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.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT01429415


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**Group Information:** The Pediatric Emergency Research Canada (PERC) Network members are listed at the end of the article.

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A

cute asthma is a leading cause of pediatric hospital-
ization.1 While inhaled β₂ agonists, anticholinergics,
and systemic corticosteroids are widely recom-
mended to reduce hospitalizations in severe asthma
exacerbations,2–4 some children have a limited response to β₂
agonists and corticosteroids.5

When administered intravenously (IV) to children with se-
vere acute asthma, magnesium has been shown to decrease
hospitalizations from the emergency department (ED).6–9 How-
ever, 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 asso-
ciated with IV insertion and because of its well-known asso-
ciation 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 nebu-
lized magnesium were small,12,13 and had methodological limi-
tations such as lack of focus on health care utilization
outcomes13–15 and not limiting participants to those not re-
sponsive to initial optimized care.12,13,15 Therefore, the
Magnesium Nebulization Utilization Management in Pedia-
tric Asthma (MAGNUM PA) Trial was designed to evaluate the
effectiveness of inhaled magnesium in children who pre-

ted to EDs with an acute asthma exacerbation and re-
mained in moderate or severe respiratory distress after evi-
dence-based standardized initial therapy. The study hypothesis
was that the administration of 3 magnesium sulfate nebu-
lization treatments added to ongoing albuterol treatment would
result in a lower 24-hour hospitalization rate compared with
albuterol nebulization with placebo.

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 published16
(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 pedi-
tric 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 diag-
nosis 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 rou-
tine 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/treat-
ment; 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, kid-
ney, neurologic, or other systemic disease; and children with
a known hypersensitivity to magnesium. Families without
adequate command of the English or French language, with-
out telephone or e-mail contact information, and those previ-
ously enrolled were also excluded.

Persistent moderate to severe asthma after the aforemen-
tioned initial therapy was defined by a Pediatric Respira-
tory 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 hospitaliza-
tions with PRAM scores of 5 or greater after initial therapy
(eTables 2 and 3 in Supplement 5). The PRAM score repre-
sents 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

days 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 coор-
dinating center produced master randomization tables,
stratified by site and age (≤5 years vs ≥6 years). Permut-
ed block randomization with block sizes of 6 and 8 with a 1:1
allocation ratio of magnesium to placebo was used. The ran-
domization 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 magne-
sium sulfate) were prepared by each pharmacy according to
the procedure manual supplied by the coordinating center.

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.
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 available at https://enseignement.chus.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 tonic-indexes. The selected dose of magnesium was at the upper end of the dosage range previously used. Because pulmonary deposition, in terms of dose/kg, of nebulization treatments in younger children is similar to that in their older counterparts, 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).

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.

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); 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). Pre-defined 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 and on the evidence that this difference has previously led to changes in national guidelines. 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. 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), age 5 years or younger, male sex, 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). 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 distri-

