Is Dexamethasone an Effective Alternative to Oral Prednisone in the Treatment of Pediatric Asthma Exacerbations?

AUTHORS
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KEY WORDS
dexamethasone, asthma

ABBRévIATIONS
CI: confidence interval
ED: emergency department
IM: intramuscular
IV: intravenous
PO: oral

abstract

BACKGROUND: A short course of systemic corticosteroids is an important therapy in the treatment of pediatric asthma exacerbations. Although a 5-day course of oral prednisone or prednisolone has become the most commonly used regimen, dexamethasone has also been used for a shorter duration (1–2 days) with potential for improvement in compliance and palatability. We reviewed the literature to determine if there is sufficient evidence that dexamethasone can be used as an effective alternative in the treatment of pediatric asthma exacerbations in the inpatient setting.

METHODS: A Medline search was conducted on the use of dexamethasone in the treatment of asthma exacerbations in children. The studies selected were clinical trials comparing the efficacy of dexamethasone with prednisone. Meta-analysis was performed examining physician revisitation rates and symptomatic return to baseline.

RESULTS: Six completed pediatric clinical trials met the inclusion criteria. All of the pediatric trials found that prednisone is not superior to dexamethasone in treating mild to moderate asthma exacerbations. Meta-analysis demonstrated homogeneity between the dexamethasone and prednisone groups when examining symptomatic return to baseline and unplanned physician revisits after the initial emergency department encounter. Some studies found potential additional benefits of dexamethasone, including improved compliance and less vomiting.

CONCLUSIONS: The current literature suggests that dexamethasone can be used as an effective alternative to prednisone in the treatment of mild to moderate acute asthma exacerbations in children, with the added benefits of improved compliance, palatability, and cost. However, more research is needed to examine the role of dexamethasone in hospitalized children.

BACKGROUND

Asthma is among the most common pediatric chronic diseases and a frequent reason for emergency department (ED) visits and hospitalization.1 One of the important mainstays in therapy for moderate to severe asthma exacerbations is a short course of systemic corticosteroids.2 By reducing airway inflammation, steroids help manage acute symptoms and reduce bronchodilator use and relapse rates.3 4
The steroid regimen used most often is a 5-day course of oral (PO) prednisone or prednisolone. However, some literature suggests that this regimen lacks consistent patient compliance and has poor palatability. One study demonstrated that complete adherence to the full course of PO prednisone for pediatric asthma exacerbation was only 64%. Another study found the filling rate of prednisone and prednisolone in a pediatric Medicaid population was as low as 45% after ED discharge and 56% after hospitalization. A recent survey study determined that 88% of parents prefer a short 1- to 2-day course versus 5 days of steroids, and therefore a shorter medication course may improve overall adherence.

Although much has been published on the equivalence of PO and intravenous (IV) corticosteroids in acute asthma exacerbations, few studies have directly compared corticosteroid formulations. Due to the aforementioned issues with prednisone, dexamethasone has been studied as an alternative. Dexamethasone is a long-acting glucocorticoid that has been used safely in children for treating conditions such as croup. It has a 36- to 72-hour half-life, compared with the 12- to 36-hour half-life of prednisone, and therefore requires fewer doses.

Furthermore, dexamethasone tastes better and costs less in terms of unscheduled revisits. Cross et al published a brief overview of the literature examining the use of single-dose dexamethasone for pediatric asthma exacerbations in ambulatory care settings. Redman and Powell also recently reviewed the current literature comparing dexamethasone and prednisone in pediatric asthma exacerbations. Both of these reviews concluded that, according to the literature, dexamethasone and prednisone are of equal efficacy in treating pediatric asthma exacerbations, but both lacked the strength of using meta-analyses to confirm those conclusions. Furthermore, Cross et al was written to address the use of these steroids in an outpatient setting, and both reviews failed to explain how to apply the evidence to the treatment of children in the hospital. The goal of the present review was to provide a more comprehensive evaluation of the evidence, including a meta-analysis comparing the efficacy of dexamethasone with prednisone in the treatment of pediatric asthma exacerbations from a hospitalist’s perspective.

