Cover Page for Approved Protocol

NCT #: 04563494

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COMIRB Protocol

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Protocol #: 20-1742
Project Title: The effects of IV vs oral dexamethasone on postoperative nausea, vomiting, pain, and drug cost in children undergoing tonsillectomy: A randomized controlled prospective non-inferiority study.
Principal Investigator: Jeremy Prager, MD
Version Date: August 20, 2025

I. Hypotheses and Specific Aims:
The hypothesis being tested in this study is that perioperative oral administration of dexamethasone, when compared to intravenous (IV) administration, offers a similar reduction in postoperative nausea and vomiting (PONV), and reduction in postoperative pain in pediatric patients undergoing tonsillectomy with or without adenoidectomy and/or tympanostomy tube placement. The specific aim of this study is to demonstrate non-inferiority of oral dexamethasone when compared to IV dexamethasone, given that there is currently a severe, sudden, and world-wide shortage of IV dexamethasone given its recent use in treating patients with covid19 disease.

II. Background and Significance:
Tonsillectomy is one of the most frequently performed ambulatory surgical procedures in children[1,2] and is associated with an incidence of postoperative nausea and vomiting (PONV) ranging between 40% and 73%.[3] Dexamethasone has been used as an antiemetic drug in patients undergoing chemotherapy with limited side effects[4] and has been found to have a prophylactic effect on postoperative nausea and vomiting in children undergoing tonsillectomy.[5-7] It may also decrease postoperative tissue injury, edema, and pain after tonsillectomy.[1,7]

Dexamethasone was recently found to be the first drug to save lives in the Covid-19 pandemic.[8] This has resulted in an immediate world-wide drug shortage, making routine perioperative use problematic. Although there are no published studies in the use of oral dexamethasone as a prophylactic agent to prevent PONV, we hypothesize that oral dexamethasone would be equally effective, more widely available, and less expensive. The parenteral form of dexamethasone costs approximately $2.50 for a 4 mg (1 mL) vial. The enteral form costs approximately $1.25 for a 4 mg dose. Bioavailability data suggests that the oral route is 53-90% bioavailable, comparable to the IV formulation, and most dosing recommendations in pharmacology and pharmacy studies do not recommend different dose or timing for IV versus PO formulations[9-11]. The relative advantage to oral dexamethasone is that it is currently widely available, that it is easy to take in a suspension formulation, and that it is less expensive than its intravenous counterpart. The potential disadvantage is that it does require taking something by mouth prior to surgery (and children occasionally resist this routine practice) and that it may not demonstrate the non-interiority we hypothesize that it will show. Thus, the aim of this randomized controlled prospective non-inferiority study is to assess the effect of a single dose of IV vs oral dexamethasone on PONV, pain, and cost in children undergoing tonsillectomy using a standardized anesthetic and surgical technique.

III. Preliminary Studies/Progress Report:
Aside from the studies referenced in the background, there have been no preliminary studies or other investigations assessing the use of oral versus IV dexamethasone in this clinical setting. The routine use of IV dexamethasone, its relatively inexpensive cost, and the hearty supply chain have never necessitated exploring oral options for surgical patients. The main driver for identifying a reasonable substitute is the covid19 pandemic and resultant worldwide shortage of this routine medication.

IV. Research Methods

A. Outcome Measure(s):
The primary outcome variable of the present study is the incidence of PONV.
The two secondary outcomes of interest are pain scores and need for surgical re-exploration for bleeding (a known surgical complication of tonsillectomy surgery).

An exploratory outcome is the cost of the treatments.

B. Description of Population to be Enrolled:
Pediatric patients 3 to 7 years of age (inclusive) undergoing tonsillectomy with or without adenoidectomy and tympanostomy tube placement, will be included in this study. Children who received antiemetics, steroids, anti-histaminic, or psychoactive drugs during the week before surgery will be excluded.

C. Study Design and Research Methods
After obtaining approval by the institutional Investigational Review Board and informed parental written consent, patients will be randomized either the day before surgery or at the time of arrival to the preoperative care center on the day of surgery. One hundred twenty-six patients, 3 to 7 years of age undergoing tonsillectomy with or without adenoidectomy and tympanostomy tube placement, will be included in this study. Children who received antiemetics, steroids, anti-histaminic, or psychoactive drugs during the week before surgery will be excluded. Patients will be prospectively randomized to receive oral or IV dexamethasone 0.5 mg/kg (maximum dose 8 mg). Patients in the IV group will receive the dose once an IV is placed in the operating room. They will receive an oral placebo once consent is obtained on arrival to the preoperative center on the day of surgery. Patients in the oral group will receive their dose once consent is obtained on arrival to the preoperative center on the day of surgery. They will receive a placebo once the IV is placed in the operating room. Randomization will be via a computer-generated table of numbers. Study drugs will be marked only with a coded number label. The anesthesiologist, surgeon, patient, and family will be unaware of drug identity. All medication preparation and handling will be done by CHCO Investigational Drug Service.

