Randomized control trial of postoperative course of oral dexamethasone and effect on opioid usage in pediatric tonsillectomies in a tertiary care center

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Purpose of the Study

The purpose of this study is to determine if a post-operative course of oral dexamethasone affects opioid usage in pediatric patients undergoing tonsillectomy. Children and young adults, 4-21 years of age undergoing elective tonsillectomy within the Duke Health System without contraindication for steroid use will be enrolled. We hypothesize that a post-operative course of steroids will reduce opioid use.

Primary Objectives:

- To understand the effect, positive or negative, that post-operative steroids have on post-operative pain control and analgesic use to optimize post-operative pain regimens
- To assess the feasibility of reducing opioid use in post-operative tonsillectomy in pediatric patients

Background & Significance

We are in an opioid epidemic. Pain control while minimizing opioid use is a major goal. Adenotonsillectomy is one of the most common ENT surgeries, done on both children and adults. In 2013, a codeine black box warning was passed, changing pain management for adenotonsillectomy in children. In February 2019, AAO-HNS included a recommendation for a single intravenous dexamethasone dose intraoperative for all pediatric tonsillectomies as a way to reduce post-operative nausea and vomiting, pain, and first oral intake. Additionally, it recommended that clinicians encourage the use of ibuprofen and acetaminophen to improve post-operative pain control and reduce opioid use. Further, oxycodone and morphine are suggested as preferable opioids given their lack of metabolism by CYP2D6 and therefore lower likelihood of unintended sedation (Mitchell 2019, Batisaki 2017, Tan 2017). There is wide variation in current post-operative narcotic prescribing practices (Horton, 2019). Chua et al., 2019 in their large cohort analysis using insurance claims did not show a change in return visits for pain associated with opioid prescription fills.

Literature on post-operative steroid courses with pediatric tonsillectomy have mixed results in terms of pain scores and post-operative benefits. Redman et al., 2018 in their retrospective chart review (n= 1200) utilized three post-operative doses of dexamethasone and noted a decreased number of patient phone calls and decreased rate of hemorrhage in the steroid group. Park et al., 2015, a randomized clinical trial (RCT) (n=198), showed decreased pain, quicker return to normal diet and increased re-epithelization one week post-operatively in the 7-day post-operative prednisolone steroid group. Palme et al.,2000, in their double blind placebo controlled RCT (n=50) also utilized a 7-day post-operative course of prednisolone and demonstrated decreased nausea post-operatively and less paracetamol use in the 8 days after surgery. This study included children and adults > 5 years old. Maccassey et al., 2012, in their double blinded placebo controlled RCT (n=215) a 5 day prednisolone course and did not demonstrate a significant difference in post-operative nausea, pain and sleep. Generally short courses of post-operative steroids are considered safe and there were no adverse side effects noted in the above studies. There is a deficit of literature however on the effects of these short steroid courses on opioid use in pediatric tonsillectomies.

Literature on post-operative steroids with adults and children greater than 12 years old undergoing tonsillectomy is also mixed. Plante et al., 2012 in a systematic review of RCTs identified 29 RCTs (n=2674 patients) demonstrated comparable rates of bleeding with systemic steroids during tonsillectomy but increased incidence of intervention. This study is reflected in the 2014 SFORL guidelines recommending against the concurrent use of steroids and NSAIDS medication post tonsillectomy (Paganelli 2014). Batistaki et al.,2017 reviewed 7 RCT pediatric tonsillectomy studies, of which included perioperative dexamethasone doses with majority of studies showing reduced opioid use or increased time to first opioid dose. However these studies did not evaluate post-operative courses of steroids. Lachance et al., 2008 preformed a similar design to the present study with the exception of subjects being adults. In this multicentric, double blind, placebo controlled, RCT (n=102) patients were randomized to receive a 4 day dexamethasone taper versus placebo.There was no statistically significant difference in visual analog pain scales scores or hydromorphone consumption between the two groups (Lachance, 2008). Stewart et al., 2002 in their double blind RCT (n=200) utilizing 8 day post-operative courses of steroids and/or anti-inflammatory v. placebo, showed lower pain scores in a combination group of dexamethasone and piroxicam as well as less analgesic requirement in the 10 days following surgery (Stewart, 2002).
There is a lack of research however on post-operative courses of steroids and optimal pain regimen for pediatric tonsillectomy. Specifically there is a deficit of research on the effect of post-operative steroid courses and opioid utilization, which the present study hopes to in part address.