METHODS
A Medline (January 1, 1965–January 11, 2014) search was conducted on January 12, 2014. It included clinical trials, systematic reviews, and comparative and observational studies using the search terms “dexamethasone AND asthma” and the Medical Subject Heading terms “infant OR child OR adolescent.” The abstracts were reviewed for studies comparing the efficacy of PO or intramuscular (IM) dexamethasone with prednisone/prednisolone in the treatment of pediatric asthma exacerbations. A meta-analysis using a fixed-effect model was performed on the data available from the studies regarding the rates of revisits to a health care provider. A separate meta-analysis was conducted to compare symptomatic improvement in the 2 groups after the initial ED visit.

RESULTS
The search returned 58 articles. Of these, 7 were found to be potentially relevant after preliminary abstract review and received full text evaluation. One of these was an ongoing study and was excluded, leaving 6 articles for inclusion in our review.

Three of the studies investigated IM dexamethasone, and 3 studied PO dexamethasone (Table 1). Primary outcomes differed between studies and included relapse rates, patient and/or parental report of the time until return to baseline activity, and changes in asthma scores. The studies also varied in the dose and duration of steroids, enrollment age, sample size, and study design.

IM Dexamethasone
Gordon et al performed a prospective, randomized trial in pediatric patients with a history of asthma, defined as >2 respiratory illnesses requiring bronchodilator therapy who presented with wheezing. Patients received either a single dose of IM dexamethasone phosphate or 5 days of PO prednisolone. The 2 groups were matched on the basis of patient characteristics, asthma history, and objective measures of their acute presentation. Investigators compared the initial ED clinical asthma score and the score measured at a follow-up ED visit 96 to 120 hours later by an examiner blinded to group assignment. Children who received dexamethasone or prednisolone had no significant difference in mean asthma score at day 4. This study’s limitations included the exclusion of patients subjectively identified to be too sick, potentially biasing toward the null. There was also potential bias in the lack of blinding...
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Type</th>
<th>Age</th>
<th>Study Size</th>
<th>Medications Compared</th>
<th>Primary Outcome Measured</th>
<th>Results</th>
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<tr>
<td>Klig et al(^26) (1997)</td>
<td>Prospective, randomized pilot study</td>
<td>3–16 y</td>
<td>42</td>
<td>Single-dose IM DEX phosphate (0.3 mg/kg; max, 15 mg) vs 3 d of PO prednisone (2 mg/kg × 1; then 1 mg/kg BID; max, 100 mg/d)</td>
<td>Patient/parent reported or clinician assessed symptomatic improvement, relapse, or clinical deterioration at day 5 (based on PIS)</td>
<td>No significant difference between the 2 groups in symptomatic improvement (all patients reported symptomatic improvement). No cases of subsequent hospitalization.</td>
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<tr>
<td>Gries et al(^27) (2000)</td>
<td>Prospective, randomized, investigator-blinded study</td>
<td>6 mo–7 y</td>
<td>32</td>
<td>Single-dose IM DEX acetate (1.7 mg/kg; max, 36 mg) vs 5 d of PO prednisone (2 mg/kg/d divided BID)</td>
<td>Change in clinical asthma score through day 5, clinical return to baseline by day 5, and albuterol use</td>
<td>Two groups had no significant difference in clinical asthma scores through day 5, percentage of patients returning to baseline by day 5 (DEX: 73%; prednisone: 65% [$P = .71$]), relapse rates at 28 d (DEX: 7%; prednisone: 18% [$P = .60$]), or daily albuterol use on day 5 (DEX: 1.4 doses; prednisone: 1.5 doses [$P = .67$])</td>
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<tr>
<td>Gordon et al(^25) (2007)</td>
<td>Prospective, randomized study</td>
<td>18 mo–7 y</td>
<td>143</td>
<td>Single-dose IM DEX phosphate (0.6 mg/kg; max, 15 mg) vs 5 d of PO prednisolone (2 mg/kg/d daily; max, 50 mg)</td>
<td>Change in asthma score at day 4</td>
<td>No significant difference in asthma score at day 4 (DEX: 3.6; prednisolone: 3.4; mean difference: 0.2 [CI: –0.4 to 0.7]; $P = .57$). No difference in admission rate or unplanned physician visits by 14 d of follow-up (DEX: 5.9%; prednisolone: 4.1%; difference: 1.8% [95% CI: –5.4 to 9.0]) and (DEX: 22.1%; prednisolone: 21.9%; difference: 0.2% [CI: –13.5 to 13.9]), respectively</td>
</tr>
<tr>
<td>Qureshi et al(^31) (2001)</td>
<td>Prospective, randomized study</td>
<td>2–18 y</td>
<td>533</td>
<td>PO DEX 2 d (0.6 mg/kg daily; max, 16 mg) vs 5 d of PO prednisone (2 mg/kg day 1, then 1 mg/kg per day; max, 60 mg/d)</td>
<td>Relapse rate within 10 d</td>
<td>No significant difference in relapse rates (DEX: 7.4%; prednisone: 6.9%; OR: 1.08 [95% CI: 0.55 to 2.08]; $P = .84$). No difference in hospital admission of those who did relapse (20% vs 17%; $P = .81$)</td>
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at the initial ED visit, although the physicians evaluating the subjects at the follow-up visit were appropriately masked.

