Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations

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Objective To determine whether 2 doses of dexamethasone is as effective as 5 days of prednisolone/prednisone therapy in improving symptoms and quality of life of children with asthma exacerbations admitted to the emergency department (ED).

Study design We conducted a randomized, noninferiority trial including patients aged 1-14 years who presented to the ED with acute asthma to compare the efficacy of 2 doses of dexamethasone (0.6 mg/kg/dose, experimental treatment) vs a 5-day course of prednisolone/prednisone (1.5 mg/kg/d, followed by 1 mg/kg/d on days 2-5, conventional treatment). Two follow-up telephone interviews were completed at 7 and 15 days. The primary outcome measures were the percentage of patients with asthma symptoms and quality of life at day 7. Secondary outcomes were unscheduled returns, admissions, adherence, and vomiting.

Results During the study period, 710 children who met the inclusion criteria were invited to participate and 590 agreed. Primary outcome data were available in 557 patients. At day 7, experimental and conventional groups did not show differences related to persistence of symptoms (56.6%, 95% CI 50.6-62.6 vs 58.3%, 95% CI 52.3-64.2, respectively), quality of life score (80.0 vs 77.7, not significant [ns]), admission rate (23.9% vs 21.7%, ns), unscheduled ED return visits (4.6% vs 3.3%, ns), and vomiting (2.1% vs 4.4%, ns). Adherence was greater in the dexamethasone group (99.3% vs 96.0%, $P < .05$).

Conclusion Two doses of dexamethasone may be an effective alternative to a 5-day course of prednisone/prednisolone for asthma exacerbations, as measured by persistence of symptoms and quality of life at day 7. *(J Pediatr 2017;191:190-6).*

Clinical Trial Registration clinicaltrialsregister.eu: 2013-003145-42.

Asthma is the most common chronic childhood disease and the leading cause of chronic disease-related morbidity, as measured by school absences, visits to the emergency department (ED), and hospitalizations.[1,2] Asthma exacerbations account for nearly 5% of ED visits, and approximately 15% may require admission.[3-6]

Treatment of exacerbations is based on rapid reversal of bronchospasm and reducing airway inflammation. International guidelines recommend corticosteroids as an essential part of the treatment.[1] They reduce inflammation and enhance the effects of bronchodilators, preventing relapses, admissions, and the need for β_2-agonist therapy.[7-9]

Traditionally, oral prednisone/prednisolone was the corticosteroid used, twice daily for 5 days, because the half-life is 12-36 hours. However, this treatment regimen, its bitter taste, and the incidence of vomiting may lead to poor adherence, with an increased risk of persistent symptoms and hospitalization.[10-13] In contrast, dexamethasone presents the advantage of a 2-dose regimen, due to its longer biologic half-life of 36-72 hours, and is a more palatable option.[14,15]

Previous randomized controlled trials proposed dexamethasone as an equivalent therapy to prednisone/prednisolone for asthma exacerbations, without differences in hospital admission, unscheduled returns, and with less vomiting.[16-23] A recent meta-analysis recommended to consider dexamethasone as a viable alternative to prednisone/prednisolone.[24] However, there are limitations to each of the trials included in terms of study design, dosing regimen, sample size, and age of patients enrolled.[24,25] Most important, all these studies have used different clinical scores, relapse, and admission rates, as main outcome variables. Thus, potential differences between the 2 treatments on the persistence of symptoms and quality of life after the ED visit remains unclear. For this reason, more evidence could help to safely introduce this change in clinical practice.

ARQoL	Asthma-Related Quality of Life
ED	Emergency department
ns	Not significant
O_2 sat	Oxygen saturation
PACT	Pediatric Asthma Control Tool
PS	Pulmonary score

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Supported by a 2014 annual research grant from the Spanish Society of Pediatric Emergency Medicine. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.08.030

We aimed to determine whether 2 doses of oral dexamethasone (experimental treatment) is as effective as 5 days of oral prednisolone/prednisone (conventional treatment) in improving symptoms of non–life-threatening asthma exacerbations and quality of life at day 7. The secondary objectives were to evaluate whether the experimental treatment is as effective as the conventional one in preventing hospital admissions and unscheduled returns to ED. Adherence to treatment and vomiting, school and work absenteeism, and parental satisfaction also were analyzed.

Patients and Methods

We conducted a prospective, randomized, open-label, noninferiority controlled trial (clinicaltrialsregister.eu: 2013-003145-42) to compare the effectiveness of the experimental treatment vs the conventional one in an acute-care teaching tertiary hospital near Bilbao, in the Basque Country (Spain). Our ED provides care to children <14 years of age, with a mean of 55 000 visits a year with approximately 3000 (5%) of these visits due to asthma exacerbations.

