly[18] (see eAppendix 2 in Supplement 5 for details).

The magnesium and placebo solutions were identical in volume, color, taste, and smell, both in the steady state and during nebulization, as verified by the coordinating center pharmacy. Study participants, research nurses, ED staff, and the study analyst were blinded to the treatment assignment (see eAppendixes 3 and 4 and eTable 4 in Supplement 5 for study blinding and unblinding procedures).

Procedures

Prior to the study start, dedicated research nurses received training about the study protocol, data collection, and treatment delivery using standardized in-person sessions. They collected patient-level data and study-related outcomes, conducted trial interventions, and entered study data into a secure electronic database. To maximize the accuracy of the PRAM measurement, all study nurses and site investigators completed an online PRAM training module[22] available at https://enseignement.chusj.org/PRAM-En.

Eligible participants received 3 consecutive nebulization treatments, consisting of 5 mg (1 mL) of albuterol and either 600 mg (1.2 mL) of magnesium sulfate (Sandoz) or 1.2 mL of 5.5% saline. Sterile water (3.8 mL) was added to each nebulization treatment in both groups to achieve identical tonicity of both intervention and placebo solutions (eAppendix 3 and eTable 4 in Supplement 5). The selected dose of magnesium was at the upper end of the dosage range previously used.[23] Because pulmonary deposition, in terms of dose/kg, of nebulization treatments in younger children is similar to that in their older counterparts,[24] we used the same magnesium dose in all participants. To optimize pulmonary deposition in all participants, we pretested and selected the AeroNebGo nebulizer (Philips) attached to the Idehaler holding chamber (La Diffusion Technique Française). This high-efficiency delivery system has been shown to deliver 20% of the medication dose to the lungs compared with 4% delivered via conventional nebulizers (eAppendix 5 in Supplement 5).[25,26]

Emergency physicians used their clinical judgment to determine the need for additional asthma therapies and made disposition determinations as per usual practice. Discharged children received prescriptions for inhaled albuterol, oral corticosteroid, and inhaled corticosteroid.

Outcomes

The primary outcome measure was physicians' decision to hospitalize children for persistent respiratory distress or the need for supplemental oxygen within 24 hours of randomization. Hospitalization is a clinically powerful and policy-relevant marker of treatment failure of importance to clinicians, families, and health care organizations because half of pediatric asthma costs relate to hospitalizations.[27]

The secondary outcomes specified a priori included changes in the PRAM score (PRAM is a validated summative pediatric acute asthma score ranging 0-12 points, where PRAM scores of 1-3, 4-7, and 8-12 points indicate mild, moderate, and severe asthma, respectively, with a change of 3 points regarded as clinically significant; Table 1)[17,20]; respiratory rate; oxygen saturation (on room air) from postrandomization baseline to 60, 120, 180, and 240 minutes (or up to the time of disposition) after starting the intervention; changes in blood pressure from baseline to 20, 40, 60, 120, 180, and 240 minutes; and the number of additional albuterol treatments administered within 240 minutes. Adverse effects included adverse events (AEs) coded using the Medical Dictionary for Regulatory Activities, version 19, and serious AEs (SAEs). Predefined expected life/disease-related occurrences, such as cough, respiratory distress, asthma-related hospitalization, IV insertion, sinus tachycardia, and bitter/salty taste of the experimental solution, were not considered AEs in either group and were not measured as such. We a priori defined SAEs as hypotension requiring medical intervention, apnea, or admission to the intensive care unit. Other (exploratory) outcomes included asthma-related (1) hospitalizations, (2) unscheduled medical visits to any facility within 72 hours of ED discharge, and (3) administration of IV magnesium in the ED after the experimental intervention.

Statistical Analyses

This trial was initially launched as a 2-center trial, with a targeted sample size of 284 patients, which was able to detect a minimally significant difference of 15 percentage points to decrease the hospitalization rate (ie, primary outcome) from 30% to 15%, with a power of 80%. This difference was determined after discussion with all study investigators. However, during this phase, the primary outcome rate had an overall event

rate of 50% (no between-group analysis was performed) and we thus realized we would be underpowered to evaluate our primary outcome. Therefore, this phase of the study was considered to be a pilot phase and the knowledge gained informed the full study design and the final protocol sample size calculations targeting a difference of 10 percentage points between groups in the primary outcome. Because the study remained blinded, and no analyses were performed, the final significance threshold remained unchanged.