Klig et al. performed a prospective, randomized pilot study comparing a single dose of IM dexamethasone with 3 days of PO prednisone in children with a history of ≥2 wheezing episodes in children and a mild to moderate asthma exacerbation based on a pulmonary index score. Age- and gender-matched patients were randomized to receive the medications. Five days later, the patients were followed up either at the clinic or by telephone, and the parents were telephoned intermittently to go over the symptom diary that included a clinical asthma score (based on frequency of wheeze and cough). Parents were also evaluated in the clinic on day 5, and the asthma score improved.

Gries et al. conducted a prospective, randomized, investigator-blinded study in patients aged 6 months to 7 years. The patients were given an initial asthma score, measuring symptoms of coughing and wheeze, and were then randomized to receive a single IM dexamethasone acetate injection or 5 days of PO prednisone. Parents of the patients kept an asthma symptom diary that included a clinical asthma score (based on frequency of wheeze and cough). Parents were telephoned intermittently to go over the symptom diary that included a clinical asthma score (based on frequency of wheeze and cough). Parents were also evaluated in the clinic on day 5, and the asthma score improved.

Tabelle 1 Continued

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<th>Medications Compared</th>
<th>Primary Outcome Measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altamimi et al. (2006)</td>
<td>Prospective, randomized, double-blind study</td>
<td>2–16 y</td>
<td>110</td>
<td>Single-dose PO DEX (0.6 mg/kg; max, 16 mg) vs 5 d of PO prednisolone (1 mg/kg BID; max, 30 mg/dose)</td>
<td>Number of days required to return to baseline based on PSAS</td>
<td>No statistically significant difference in the mean number of days for the PSAS to return to baseline (DEX: 5.21 d; prednisolone: 5.22 d; mean difference: -0.01 [CI: -0.70 to 0.68]) or in the mean PSAS at day 5 (DEX: 0.4; prednisolone: 0.3; mean difference: 0.1 [CI: -0.25 to 0.49])</td>
</tr>
<tr>
<td>Gries et al. (2008)</td>
<td>Prospective, randomized, double-blind study</td>
<td>2–18 y</td>
<td>89</td>
<td>PO DEX 2 d (0.6 mg/kg; max, 16 mg) vs 5 d of PO prednisone (2 mg/kg day 1; then 2 mg/kg divided BID; max, 80 mg/d)</td>
<td>Relapse rate within 10 d</td>
<td>No significant difference in relapse rates (DEX: 16%; prednisone: 8% [P = .27])</td>
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BID, twice daily; DEX, dexamethasone; max, maximum; OR, odds ratio; PIS, pulmonary index score; PSAS, patient self-assessment score.
score was repeated. On day 28, parents were again contacted to report symptom relapse within 2 weeks of asthma exacerbation resolution. There was no difference between the 2 groups in the proportion of patients who returned to baseline based on asthma scoring performed on day 5 or who had a “relapse” within 1 month. One of the study’s major limitations, in addition to the small sample size, was the inclusion of children <2 years old, who may have had bronchiolitis and for whom steroids do not have a demonstrated benefit.28