The treating physician identified the eligible participants who were children aged 12 months to 14 years old with asthma exacerbations who presented to the ED from September 2014 to October 2015. Asthma was defined as either previous medical diagnosis of asthma or at least 2 previous episodes of β_2-agonist–responsive wheeze or a first episode of wheezing in children over 2 years and history of atopy. An exacerbation of asthma was defined as acute asthma that prompts ED assessment, with any or all of the following clinical features: dyspnea, wheeze, acute cough, increased work of breathing, and/or increased requirement for bronchodilators from baseline use.[17-19,22,23] Parents or legal guardians of eligible participants received oral and written information about the study before written informed consent was obtained. When applicable, informed assent was obtained from the patient.

Children were excluded for any of the following reasons: presentation with critical or life-threatening asthma exacerbation, reported use of oral or parenteral corticosteroids in the previous 4 weeks, or presentation with respiratory failure that needed further support such as intravenous steroids, intravenous magnesium sulfate, and/or high-flow oxygen and admission to the pediatric intensive care unit. The treating physician was permitted to exclude patients if time constraints made enrollment unfeasible.

Before the trial, the research team was trained to conduct the follow-up interviews and performed information sessions for ED and ward staff. Primary Care pediatricians received an information letter.

After written informed consent was obtained, enrolled patients were randomized to 1 of 2 treatment groups. Randomization was performed by the statistical team with the software nQuery 7.0 (Statsols, Cork, Ireland). The randomization list generated by this process was concealed and safeguarded by the statistical team. The research team and treating physicians did not have access to this list. Allocation concealment was maintained by the use of sequentially numbered opaque envelopes containing a letter A (experimental treatment) or B (conventional treatment), following the randomization list. They were kept in the ED and opened by the treating physician after enrollment.

Interventions

All patients presenting to our ED with asthma exacerbations were managed according our current asthma protocol. To summarize, using the pulmonary score (PS)[26] and oxygen saturation (O_2 sat), patients were classified into 1 of 3 levels: mild (PS ≤3, O_2 sat >94%), moderate (PS 4-6, O_2 sat 91%-94%), or severe (PS > 6, O_2 sat <91%). Children received the first 2-3 β_2-agonist (albuterol) inhalations at 20-minute intervals, and subsequent doses or the addition of ipratropium bromide were given as ordered by the physician in charge according to the current protocol in our ED. Supplemental oxygen was administered to maintain O_2 sat ≥93%. Oral corticosteroids were prescribed during the first hour of treatment.

Patients allocated to the experimental treatment received an oral dose of dexamethasone (1 mg/mL) in the ED (0.6 mg/kg, maximum 12 mg), followed by a second dose in 24 hours. The selected dose of dexamethasone was based on previous asthma trials.[19,22] The pharmacy department prepared the oral formulation of dexamethasone. All patients allocated to dexamethasone arm received such oral formulation.

Patients allocated to the conventional treatment received a first dose of oral prednisone/prednisolone of 1.5 mg/kg in ED (maximum 60 mg), followed by 1 mg/kg/d (maximum 60 mg), twice-daily, on days 2-5, based on previous asthma guidelines.[1,22] Both the solution and tablet was the standard oral preparation. The choice between liquid or tablet was based on the age and preference of the child.

The dose of either medication was readministered orally if the patient vomited within 30 minutes. No further systemic steroids were prescribed before discharge.

Lack of response to treatment and/or persistent hypoxemia was a criterion for hospitalization. At discharge, families received prepackaged doses to take at home (with an extra dose if vomiting) and a follow-up by primary healthcare pediatricians in 24 hours was recommended in both groups. Our healthcare system provides free, universal, and comprehensive coverage. Albuterol inhalations were recommended on a 2- to 6-hour basis for the first day, then as ordered by primary care pediatricians. If children were admitted, randomized treatment was continued, and the dosing of β_2-agonist was at the discretion of the medical team.

Methods of Measurement

The research team completed standardized data collection sheets to record demographic and clinical variables. Data of unscheduled returns to ED and primary healthcare follow-up were retrieved from electronic records of the Basque Health Service.

The research team contacted study patients by telephone at day 7 and day 15 after the ED visit. At day 7, they performed a structured interview using validated questionnaires to assess the persistence of symptoms (using the pediatric asthma control