The new targeted difference of 10 percentage points was based on a national survey of pediatric emergency medicine physicians[10] and on the evidence that this difference has previously led to changes in national guidelines.[28] Using a type I, 2-sided error of .05 and 80% power, our new targeted sample size was 816 participants.

All analyses were specified a priori and performed according to the assigned randomization group. All significance thresholds were 2-sided. To account for the multiple comparisons required to assess secondary outcomes, we used the Holm method, resulting in a significance level of 0.008 for each of the 6 secondary outcomes.[29] Other outcomes were not adjusted for multiplicity. Because adverse effects were uncommon, these were reported only in a descriptive way.

The data monitoring committee met annually (eAppendix 6 in Supplement 5). There was 1 planned interim analysis after the first 200 randomized patients, with a 1-sided hypothesis for the primary outcome set at 0.01 significance level. Because this 1-tailed test would only reject the null hypothesis if hospitalizations were more frequent in the magnesium than in the placebo group (contrary to the study hypothesis), the significance level for the final analysis of efficacy was not adjusted.

Baseline variables were summarized with descriptive statistics. For our primary analysis, we used a 2-sided Fisher exact test to examine the treatment effect on hospitalization within 24 hours. Further, we performed post hoc analyses using generalized linear mixed modeling for the primary and all other outcome analyses to control for randomization stratification by age group and site, where the site was treated as a random effect. This method was also used in the per-protocol analysis to estimate treatment effect of magnesium in children who received all experimental treatments. Adjusted relative risk differences were used to quantify effect sizes. We used the following a priori–identified subgroups for subgroup analyses: postrandomization baseline PRAM score of 8 or greater (indicating severe asthma),[17,20] age 5 years or younger,[30] male sex,[31] personal history of atopy, and historical report of viral-induced preschool wheeze (defined as age ≤5 years without atopy or cough between upper respiratory infections).[32] For subgroup analyses, we used generalized linear mixed modeling with treatment group-subgroup interaction factor, controlling for stratification variables, and reported adjusted risk differences for each subgroup. To analyze our secondary outcomes, we used the mixed-model method to compare changes from baseline in PRAM score, respiratory rate, oxygen saturation, and blood pressure between groups for the times previously specified, and generalized linear mixed modeling with negative binomial distribution to compare the number of additional albuterol ED treatments administered within 240 minutes between groups. The aforementioned generalized linear mixed modeling was also used to examine magnesium treatment effect on hospitalizations within 72 hours, revisits within 72 hours, and IV magnesium treatment after the experimental therapy.

No imputation was conducted for the missing data. Overall significance for primary and secondary outcomes was set at .05 (2-sided). Statistical analysis was performed using version 9.4 of the SAS system for Windows (SAS Institute, 2002-2012) and the open source statistical software R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria, 2019).

Results

Between September 26, 2011, and November 19, 2019, 818 participants were randomized. A total of 99.8% (409/410) of children in the magnesium sulfate and 99.8% (407/408) of those in the placebo groups completed follow-up (**Figure 1**). Because 2 participants could not be included in the primary analysis, our data monitoring committee agreed with expanding enrollment to 818 patients. Trial groups were similar with respect to baseline characteristics (**Table 2**). Overall, 756 children (93%) received all 3 intervention treatments; 88.3% (361/409) in the magnesium and 97.1% (395/407) in the placebo groups.

Missing data were negligible (<5%) to none, with the exception of the preschool wheeze subgroup (missing data, 12%). Nonimputed data were used in the presented results.