Although studies have shown that parents prefer a shorter course of corticosteroids13 even if it requires IM injections,29 this option is usually reserved for children who cannot take PO formulations or for whom IV access cannot be acquired.30 The following studies compared PO corticosteroid preparations.

**Oral Dexamethasone**

Qureshi et al31 performed the largest study to date comparing dexamethasone with prednisone. The study included pediatric patients with a history of asthma, defined as >2 wheezing episodes treated with bronchodilators and/or corticosteroids. Patients were randomized to receive either PO dexamethasone in the ED and were given a second, prepared dose to take 24 hours later, or PO prednisone, including a prescription for the final 4 doses after the first dose given in the ED. The primary outcome measure was relapse rate within 10 days, defined as an unscheduled medical provider visit for worsening or persistent symptoms. There was no significant difference in relapse rates between the dexamethasone and prednisone groups. In addition to the lack of blinding, the major limitation of this study was the fact that children in the dexamethasone arm were provided a home dose on discharge, whereas those in the prednisone group were given a prescription to fill, potentially creating a discrepancy in adherence.

Altamimi et al32 compared a single dose of PO dexamethasone with 5 days of PO prednisolone in a prospective, randomized, double-blind study. Patients with mild to moderate asthma were randomized to receive either dexamethasone or prednisolone in the ED, then discharged with 5 days of placebo or liquid prednisolone, respectively. Parents and patients completed a patient self-assessment sheet of asthma symptoms twice daily for 5 days, and patients were reevaluated in the ED on day 5. The number of days needed for the patient self-assessment sheet score to return to baseline was not significantly different. Patients initially admitted from the ED were continued in the study and received the study medications. There was no difference in mean length of stay between groups (mean difference of 0.1, favoring prednisolone [confidence interval [CI]: –0.56 to 0.76]). The major limitation of this study was the use of subjective scoring relying on parental interpretation of patient symptoms.

Greenberg et al33 compared 2 daily doses of PO dexamethasone and 5 days of PO prednisone in preventing relapse for asthma exacerbations. In this prospective, randomized, double-blind study, children with a history of asthma were randomized to treatment, evaluated by using a pediatric asthma score, treated in the ED, and then sent home with either 1 more day of dexamethasone plus 3 days of placebo or 4 more days of prednisone. Patients received the medications in prepared blister packs before their discharge from the ED. The patients/families were contacted by telephone 10 days later and asked about relapse, defined as an unscheduled medical provider visit or hospitalization due to persistent or worsening asthma symptoms. There was no significant difference in relapse rates between the dexamethasone and the prednisone groups (16% vs 8%, respectively; P = 0.27). The dexamethasone group had a slightly higher mean pediatric asthma score at presentation compared with the prednisone group (8 vs 6; P = 0.003), potentially explaining the higher relapse rate in the dexamethasone group, although this change was not statistically significant. One limitation of this study is that ~50% of the patients were ultimately excluded (due mostly to admission or loss to follow-up).