bution 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];
Table 2. Characteristics of the Enrolled Participants at Randomization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Magnesium (n = 409)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>4.0 (3.0-7.0)</td>
</tr>
<tr>
<td>Age ≤5 y</td>
<td>253 (61.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>257 (62.8)</td>
</tr>
<tr>
<td>Female</td>
<td>152 (37.2)</td>
</tr>
<tr>
<td>Hospitalized for asthma in preceding year</td>
<td>105/408 (25.7)</td>
</tr>
<tr>
<td>Previous ICU admission for asthma</td>
<td>43/408 (10.5)</td>
</tr>
<tr>
<td>Personal history of atopy</td>
<td>253/401 (63.1)</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>307/403 (76.2)</td>
</tr>
<tr>
<td>Preschool wheeze</td>
<td>63/363 (17.4)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>293 (71.6)</td>
</tr>
<tr>
<td>Duration of respiratory distress prior to ED arrival, median (IQR), h</td>
<td>16.0 (12.0-24.0)</td>
</tr>
<tr>
<td>Prior ED visit during this episode</td>
<td>78 (19.1)</td>
</tr>
<tr>
<td>Self-administered albuterol within 48 h preceding ED arrival</td>
<td>368 (90.0)</td>
</tr>
<tr>
<td>Oral corticosteroid administered within 48 h preceding ED arrival</td>
<td>73 (17.8)</td>
</tr>
<tr>
<td>Inhaled corticosteroid administered within 48 h preceding ED arrival</td>
<td>248 (60.6)</td>
</tr>
<tr>
<td><strong>PRAM score, median (IQR)</strong></td>
<td><strong>6 (5-7)</strong></td>
</tr>
<tr>
<td><strong>PRAM score ≥8</strong></td>
<td><strong>61 (14.9)</strong></td>
</tr>
<tr>
<td>Respiratory rate/min, median (IQR)**</td>
<td><strong>36 (32-44)</strong></td>
</tr>
<tr>
<td>Heart rate/min, median (IQR)**</td>
<td><strong>147 (135-158)</strong></td>
</tr>
<tr>
<td>Oxygen saturation, median (IQR), %</td>
<td><strong>94 (92-96)</strong></td>
</tr>
<tr>
<td>Blood pressure, median (IQR), mm Hg</td>
<td><strong>108 (101-116)</strong></td>
</tr>
<tr>
<td>Systolic</td>
<td>62 (56-68)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
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</tbody>
</table>

**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*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group, No. (%)</th>
<th>Unadjusted Risk difference (95% CI)</th>
<th>P value</th>
<th>Adjusted Risk difference (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hospitalization within 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Magnesium (n = 409)</td>
<td>178 (43.5)</td>
<td>194 (47.7)</td>
<td>−0.04 (−0.11 to 0.03)</td>
<td>.26</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 407)</td>
<td>180 (44.01)</td>
<td>196 (48.16)</td>
<td>−0.04 (−0.11 to 0.03)</td>
<td>.26</td>
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<tr>
<td>Secondary outcome (additional albuterol treatments within 240 min)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional albuterol treatments, unadjusted mean (95% CI)</td>
<td>1.49 (1.32–1.69)</td>
<td>1.59 (1.41–1.79)</td>
<td>0.94 (0.79 to 1.11)*</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium group (n = 409)</td>
<td>158/361 (43.8)</td>
<td>188/395 (47.6)</td>
<td>−0.04 (−0.11 to 0.03)</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>Placebo group (n = 407)</td>
<td>178 (44.01)</td>
<td>196 (48.16)</td>
<td>−0.04 (−0.10 to 0.03)</td>
<td>.25</td>
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</tbody>
</table>

* All comparisons have controlled for stratification at randomization for age group.
** Post hoc adjustment was made for stratification at randomization for age group with site as a random effect.

Table 4. Secondary Outcomes of the Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Magnesium group (n = 409)</th>
<th>Placebo group (n = 407)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preintervention, mean (SD)</td>
<td>Postintervention, mean (SD)</td>
<td>Preintervention, mean (SD)</td>
<td>Postintervention, mean (SD)</td>
</tr>
<tr>
<td></td>
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<tr>
<td>PRAM†</td>
<td>6.18 (1.33)</td>
<td>3.84 (1.94)</td>
<td>2.34 (2.16 to 2.69)</td>
<td>6.37 (1.27)</td>
</tr>
<tr>
<td></td>
<td>1.49 (1.32–1.69)</td>
<td>1.59 (1.41–1.79)</td>
<td>0.94 (0.79 to 1.11)*</td>
<td>.47</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>38.09 (9.41)</td>
<td>34.35 (8.86)</td>
<td>4.01 (2.93 to 5.09)</td>
<td>38.21 (9.86)</td>
</tr>
<tr>
<td></td>
<td>0.31 (−1.17 to 1.79)</td>
<td>.68</td>
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<tr>
<td>Oxygen saturation (%)</td>
<td>94.00 (1.11)</td>
<td>94.50 (3.04)</td>
<td>−0.91 (−1.27 to −0.55)</td>
<td>94.20 (3.07)</td>
</tr>
<tr>
<td></td>
<td>−0.05 (−0.54 to 0.45)</td>
<td>.86</td>
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<td></td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>108.4 (11.82)</td>
<td>108.31 (12.41)</td>
<td>0.24 (−1.41 to 1.89)</td>
<td>108.0 (10.75)</td>
</tr>
<tr>
<td></td>
<td>0.61 (−1.64 to 2.85)</td>
<td>.60</td>
<td></td>
<td></td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>62.59 (11.24)</td>
<td>59.64 (11.6)</td>
<td>2.95 (1.41 to 4.45)</td>
<td>63.13 (10.65)</td>
</tr>
<tr>
<td></td>
<td>−1.35 (−3.70 to 0.99)</td>
<td>.26</td>
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</table>