Primary Outcome

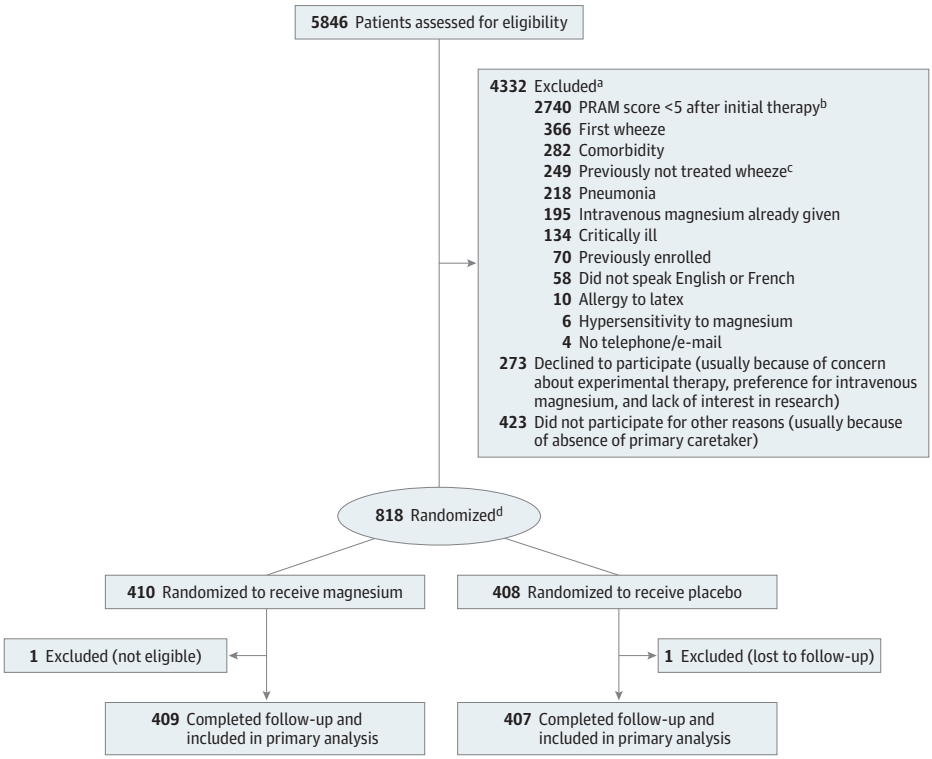
Overall, 372 of 816 participants (45.6%) were hospitalized within 24 hours: 178 of 409 (43.5%) in the magnesium group vs 194 of 407 (47.7%) in the placebo group (difference, −4.2%; absolute risk difference 95% [exact] CI, −11% to 2.8%; $P = .26$; **Table 3**, **Table 4**, and **Table 5**). Specifically, 364 children were hospitalized at the index ED visit (magnesium: 172 [42.1%] vs placebo: 192 [47.2%]) and 8 were admitted during a return visit after initial discharge (magnesium: 6, placebo: 2). Controlling for stratification at randomization for age group and site confirmed lack of statistically significant association between treatment assignment and the primary outcome (Table 3, Table 4, and Table 5). The analysis restricted to the 756 children who completed all experimental treatments also did not reveal a significant association between hospitalization and treatment assignment (Table 3).

There was no statistically significant treatment effect of magnesium and albuterol vs placebo and albuterol in any of the subgroups (**Figure 2**).

Secondary Outcomes

There were no significant between-group differences in the changes from baseline to 240 minutes in PRAM score (difference in changes, 0.14 points [95% CI, −0.23 to 0.51]; $P = .45$); respiratory rate (0.31 breaths/min (95% CI, −1.17 to 1.79];

Figure 1. Enrollment and Randomization in the Trial



PRAM indicates Pediatric Respiratory Assessment Measure.

[a] Some participants were excluded for more than 1 criterion.

[b] See Table 1 for PRAM calculation and severity interpretation.

[c] Children with previous wheeze not treated with bronchodilators or corticosteroids.