Patients will be fasted for solid foods for eight hours before surgery; clear liquids will be permitted until two hours before surgery. A standard anesthetic technique will be used. Premedication with oral acetaminophen 12.5-15 mg/kg will be given on arrival to the preoperative center. After obtaining consent study drug or placebo will be given at least 20 minutes before surgery. General anesthesia will be induced with sevoflurane and 60% nitrous oxide in oxygen via mask followed by insertion of an intravenous (IV) cannula. Dexamethasone or placebo will be given immediately following IV placement. Propofol 2 mg/kg and fentanyl 1 µg/kg will be given to facilitate intubation. Anesthesia will be maintained with a mixture of sevoflurane and air (FiO_2 < 0.3All children will receive fentanyl 1-3 µg/kg (titrated to pain response in the operating room) and dexmedetomidine 0.5 µg/kg once surgery starts. All children will receive ondansetron 0.1 mg/kg (maximum dose 4 mg).All children will receive 20 mL/kg lactated Ringer's solution during surgery (maximum IV fluid 750 mL given short time of surgical procedure). Routine monitoring including heart rate (ECG), arterial oxygen saturation (SpO2), blood pressure, temperature and end-tidal CO2 will be used

throughout surgery. Surgical technique will be standardized with the exception of not suctioning their stomachs at the completion of surgery.

Each subject will be assessed by nursing staff utilizing standard of care practices in the PACU and patients will stay in the PACU (phase one and two) for 4 hours after surgery. Postoperative nausea and vomiting (PONV) will be defined as vomiting and/or retching without expulsion of gastric content and will be treated with IV phenergan (0.25 mg/kg, maximum 25 mg) followed, if necessary, by IV diphenhydramine (1 mg/kg maximum 50 mg). Pain will be assessed using the numeric pain scale 0-10, Faces, Legs, Arms, Crying, Consolability Scale (FLACC Scale), or Revised Faces Scale.[12,13] Pain scores > 5 will be treated with IV fentanyl 0.5 µg/kg that can be repeated every 5 minutes for pain when necessary.

The following parameters were observed and recorded: incidence of PONV throughout PACU stay and need for treatment (phenergan and/or diphendydramine); postoperative pain in the PACU until discharge to the ward or home; and incidence of surgical re-exploration for bleeding. On the second postoperative day, the incidence of PONV and pain severity were evaluated by a phone call to the parents. Assessment of postoperative pain will be performed using the postoperative pain measure for parents (PPMP) scale and parents will be asked if their child vomited at home.[14]

D. Description, Risks and Justification of Procedures and Data Collection Tools:

The only additional procedure for this study is the administration of an oral liquid medication in the preoperative area. No additional procedures will be done. All patients will receive routine perioperative care they would be receiving as part of their normally scheduled surgery and anesthesia.

Risks to the patient are minimal and are as follows: Potential annoyance or difficulty taking the oral medication (or placebo) in the preoperative area, the risk that the oral medication may not work as well as the IV form (for patients who are randomized to the oral arm), and the uncertainty of randomization may make some parents uncomfortable.

De-identified data will be managed using REDCap online service (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). A multi-institutional consortium that includes University of Colorado-Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management, developed the system. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry.

E. Potential Scientific Problems:

The only potential scientific problem we currently identify is if our current supply of IV dexamethasone does not last long enough to enroll enough patients to demonstrate non-inferiority. We have an approximate supply of 2-3 months of IV dexamethasone and based on current case volumes we estimate it will take about 2 months to enroll patients to achieve the number needed to demonstrate our aims.

F. Data Analysis Plan:

The primary outcome variable of the present study is the incidence of PONV. Previous studies reported an incidence of PONV of 40-70% and a reduction of this incidence by about 50% with IV dexamethasone (i.e., to 20-35% incidence of PONV with dual-agent PONV prophylaxis). Based on this prior data, we would need to enroll 63 participants in each group, up to 160 total participants in total, to achieve 80% power with α=0.025 to declare non-inferiority under a null hypothesis of a 20% incidence of PONV with no difference between groups and a clinically meaningful non-

inferiority margin of 20%. The margin of 20%, while somewhat broad, was chosen given the wide range of PONV in this age group as well as the inevitable and sudden unavailability of the IV medication and need to find a “reasonable” substitute. (ie our hand is forced to accept a broader definition of what is “reasonable” given that the IV medication will be gone due to covid-19 with no replacement identified prior to the drugs unavailability)The primary outcome will be evaluated with a two-sample test of proportions and the 95% confidence interval for the differences will be compared to evaluate if it includes the non-inferiority margin. Data will be analyzed as per-protocol.

The two secondary outcomes of interest are pain scores and need for surgical re-exploration for bleeding. Both of these will similarly assume a non-inferiority approach where the non-inferiority margin for PO dexamethasone is set at no more than 20% of the observed pain or incidence in the IV dexamethasone. The incidence of bleeding will be evaluated using a two-sample test of proportions. The pain scores will be evaluated using a two-sample t-test and the 95% confidence interval compared to the non-inferiority margin. If the pain scores are not normally distributed, as evaluated graphically and by the Shapiro-Wilk test for normality, alternative methods will be considered including bootstrap methods or quantile regression for the median pain score.

An exploratory outcome is the cost of the treatments. Given that PO dexamethasone is approximately 50% cheaper than IV dexamethasone, this will be described with summary statistics for cost per unit administered. Demographic measures and summaries will be presented as mean (standard deviation) or median (interquartile range) for continuous measures and count (percent) for categorical measures. All analyses will be completed using R (Vienna, Austria) and SAS (Cary, North Carolina).

G. Summarize Knowledge to be Gained:

We will gain knowledge about if oral dexamethasone can be utilized as a reasonable substitute for IV dexamethasone in this patient population. We also intend for the results of this study to be useful for our colleagues around the world, who are trying to continue to care for patients routine surgical and medical needs in the setting of severe challenges brought on by the covid19 pandemic.

H. References:

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