Table 5. Other Outcomes of the Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group, No. (%)</th>
<th>Unadjusted Risk difference (95% CI)</th>
<th>P value</th>
<th>Adjusted Risk difference (95% CI)*</th>
<th>P value</th>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hospitalization within 72 h</td>
<td>Magnesium (n = 409)</td>
<td>180 (44.01)</td>
<td>196 (48.16)</td>
<td>−0.04 (−0.11 to 0.03)</td>
<td>.23</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 407)</td>
<td>152 (37.8)</td>
<td>156 (38.5)</td>
<td>−0.04 (−0.11 to 0.03)</td>
<td>.23</td>
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</tr>
<tr>
<td>Revisit to any medical facility within 72 h</td>
<td>Magnesium (n = 409)</td>
<td>21/236 (8.90)</td>
<td>15/215 (6.98)</td>
<td>0.02 (−0.03 to 0.07)</td>
<td>.45</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 407)</td>
<td>21/236 (8.90)</td>
<td>15/215 (6.98)</td>
<td>0.02 (−0.03 to 0.07)</td>
<td>.45</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous magnesium in emergency departmentb</td>
<td>Magnesium (n = 409)</td>
<td>100 (24.45)</td>
<td>115 (28.26)</td>
<td>−0.04 (−0.10 to 0.02)</td>
<td>.22</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 407)</td>
<td>100 (24.45)</td>
<td>115 (28.26)</td>
<td>−0.04 (−0.09 to 0.02)</td>
<td>.19</td>
</tr>
</tbody>
</table>

* Post hoc adjustment was made for stratification at randomization for age group, with site as a random effect.
** Intravenous magnesium was administered after the experimental therapy.

Abbreviation: PRAM, Pediatric Respiratory Assessment Measure.
† Post hoc adjustment was made for stratification at randomization for age group, with site as a random effect.
‡ 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.
§ This was a sensitivity analysis, with the full experimental therapy defined as completion of all 3 study treatments.
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

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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. 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 β2 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.36,37 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 al15 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 al14 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 asthma-like 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 reliability20 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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Effect of Nebulized Magnesium vs Placebo Added to Albuterol Among Children With Refractory Acute Asthma

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Author Contributions: Dr Schuh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Schuh, Coates, Willan, Zemek, Plint, Gravel, Ducharme, Johnson, Black, Curtis, Klassen, Nicky, Freedman. Acquisition, analysis, or interpretation of data: Sweeney, Rumantir, Willan, Stephens, Atenafu, Finleinstein, Thompson, Zemek, Plint, Black, Curtis, Beer, Nicky, Freedman.

Drafting of the manuscript: Schuh, Stephens, Curtis, Nicky, Freedman. Critical revision of the manuscript for important intellectual content: Schuh, Sweeney, Rumantir, Coates, Willan, Stephens, Atenafu, Finleinstein, Thompson, Zemek, Plint, Gravel, Ducharme, Johnson, Black, Curtis, Beer, Klassen, Freedman. Statistical analysis: Willan, Stephens, Atenafu.


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REFERENCES
Effect of Nebulized Magnesium vs Placebo Added to Albuterol Among Children With Refractory Acute Asthma

Original Investigation Research

children.