[d] Randomization was stratified by site and age group

Table 2. Characteristics of the Enrolled Participants at Randomization

Characteristic	Group, No. (%)	
	Magnesium (n = 409)	Placebo (n = 407)
Age, median (IQR), y	4.0 (3.0-7.0)	5.0 (3.0-7.0)
Age ≤5 y	253 (61.9)	250 (61.4)
Sex		
Male	257 (62.8)	260 (63.9)
Female	152 (37.2)	147(36.1)
Hospitalized for asthma in preceding year	105/408 (25.7)	92/401 (22.9)
Previous ICU admission for asthma	43/408 (10.5)	36/401 (9.0)
Personal history of atopy[a]	253/401 (63.1)	240/398 (60.3)
Family history of atopy[b]	307/403 (76.2)	296/398 (74.4)
Preschool wheeze[c]	63/363 (17.4)	56/349 (16.0)
Upper respiratory infection	293 (71.6)	279 (68.6)
Duration of respiratory distress prior to ED arrival, median (IQR), h	16.0 (12.0-24.0)	17.0 (10.0-24.0)
Prior ED visit during this episode	78 (19.1)	79 (19.4)
Self-administered albuterol within 48 h preceding ED arrival	368 (90.0)	374 (91.9)
Oral corticosteroid administered within 48 h preceding ED arrival	73 (17.8)	72 (17.7)
Inhaled corticosteroid administered within 48 h preceding ED arrival	248 (60.6)	223 (54.8)
PRAM score, median (IQR)[d]	6 (5-7)	6 (5-7)
PRAM score ≥8[d]	61 (14.9)	69 (16.9)
Respiratory rate/min, median (IQR)[d]	36 (32-44)	38 (30-44)
Heart rate/min, median (IQR)[d]	147 (135-158)	146 (134-160)
Oxygen saturation, median (IQR), %[d]	94 (92-96)	94 (92-96)
Blood pressure, median (IQR), mm Hg[d]		
Systolic	108 (101-116)	106 (100-115)
Diastolic	62 (56-68)	63 (57-70)

Abbreviations: ED, emergency department; DBP, diastolic blood pressure; ICU, intensive care unit; IQR, interquartile range; PRAM, Pediatric Respiratory Assessment Measure (see Table 1 for calculation and interpretation); SBP, systolic blood pressure.

[a] History of asthma, allergic rhinitis, or eczema.

[b] History of asthma, allergic rhinitis, or eczema in parents or siblings.

[c] Age 2-5 years, with history of no cough/wheeze between colds and no personal atopy.

[d] Measured at enrollment.

Table 3. Primary Outcome of Hospitalization and Secondary Outcome of Need for Additional Albuterol[a]

Outcome	Group, No. (%)		Unadjusted		Adjusted	
	Magnesium (n = 409)	Placebo (n = 407)	Risk difference (95% CI)	*P* value	Risk difference (95% CI)[b]	*P* value
Primary outcome						
Hospitalization within 24 h						
All patients	178 (43.5)	194 (47.7)	−0.04 (−0.11 to 0.03)	.26	−0.05 (−0.13 to 0.02)	.18
Patients with full experimental therapy[c]	158/361 (43.8)	188/395 (47.6)	−0.04 (−0.11 to 0.03)	.29	−0.04 (−0.10 to 0.03)	.25
Secondary outcome (additional albuterol treatments within 240 min)[d]						
Additional albuterol treatments, unadjusted mean (95% CI)	1.49 (1.32-1.69)	1.59 (1.41-1.79)	0.94 (0.79 to 1.11)[e]	.47	0.94 (0.78 to 1.14)[e]	.53

[a] All comparisons have controlled for stratification at randomization for site and age group.

[b] Post hoc adjustment was made for stratification at randomization for age group, with site as a random effect.

[c] This was a sensitivity analysis, with the full experimental therapy defined as completion of all 3 study treatments.

[d] The 240-minute interval was chosen to show the potential effect of magnesium over the time period when most hospitalization decisions in asthma are made.

[e] Risk ratio (95% CI).