**Meta-analysis**

A number of different outcome measures were reported in the 6 studies, but only 2 outcomes were consistently measured to be suitable for meta-analysis. The number of unscheduled physician visits after discharge was reported in all 6 studies. The pooled risk difference of 0.02 (95% CI: −0.02 to 0.05) favoring prednisone was not significantly different (Fig 1). Four studies reported symptomatic improvement to baseline after the initial ED visit. Meta-analysis demonstrated no significant difference between the dexamethasone and prednisone/prednisolone groups (pooled risk difference of 0.98, favoring dexamethasone [95% CI: 0.71 to 1.35]) (Fig 2).

**Adverse Effects**

In addition to comparing the efficacy of dexamethasone versus prednisone,
several of the studies’ secondary outcomes evaluated adverse effects, especially vomiting. Findings were mixed. Qureshi et al demonstrated significantly more repeated vomiting in the ED in children in the prednisone group compared with the dexamethasone group (3% vs 0.3%; $P = 0.008$), but there was no difference in rate of vomiting at home (4% vs 2%; $P = .17$). Gordon et al found 13% of their prednisolone group vomited at least once after taking the home medication. Alternatively, Greenberg et al found no difference in rate of vomiting between patients given prednisone and dexamethasone in the ED (18% vs 10%; $P = .27$).

**Compliance**

The potential for better compliance with either the IM preparation or a shorter course of PO dexamethasone is largely touted as one of its benefits. A few studies investigated compliance internal to their studies. Gries et al measured parent-reported compliance of PO prednisone and found that 17% of children refused >75% of their prednisone doses, and 24% missed between 30% and 50% of their doses. Qureshi et al found more patients in the prednisone group were noncompliant compared with the dexamethasone group (4% vs 0.4%; $P = .004$) due to lack of funds or forgetting to fill the prescription. However, this discrepancy may reflect the study design in which the dexamethasone group received a dispensed second dose whereas the prednisone group had to fill a prescription.

**DISCUSSION**

The use of corticosteroids is standard of care for the treatment of asthma exacerbations and reduces the rate of hospitalization and relapse. Despite variations in study design, medication formulation, dosing regimen, and sample size, none of the existing pediatric clinical trials found any differences when comparing dexamethasone and prednisone in treating mild to moderate asthma exacerbations. Furthermore, our meta-analysis demonstrated no difference in unscheduled physician revisits and symptomatic return to baseline after ED discharge.

In asthma, as with any other chronic illness, adherence to medication is critical. Numerous factors contribute to compliance. These include palatability, frequency of dosing, treatment course length, adverse effects, and cost. If dexamethasone is as effective as prednisone, then these other factors contribute to its potential benefits. Liquid dexamethasone has also been shown to be more palatable than prednisone.

**FIGURE 1** Comparison of studies reporting unscheduled physician visits between the dexamethasone and prednisone groups.

**FIGURE 2** Comparison of studies reporting symptomatic return to baseline between the dexamethasone and prednisone groups.

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up (days)</th>
<th>Dexamethasone Revisits (%)</th>
<th>Prednisone Revisits (%)</th>
<th>Risk Difference (95% CI)</th>
<th>Weight (%)</th>
<th>Risk Difference (95% CI)</th>
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<tbody>
<tr>
<td>Altamimi et al</td>
<td>5</td>
<td>4/61 (6.6)</td>
<td>1/56 (1.8)</td>
<td>0.05 (−0.02 to 0.12)</td>
<td>19</td>
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<tr>
<td>Gordon et al</td>
<td>14</td>
<td>15/68 (22.1)</td>
<td>16/73 (21.9)</td>
<td>0.00 (−0.14 to 0.14)</td>
<td>5.1</td>
<td></td>
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<tr>
<td>Greenberg et al</td>
<td>10</td>
<td>8/51 (15.7)</td>
<td>3/38 (7.9)</td>
<td>0.08 (−0.05 to 0.21)</td>
<td>5.6</td>
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<tr>
<td>Gries et al</td>
<td>28</td>
<td>0/15 (0)</td>
<td>0/17 (0)</td>
<td>0.00 (−0.11 to 0.11)</td>
<td>7.4</td>
<td></td>
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<tr>
<td>Klig et al</td>
<td>5</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
<td>0.00 (−0.09 to 0.09)</td>
<td>12.4</td>
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<tr>
<td>Qureshi et al</td>
<td>10</td>
<td>20/272 (7.4)</td>
<td>18/261 (6.9)</td>
<td>0.00 (−0.04 to 0.05)</td>
<td>50.5</td>
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<td>Overall effect</td>
<td></td>
<td></td>
<td></td>
<td>0.02 (−0.02 to 0.05)</td>
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**FIGURE 1** Comparison of studies reporting unscheduled physician visits between the dexamethasone and prednisone groups.

