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Randomized controlled trial of dexamethasone oral preparations to assess palatability and adverse effects in children with asthma and croup

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Study Description and Protocol

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I. Specific Aim and Study Hypothesis

Specific Aim: To examine the palatability and acceptability of oral dexamethasone tablets crushed in apple sauce or pudding in comparison with the IV solution mixed with sugar syrup.

Hypothesis: We hypothesize that dexamethasone tablets crushed and administered in apple sauce or pudding at a dose of 0.6 mg/kg will be more palatable and acceptable in comparison to the IV form of the drug mixed in sugar syrup, for acute asthma exacerbations or croup in children aged 1 – 7 years in a pediatric emergency department.

II. Summary of Approach

To address the Specific Aim we will conduct a 2-arm RCT of dexamethasone tablets crushed in apple sauce or pudding in comparison to the current approach in the VCH ED, dexamethasone IV solution mixed in sugar syrup. The outcome, palatability and acceptability, will be assessed using a smiley-face analog scale and questionnaire that will be completed by the participant's parent 1-hour after administration of dexamethasone.

Treatment allocation (randomization) will be determined by a pre-determined randomization sequence in randomly-permuted blocks of 4, to be generated using Stata statistical software. Envelopes containing treatment allocation by sequential participant ID will be in the VCH-ED charting room where physicians and nurse practitioners enter orders for this medication in Epic. When a parent and patient provide consent/assent, the next envelope will be opened to determine treatment allocation. The clinician will then enter the order for dexamethasone tablets or IV solution in accordance with this. The clinician will ask the participant's parent to complete the data collection form (enclosed with this application) 1-hour after medication administration.

Treatment allocation cannot be blinded because the vehicle (apple sauce, pudding or sugar syrup) may be associated with palatability and acceptability.

III. Background

Asthma is the most prevalent chronic serious disease of childhood and the most frequent reason for childhood hospitalization in the United States. Asthma and croup are common patient diagnoses in the pediatric emergency department, and national guidelines recommend oral dexamethasone (a corticosteroid) as a fundamental treatment for both conditions. Dexamethasone is the preferred corticosteroid because the duration of clinical effect is 2-3 days, a period sufficient to treat these conditions. The current dexamethasone preparation used at VCH is the intravenous (IV) preparation mixed with cherry syrup. Our nursing staff prefers this preparation. However, some children spit this preparation out or have vomiting afterward.

IV. Inclusion and Exclusion Criteria

a. Inclusion criteria

i. Diagnosis of acute asthma exacerbation or croup (laryngotracheitis) in the VCH ED
ii. Age 1 to 7 years
iii. Dexamethasone treatment indicated
iv. No other acute or chronic process accounting for signs and symptoms (e.g., foreign body aspiration, pneumonia, cystic fibrosis)
v. Have not received systemic corticosteroid for current episode prior to enrollment

b. Exclusion criteria

i. Allergy to dexamethasone or apple sauce and pudding
ii. Unable to take medication orally

V. Subject Recruitment and Enrollment

We will enroll a convenience sample of 220 children 1-7 years of age and their parent, who will provide secondary data on their child. The investigators will be clinicians (attending physicians, fellows, pharmacists, nurses, or nurse practitioners) caring for patients in the VCH ED and will identify patients presenting with signs (e.g., tachypnea, wheezing, accessory muscle use) and symptoms (e.g., respiratory distress, dyspnea, cough,) consistent with an asthma exacerbation or croup (barky cough, inspiratory stridor).

The investigator will seek written informed consent from the parent and verbal assent from the child. If these are provided, the patient will be enrolled as a participant. Based on the proposed sample size described in a later section of the protocol, we anticipate enrollment of 220 patients and 220 parents.

VI. Study Procedures

Study Design

The study design will be an RCT with randomization in randomly-permuted blocks of four. After participant enrollment and ascertainment of treatment allocation (randomization), the clinician will order dexamethasone accordingly in tablet or IV form. The investigator will provide the parent with the study data form and instruct the parent in completion of this form 1-hour after dexamethasone administration.

VII. Predictor Variables

The predictor variable will be treatment-allocation (dexamethasone tablet or IV preparation administered orally.

VIII. Outcome Variables

The outcome variable will be palatability as defined by a 5-point "smiley-face" visual analog scale that the parent will complete on the study data form. Secondary outcomes will include emesis; need to re-administer the medication, need to provide alternate vehicle for medication (e.g., intravenous or intramuscular).

IX. Ethical Considerations

Systemic corticosteroid is a fundamental component of treatment for acute asthma exacerbations and croup, and dexamethasone has been identified at VCH and nationally as the optimal systemic corticosteroid for these children. The IV form of dexamethasone is used currently at VCH and in most pediatric ED's nationally. However, previous research has demonstrated that dexamethasone tablets are better tolerated than prednisolone (a different corticosteroid) syrup. There is equipoise whether dexamethasone as the IV form or tablet is more palatable and acceptable to these children, and this research seeks to answer the important question whether we should be using the tablets.