Table 4. Secondary Outcomes of the Trial

Outcome	Magnesium group (n = 409)			Placebo group (n = 407)			Unadjusted		Adjusted	
	Preintervention, mean (SD)	Postintervention, mean (SD)	Unadjusted difference (95% CI)	Preintervention, mean (SD)	Postintervention, mean (SD)	Unadjusted difference (95% CI)	Difference-in-difference (95% CI)	*P* value	Difference-in-difference (95% CI)[a]	*P* value
Changes from baseline to 240 min[b]										
PRAM[c]	6.18 (1.33)	3.84 (1.94)	2.43 (2.16 to 2.69)	6.37 (1.27)	4.13 (2.04)	2.29 (2.04 to 2.54)	0.14 (−0.23 to 0.50)	.46	0.14 (−0.23 to 0.51)	.45
Respiratory rate (breaths/min)	38.09 (9.41)	34.35 (8.86)	4.01 (2.93 to 5.09)	38.21 (9.86)	34.54 (8.86)	3.84 (2.81 to 4.87)	0.17 (−1.32 to 1.67)	.82	0.31 (−1.17 to 1.79)	.68
Oxygen saturation (%)	94.00 (3.11)	94.50 (3.04)	−0.91 (−1.27 to −0.55)	94.20 (3.07)	94.90 (2.96)	−0.87 (−1.21 to −0.53)	−0.04 (−0.53 to 0.46)	.88	−0.05 (−0.54 to 0.45)	.86
Systolic blood pressure, mm Hg	108.4 (11.82)	108.31 (12.41)	0.24 (−1.41 to 1.89)	108.0 (10.75)	108.77 (12.96)	−0.54 (−2.08 to 1.01)	0.78 (−1.48 to 3.03)	.50	0.61 (−1.64 to 2.85)	.60
Diastolic blood pressure, mm Hg	62.59 (11.24)	59.64 (11.6)	3.12 (1.41 to 4.83)	63.13 (10.65)	58.85 (10.47)	4.45 (2.84 to 6.07)	−1.33 (−3.68 to 1.02)	.27	−1.35 (−3.70 to 0.99)	.26

Abbreviation: PRAM, Pediatric Respiratory Assessment Measure.

[a] Post hoc adjustment was made for stratification at randomization for age group, with site as a random effect.

[b] The 240-minute interval was chosen to show the potential effect of magnesium over the time period when most hospitalization decisions in asthma are made. Additional time points are included in eTable 5 in Supplement 5.

[c] See Table 1 for score calculation and severity interpretation.

Table 5. Other Outcomes of the Trial

Outcome	Group, No. (%)		Unadjusted		Adjusted	
	Magnesium (n = 409)	Placebo (n = 407)	Risk difference (95% CI)	*P* value	Risk difference (95% CI)[a]	*P* value
Hospitalization within 72 h	180 (44.01)	196 (48.16)	−0.04 (−0.11 to 0.03)	.23	−0.05 (−0.10 to 0.02)	.19
Revisit to any medical facility within 72 h	21/236 (8.90)	15/215 (6.98)	0.02 (−0.03 to 0.07)	.45	0.02 (−0.07 to 5.57)	.54
Intravenous magnesium in emergency department[b]	100 (24.45)	115 (28.26)	−0.04 (−0.10 to 0.02)	.22	−0.04 (−0.09 to 0.02)	.19

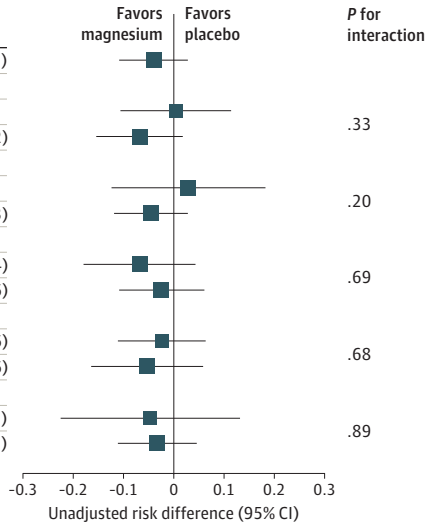
[a] Post hoc adjustment was made for stratification at randomization for age group, with site as a random effect.

[b] Intravenous magnesium was administered after the experimental therapy.

