New York Methodist Hospital

Trial of One Versus Two Doses of Dexamethasone for Pediatric Asthma Exacerbation

NCT02725008

Study Protocol and Statistical Analysis Plan

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I BACKGROUND AND SIGNIFICANCE

Asthma is common cause of morbidity and mortality in Emergency Medicine. Oral steroids are a cornerstone of emergency management of asthma exacerbation. The traditionally recommended steroid regimen consists of 3 - 5 days of oral prednisone or prednisolone. However a growing body of literature supports the use of aone or two dose course of dexamethasone in lieu of prednisolone. The theoretical benefits of a shorter duration of treatment include lower cost, less caregiver burden and greater likelihood of compliance. The rationale behind the use of dexamethasone is its longer half-life and duration of action compared to prednisolone. In addition it is less foul-tasting and more palatable to young children, therefore increasing the ease of administration for caregivers.[i]

Several small to medium-sized randomized trials have compared dexamethasone to prednisolone[ii,iii,iv,v,vi,vii,viii]. There has been significant heterogeneity in trials with respect to the dosing and route of administration of dexamethasone. Two studies used a single dose of intramuscular dexamethasone, one study used a single oral dose, and two studies used two oral doses. An additional study not included in the meta-analysis used nebulized dexamethasone. None have demonstrated a clear clinical benefit to one particular course of treatment. A recent meta-analysis[ix] analyzed several of these studies and did not show clinical superiority of one medication over the other.

Based on this body of literature there is convincing evidence that dexamethasone is as effective as prednisolone or prednisone in the treatment of mild to moderate acute asthma exacerbations. However the optimal dosing strategy is unclear. Ideally one oral dose could be given in the emergency department, obviating the need to fill an outpatient prescription. At least one editorial has recommended this practice based on the findings in the above-mentioned studies and the theoretically equivalent bioavailability of dexamethasone after both intramuscular and oral administration[x] However only one study actually used a single oral dose regimen. They found no difference in their primary outcome, however there was a non-significant increased risk of unplanned return to ED in the dexamethasone group[8].

As of yet no randomized double blinded placebo-controlled study has directly compared the effectiveness of single versus two dose of dexamethasone for asthma. This question was addressed by a randomized open-label trial which found no significant difference.[xi] Another study investigated the question in a population of patients with first-time wheezing presumed to be bronchiolitis; again, no significant difference was found.[xii] However steroids are largely ineffective for bronchiolitis, so it is impossible to apply the results of that study to the treatment of asthma[xiii].

II. SPECIFIC AIMS

Our aim is to compare the effect of single versus repeated doses of oral dexamethasone on the rate of treatment failure in patients treated for a mild to moderate acute asthma exacerbation in the pediatric emergency department of an urban community hospital.

III. SUBJECT SELECTION

Subjects will be children aged 18 months to 20 years with a history of asthma - defined as at least 2 prior episodes of respiratory illness involving coughing, wheezing, or shortness of breath that responded to inhaled bronchodilators - who present to the Pediatric Emergency Department with symptoms consistent with asthma exacerbation, an initial Pulmonary Index Score of 12 or less, who have persistent symptoms after one dose of nebulized short acting beta-agonist.

Exclusion Criteria will include:

1. Hospitalization for asthma or respiratory complaint in past two months
2. Course of oral steroids within the past month
3. History of chronic pulmonary disease including cystic fibrosis or bronchopulmonary dysplasia,

4. History of any other severe chronic metabolic, endocrine, neuromuscular, cardiac, renal or hepatic disorder
5. Severe asthma exacerbation (PIS >11)
6. Girls and women over 14 years of age will need to complete a urine pregnancy test prior to enrollment, those currently pregnant will be ineligible. Subjects who become pregnant during the study will be withdrawn.

IV. SUBJECT ENROLLMENT

Patients will be eligible for enrollment whenever a study investigator is present in the pediatric emergency department. Families will be approached for enrollment and informed consent will be obtained after the decision to discharge the patient has been made by the ED provider. Verbal assent will be obtained from children over 6 years of age.

If enrolled participants will be randomized to receive either the study medication or placebo. Randomization will be in blocks by severity of exacerbation.

The study investigator will enter patient demographic information on a registration form that will be placed in a locked file cabinet. All further study information will be collected on forms identified only by an anonymous randomized study identification number.

V. STUDY PROCEDURES

As part of an ongoing quality improvement project designed to standardize treatment of patients with asthma in the pediatric ED, all patients felt by the triaging RN to have symptoms consistent with an asthma exacerbation will be seen as soon as possible after arrival by a provider [NP, resident, attending, fellow or 4th year medical student]. The severity of their exacerbation will be determined using a validated clinical assessment tool, the Pulmonary Index Score. The PIS will be charted in the medical record and used to select an appropriate clinical pathway corresponding to the severity of exacerbation. As part of the standardization effort, all patients with a mild or moderate exacerbation [PIS $\leq$ 11] will receive oral dexamethasone 0.6 mg/kg up to 16 mg orally as part of their ED therapy.