**FIGURE 2** Comparison of studies reporting symptomatic return to baseline between the dexamethasone and prednisone groups.
than liquid prednisolone. One of dexamethasone’s biggest advantages is its shorter course due to its half-life of 36 to 72 hours and its approximately sixfold higher potency compared with prednisone, potentially improving compliance and reducing relapse. A shorter course of corticosteroids also limits cost. A recent cost-effectiveness analysis by Andrews et al., incorporating costs of return ED visits or subsequent hospitalization, found 2 days of PO dexamethasone provided a predicted cost savings of $3500 to $7000 per 100 patients compared with 5 days of prednisone.

Currently, the data are encouraging, but findings are mostly limited to small studies of mild to moderate asthma. None of these studies were true equivalence studies. Although recent reviews have been published regarding this question, this is the first to use meta-analysis for certain outcome measures. If there is a minor benefit of either therapy, smaller studies may not detect it (type II error). By including younger children with wheeze and cases of mild asthma that may otherwise have resolved without any corticosteroids, the results might not be extrapolated to children with acute, severe asthma, especially those requiring hospitalization. Furthermore, most studies excluded hospitalized patients. One small study by Ebrahimi and Sarkari found that a single dose of IV dexamethasone (0.6 mg/kg) resulted in a shorter length of stay in hospitalized children with asthma compared with 2 days of IV hydrocortisone. More evidence is required in the use of dexamethasone for patients hospitalized for asthma. One intriguing benefit to the hospitalist is the potential to dispense a second dose in the hospital before discharge, thereby ensuring a high degree of compliance and obviating the need for a prescription, which as many as 33% to 65% of pediatric patients fail to have filled. A prospective, randomized controlled trial would be useful in evaluating these issues.

**SUMMARY FOR THE PEDIATRIC HOSPITALIST**

**Formulation**

PO dexamethasone has a few different preparations and concentrations available for children. Providers can crush tablets (2 or 4 mg) and mix it in liquid or food or use premixed dexamethasone solution (0.5 mg/5 mL, 1 mg/mL). IV dexamethasone sodium phosphate (10 mg/mL) can also be given as an PO formulation. There have been studies demonstrating the ease and stability of giving IV dexamethasone sodium phosphate as an oral solution. The benefits of using the IV formulation orally include ease of delivery rather than crushing tablets to constitute in solution and the lower volume compared with premixed solution (the IV form is 10–100 times more concentrated). This preparation’s superior palatability compared with prednisolone has been confirmed, and the IV formulation given as an oral solution has been used in previous studies investigating dexamethasone treatment for bronchiolitis and croup.

**Dosing**

Each study of PO dexamethasone reviewed here used 0.6 mg/kg per dose, and all but 1 study investigated 2 daily doses. Collaboration between ED and inpatient providers is required for this regimen to be feasible in the hospital setting. Potentially, patients could be given the first dose of the IV form orally in the ED on admission, and the second dose on the inpatient unit on hospital day 2, eliminating the need for a prescription at discharge.

**CONCLUSIONS**

There is growing evidence that a shorter course of dexamethasone is as efficacious as prednisone in the treatment of mild to moderate asthma exacerbations in children presenting to the ED. However, a large, high-quality randomized controlled trial is needed to examine the role of dexamethasone versus prednisone in hospitalized children.

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