P = .68); oxygen saturation (−0.05% [95% CI, −0.54% to 0.45%]; *P* = .86); systolic blood pressure (0.61 mm Hg [95% CI, −1.64 to 2.85]; *P* = .60); or mean number of additional albuterol treatments (magnesium: 1.49, placebo: 1.59 [adjusted risk ratio, 0.94 [95% CI, 0.78 to 1.14]; *P* = .53). While the small differences in diastolic blood pressure changes at 20, 40, and 60 minutes reached significance, the directionality was contrary to the study hypothesis. The results of the changes in these outcomes to prespecified end points are summarized in eAppendix 7 in Supplement 5 and eTable 5 in Supplement 5. The

Figure 2. Subgroup Analyses for the Primary Outcome

Source	No./total No. Magnesium	Placebo	Unadjusted risk difference (95% CI)	P for interaction
Overall total	178/409	194/407	-0.04 (-0.11 to 0.03)	
Age, y				
≤5	68/156	68/157	0.00 (-0.11 to 0.11)	.33
>5	110/253	126/250	-0.07 (-0.16 to 0.02)	
PRAM score				
≥8	45/61	49/69	0.03 (-0.13 to 0.18)	.20
<8	133/348	145/338	-0.05 (-0.12 to 0.03)	
Sex				
Female	68/152	76/147	-0.07 (-0.18 to 0.04)	.69
Male	110/257	118/260	-0.03 (-0.11 to 0.06)	
Atopy				
Yes	110/253	110/239	-0.03 (-0.11 to 0.06)	.68
No	66/148	79/158	-0.05 (-0.17 to 0.06)	
Preschool wheeze				
Yes	33/63	32/56	-0.05 (-0.23 to 0.13)	.89
No	123/300	130/293	-0.03 (-0.11 to 0.05)	



Numbers and percentages shown are number of patients hospitalized / number of patients at risk. PRAM indicates Pediatric Respiratory Assessment Measure; see Table 1 for details. Preschool wheeze is defined as age 5 years and younger without atopy or cough between upper respiratory infections. Atopy indicates a personal history of asthma, eczema, or allergic rhinitis.

Table 6. Adverse Events in Study Participants

Adverse event[a,b]	Relation to study drug[c]	Magnesium group (n = 409)	Placebo group (n = 407)
Nausea/vomiting	Total	9	5
	Unlikely	5	4
	Possibly	3	1
	Other	1	0
Sore throat/nose, burning tongue, epistaxis	Total	8	0
	Possibly	7	0
	Definitely	1	0
Rash	Total	2	1
	Unlikely	1	1
	Possibly	1	0
Ear pain	Possibly	1	0
Headache	Unlikely	0	1
Hyperglycemia	Unlikely	1	0
Hypertension	Possibly	1	0
Hypotension	Unlikely	0	1
Metabolic acidosis	Unlikely	2	0
Night terrors	Unlikely	0	1
Possible pneumonia	Unlikely	0	1
Possible sepsis	Unlikely	0	1
Status asthmaticus	Unlikely	1	0
Any adverse event		25	11
Any serious adverse event[d]		5	14

[a] No patient had more than 1 adverse event.

[b] These a priori–defined asthma/study-related occurrences were not considered adverse events: cough, respiratory distress (disease-related), asthma-related hospitalization, intravenous insertion, sinus tachycardia, and bitter/salty taste of the experimental solution.

[c] Relation of adverse events to the study drug was evaluated by site investigators according to clinical relationship or theoretical pharmacologic relationship, using the following scale: not related, unlikely related, possibly related, definitely related, other.

[d] Serious adverse events were defined a priori as hypotension requiring medical intervention, apnea, or admission to intensive care unit. All observed serious adverse events consisted of admissions to intensive care unit and none were attributed to the experimental therapy.

number of additional albuterol treatments administered within 240 minutes was also not statistically significantly different between the trial groups (Table 3, Table 4, and Table 5).

Other Outcomes

There was no statistically significant treatment effect on hospitalizations or revisits within 72 hours or on administration of IV magnesium after the experimental therapy (Table 3, Table 4, and Table 5). Adverse events were infrequent and generally not attributed to the experimental therapy (**Table 6**). A total of 33 of 36 AEs were judged to be mild and 3 were moderate (magnesium: 1 [status asthmaticus]; placebo: 2 [pneumonia, sepsis with antibiotic therapy]). SAEs consisted exclusively of asthma-related admissions to the intensive care unit (Table 6) and none were attributed to the experimental treatment.

Discussion

In this randomized trial of children with acute asthma refractory to optimized initial therapy, administration of nebulized magnesium with albuterol did not significantly decrease hospitalizations within 24 hours compared with placebo with albuterol.