Once the decision is made to discharge the patient, the family will be approached by the study investigator for enrollment and obtainment of informed consent. If the family declines enrollment, then the decision to discharge home with an outpatient prescription for oral steroids will be made at the discretion of the ED provider caring for the patient.

If the family agrees to enroll, the study investigator will record the patient's name, contact information, preferred method of contact, primary care physician's name and contact information and medical record number on the enrollment form which will be placed in a locked file cabinet. The patient's ED provider will place a computerized medication order for study medication.

Once a medication order is place, our pharmacy will randomize the patient to either the treatment or control groups. They will prepare a syringe with the appropriate volume of dexamethasone injectable solution mixed with cherry syrup, or an equivalent volume of taste- and texture-matched placebo. This will be labeled with the patient's name and MRN as well as administration instructions. The pharmacy will maintain records of group allocation in a locked and sealed location, which will be broken only in the event of a significant adverse event, for planned interim analysis and after enrollment has been completed.

In the event that a caregiver loses the medication prior to administration, or the child vomits it at home, they will be instructed to call the ED, further management will be at the discretion of the provider present at that time, and the patient data will analyzed with their initial group under the intention-to-treat principle.

Patients will also be given a letter to take to their primary care physician, or any other follow-up provider, explaining their participation in the study and a request to contact the study coordinator if any of the events defining treatment failure is identified at the follow-up visit.

At the time of discharge families will be given a symptom questionnaire (Patient Self Assessment Score, PSAS) to complete every 24 hours. They will be asked to return to Emergency Department on day 5 for re-examination. They will be seen by a study investigator; a repeat PIS will be calculated at that time. A brief structured questionnaire will be administered asking about presence of any primary outcomes. If the family does not return for 5 day follow-up, they will be contacted by preferred means - phone, text message or e-mail the same questionnaire will be administered.

VI. STATISTICAL ANALYSIS

- **Primary Outcome:**
  - **Treatment failure** as defined by any of the following: unplanned hospitalization for asthma symptoms; unplanned return to emergency department, urgent care or clinic for asthma symptoms; or prescription of additional course of steroids within 5 days of enrollment.

    ●.○.1. Relative Risk of treatment failure between the experimental and control groups

    ●.○.2. Relative risk of treatment failure in each of the predefined subgroups (mild and moderate)

    ●.○.3. Time to treatment failure will be compared between the two groups using the Kaplan Meier analysis

- **Secondary Outcomes:**
  - Change in PIS between initial and follow-up visit
  - Change in PSAS over time -
  - Presence of adverse events including vomiting in the ED or at home, symptomatic hyperglycemia, subjective behavior change or subjective insomnia -
  - Caregiver preference for treatment regimen compared to prior steroid treatments.

  Categorical variables will be analyzed with the Chi-squared test.
  Continuous variables will be analyzed with the Mann-Whitney-U test
  Survival curves will be analyzed with the Kaplan-Meier test

- **Sample Size and Power Analysis**
  - We estimate a sample size of 220 will give us a power of 0.9 to detect a 9% difference in treatment failure at a significance of 0.05, inferring effect size from prior published studies comparing various dosing regimen of dexamethasone to prednisolone.

- **VII RISKS & DISCOMFORTS**
  - Significant side effects of single or multiple doses of dexamethasone are rare, and do not vary significantly from those experienced with prednisolone, with the exception of vomiting which is less common with dexamethasone.[8]

VIII. BENEFITS & RISKS

Potential benefits to study participants include potentially decreased exposure to steroids, decreased caregiver burden, increased ease of medication compliance. Potential risks to participants include toxicities associated with dexamethasone, potentially increased risk of treatment failure, potential need for unplanned or emergent return to ED or hospitalization.

The potential benefit to society determination of the optimal dosing strategy for dexamethasone in acute asthma exacerbation. The ideal regimen would be that which involves the fewest doses of medication and least burden on caregivers in terms of having to fill prescriptions and administer medications to often-recalcitrant patients without an increased risk of relapse or treatment failure.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data
   -Not applicable
b. Safety monitoring (e.g., Data Safety Monitoring Board, etc.)
   -A Data Safety Monitoring Board will be composed of the Principle Investigator, Departmental Research Coordinator and Pediatric Emergency Medicine physicians to investigate any serious side effects that occur during the study.
c. Outcomes monitoring
   -Preliminary statistics will be computed when we have enrolled 50% of the expected number of participants, if a significant difference (RR > 4) in favor of the control group is found in terms of the primary endpoint, the study will be ended at that point..
d. Adverse event reporting guidelines
   -Any unexpected or serious adverse events will be reported to the IRB, any security breaches will be reported to Hospital Security.

X REFERENCES

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