X. Risks of Study Participation

The risk to participants is not increased over current practice pertaining to administration of dexamethasone orally. The IV form is currently in use, and the tablets are widely acknowledged to be well tolerated by children. However, any apparent adverse events (e.g., allergy to apple sauce or pudding) will be reported by the investigators to Dr. Arnold who will immediately inform the IRB as noted below.

XI. Reporting of Adverse Events or Unanticipated Problems involving Risk to Subjects or Others

Any unexpected problems involving risks to subjects or others will be immediately reported to the Institutional Review Board of Vanderbilt University within ten days using the IRB form #1105.

XII. Study Withdrawal or Discontinuation

We are taking several measures to ensure that there is a clear distinction for the patient and parent/guardian(s) between clinical care and the research data collection for this investigation. Patients and their parent/guardian(s) will be told very explicitly by the investigators that their participation in this research investigation is entirely voluntary and that they may withdraw at any time. We will further emphasize verbally and in the informed consent document that a decision on the part of the patient or parent/guardian(s) to not participate will in no way change, compromise or jeopardize the patient's care. Indeed, we anticipate that some eligible patients will not be enrolled on this basis.

XIII. Data Management

A *Subject Data Form* will be used for data acquisition. All data will be entered in a secure REDCap database. This data will then be entered into Stata® (v.8, College Station, TX) for statistical analysis.

XIV. Clinicaltrials.gov registration: Pending

XV. Statistical Considerations

We will examine palatability using the 5-point analog ("smiley-face") scale and will ask the parent to make a mark on this scale. This mark will be used to estimate palatability as a continuous variable (e.g., 5.6 cm).

XVI. Sample Size

In a cohort of children aged 2 – 10 years who received oral dexamethasone as the elixir and using a 5-point Hedonic scale ("smiley-face" scale) was used to assess palatability,[1] Aljebab and colleagues reported a mean value for palatability of 3 with SD 1.1. If the true, mean difference between dexamethasone tablet and IV solution administered orally is 0.5, we will need to study 103 experimental subjects and 103 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05.

With the above in mind, we propose to enroll *110 participants in each treatment-allocation arm* of this RCT to account for dropouts and missing data.

XVII. Privacy and Confidentiality Issues

After the parents have signed the consent, one copy will be given to the parents and one copy will be kept by Dr. Arnold in his office. All efforts, within reason, will be made to keep protected health information (PHI) private. PHI is health information that is or has been gathered or kept by Vanderbilt as a result of a subject's healthcare. This includes data gathered for research studies and can be traced back to the subject. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, subjects are agreeing ("authorization") to the uses and likely sharing of PHI. If a patient decides to be in this research study, he/she is also agreeing to let the study team use and share PHI as described below.

As part of the study, Dr. Arnold and his study team may share the results of a subjects' study and/or non-study linked lab tests, as well as parts of the medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep PHI private. Dr. Arnold may give health data, without a subject's name, to others or use it for other research projects. Vanderbilt and Dr. Arnold and his staff will keep each subject's PHI in strict confidence, and will comply with any and all laws regarding the privacy of such information.

The study results will be kept in the subject's research record for at least six years after the study is finished. At that time, the research data that has not been put in the subject's medical record will be destroyed. Any research data that has been put into the medical record will be kept for an unknown length of time.

XVIII. Follow-up and Record Retention

The study results will be kept in the subject's research record for at least six years after the study is finished. At that time, the research data that has not been put in the subject's medical record will be destroyed. Any research data that has been put into the medical record will be kept for an unknown length of time.

XIX. Data Safety and Monitoring Plan

Surveillance for medical risks, including but not limited to exacerbation of airway obstruction and respiratory distress, will be performed continuously during the study of each subject by the study investigators. The clinical care team also monitors continuously for exacerbation of airway obstruction and is prepared to intervene immediately.

The Principal Investigator (Dr. Arnold) will closely oversee the protocol to monitor for any adverse events. Any adverse events will be reported as per IRB guidelines as noted above. Electronic data have several levels of protection. Any file that may contain patient identifiers will be password protected. All computers upon which data are stored are likewise password protected and are running anti-virus programs that automatically update definitions. All data are automatically backed-up to a secondary hard drive on a nightly basis. Access to the Vanderbilt computer network is protected at the level of firewalls, TCP wrappers and university assigned user ID's. Data are secured with encryption algorithms and the network is maintained by the Medical Center's Network Computer Services.

REFERENCES

1. Aljebab F, Alanazi M, Choonara I, Conroy S. Observational study on the palatability and tolerability of oral prednisolone and oral dexamethasone in children in Saudi Arabia and the UK. Arch Dis Child. 2018;103(1):83-8. Epub 2017/07/25. doi: 10.1136/archdischild-2017-312697. PubMed PMID: 28735259; PMCID: PMC5754874.