An important challenge in the management of moderate to severe acute asthma is that the response to the first-line ED treatment is variable. One well-documented reason for these treatment failures are genetic polymorphisms leading to varied response to inhaled β_2 agonists and delayed improvement after corticosteroids.[33-36] In children refractory to the initial optimized therapy, inhaled magnesium would in theory seem to be an attractive second-line agent. To date, however, there have been relatively few published studies, and those have been criticized for use of poorly standardized entry criteria, heterogeneous outcome measures, and widely varying co-interventions.[8,37] Consequently, current systematic reviews of nebulized magnesium in childhood asthma conclude there is substantial uncertainty about its effectiveness.[8,37,38]

More specifically, 2 larger pediatric randomized trials of inhaled magnesium have been published.[14,15] On one hand, Alansari et al[15] concluded that nebulized magnesium did not significantly reduce time to discharge readiness in 365 hospitalized patients in a single center in Qatar. On the other hand, in a multicenter ED-based trial of 508 children in the United Kingdom, Powell et al[14] demonstrated that receipt of inhaled magnesium resulted in a statistically significant but clinically small improvement in the Yung asthma score. This study led the British Thoracic Society Scottish Intercollegiate Guidelines Network to recommend that inhaled magnesium be added to each bronchodilator treatment in the first hour in children with severe asthma and short symptom duration or oxygen saturation of less than 92%.[39]

To overcome limitations of previous studies, this trial used standardized patient entry criteria assessed by a validated PRAM score, optimized initial therapy prior to screening for study eligibility, tested a large magnesium dose delivered via high-efficiency nebulizer, and ensured adequate power for assessment of a health care utilization outcome. This study provides evidence that children who remain in moderate to severe respiratory distress despite aggressive initial therapy do not derive benefit from inhaled magnesium.

Plausible reasons for lack of benefit of inhaled magnesium deserve consideration. First, it is unlikely that insufficient magnesium dose or inadequate delivery were responsible. While 7% of children did not receive all 3 magnesium doses, analyses limited to children who received all 3 doses showed similar results, suggesting that this issue did not confound the results. Second, because a high-efficiency nebulizer was used to administer albuterol along with the study drug and/or placebo, participants received a much larger dose of albuterol to the lower airways than is achieved with conventional nebulizers. Therefore, some children who experienced inadequate responses to the initial treatment regimen, which included standard dose of albuterol, may have improved due to the augmented albuterol deposition provided by the high-efficiency nebulizer. This response may have masked any added benefit of magnesium. Additionally, while the pragmatic study design may have increased generalizability of the study findings, lack of standardized hospitalization criteria may have contributed to the null result.

Limitations

This trial has several limitations. First, it was not feasible to confirm physician-diagnosed asthma at the time of enrollment in all participants. To mitigate the risk of enrollment of children without asthma, children younger than 2 years of age and those presenting with their first episode of asthmalike phenotype who may have had other diagnoses were excluded.

Second, only a small proportion of enrolled children had severe respiratory distress because some children with very high presenting PRAM scores received IV magnesium shortly after arrival based on physician judgment.

Third, while severe PRAM denotes a risk for hospitalization, the subgroup analyses suggest lack of statistically significant treatment effect of nebulized magnesium in children with PRAM scores of 8 or higher. Therefore, the results do not support that children with severe presentation might derive benefit from magnesium.

Fourth, while the PRAM scoring has been shown to have good interrater reliability[20] and PRAM is routinely used to monitor response to therapy in children with asthma in Canadian EDs, the decision to hospitalize children is not standardized and is influenced by multiple patient-level and system factors. However, the randomized study design used does minimize the effect of such variation on the outcomes of interest.

Fifth, because the 95% CI around the difference in the primary outcome includes 10%, the study may have been underpowered to detect small differences in favor of magnesium. In addition, the study results are not generalizable to magnesium therapy administered intravenously.

Conclusions

Among children with refractory acute asthma in the ED, nebulized magnesium with albuterol, compared with placebo with albuterol, did not significantly decrease the hospitalization rate for asthma within 24 hours. The findings do not support use of nebulized magnesium with albuterol among children with refractory acute asthma.

ARTICLE INFORMATION

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