Design & Procedures

This is a randomized control trial of pediatric subjects who are scheduled to undergo tonsillectomy or adenotonsillectomy. Patients will be randomized to receive a post-operative steroid course of oral dexamethasone in addition to opioids/acetaminophen/NSAIDs or opioids/acetaminophen/NSAIDS alone. All drugs will be given per approved FDA labeling, Dosing regimen in line with Cramer et al., (2020). Randomization will be based on odd or even day of surgery to be determined at time of scheduling surgery (at least 24 hours prior to surgery), with odd day receiving steroids. Patients will be considered off study after their follow-up appointment approximately 4-6 weeks post operatively. Steroid dosage will be weight based dexamethasone solution or tablet (depending on age/preference of patient) at 0.5mg/kg/day max of 8mg/day, administered on post-operative days 1,3,5,7. This is based on current practices of surgeons at Duke and in line with post-operative steroid courses utilized in the literature (Park 2015, Maccassey 2012, Redman 2018, Lachance 2008, Palme 2000).

There will be standardization of post-operative analgesics (narcotics and non-narcotic medication).

- Oxycodone solution or tablet (depending on age of patient) at 0.05-0.1 mg/kg/dose every 6hrs; max 5mg (obese/OSA); prescribe 30 doses
- Acetaminophen 10-15 mg/kg/dose every 6 hours; max 500mg per dose; prescribe 56 doses (over the counter medication)
- Ibuprofen 5-10 mg/kg/dose every 6 hours; max 200 mg/dose; prescribe 56 doses (over the counter medication)

Patients (or with the aid of parents/legal guardian for subjects unable to complete on their own) will complete a pain diary electronically twice a day (AM and PM) for 14 days post operatively. Variables elicited will include: Pain score (Visual analog scale and Oucher as utilized in Park et al 2015, last analgesic administration (time before survey), missed steroid doses (if applicable), tolerance of soft/regular diet, and analgesic consumption (e.g. ibuprofen, acetaminophen, oxycodone) over the preceding 12 hours, as well as nausea/emesis fever, bleeding, and insomnia.

Post-operative complications including emergency department (ED) presentation, readmission or re-operation within 30 days of surgery will be recorded as well as if admitted post operatively: post-operative length of stay, medication administration and oral intake during hospitalization. Subjects/parents/legal guardians will be called within two weeks (plus or minus 5 business days) postoperatively to check in on compliance and any complications.

Remaining steroid and opioid medication will be measured either in person at the post-op visit or via video conference within 4-6 weeks postoperatively for research purposes only. Zoom or Webex will be used in this case. If performed via video and the patient was prescribed tablets, they will count the pills in front of the PI or study team. If performed via video and the patient is using solution, the patient will be asked to use syringe/dropper to suck up the medicine until it is gone. They will hold the syringe/dropper close to the camera so the PI or study team can see how many mLs are left.
If for some reason the subject needs additional steroids postoperatively, this will be noted and they will be removed from the study regardless of which arm they are in. Chart review data and collected responses will be included in analysis. Total follow up period of 2-6 weeks.

Other variables to be collected on enrolled subjects will include demographics including MRN of the subject, name of subject and parent/guardian, phone number of parent/guardian, email address of the parent/guardian, age, gender, race/ethnicity, weight, BMI, tonsil size, surgical details including surgeon, operative technique and date, indication for surgery, American Society of Anesthesiologists (ASA) category, length of hospital stay, comorbidities and pain medication refills. Data will be collected and stored within an encrypted Redcap database.

Selection of Subjects

Inclusion Criteria

- Age 4-21 years at time of surgery
- Scheduled for tonsillectomy or adenotonsillectomy surgery

Exclusion Criteria

- Prior history of intracapsular tonsillectomy
- Previous diagnoses of Down Syndrome or developmental delay
- Presence of gastrostomy (g) tube
- A contraindication to steroids or steroid usage within 30 days prior to surgery including diabetes, allergy to steroid, already on chronic steroid, immune deficiency
- Active infection at the time of surgery

- Concurrent invasive operative procedures at the time of surgery (Excluding: Exam under Anesthesia; Auditory Brainstem Response, Imaging studies, Pressure Equalization tubes, Direct Laryngoscopy +/- Bronchoscopy without intervention).
- Unable to read or speak English
- Pregnant or breastfeeding females

Subject Recruitment and Compensation

We anticipate enrolling a total of 60 subjects at Duke University Medical Center (DUMC) including the Children's Health Center, South Durham clinics and Duke Raleigh.

Patients will be identified from pediatric Head and Neck clinics at Duke and Duke Raleigh. Patients who meet the inclusion and exclusion criteria listed above will be approached for possible study participation after a member of the clinical care team asks the patient's/parent or guardian's permission to be contacted by the study team. The study coordinator (or member of the research team) will then review the records, and upon determination that the patient is deemed eligible for this protocol, the clinical research coordinator (CRC) will contact the patient. This may occur in clinic or via phone using an IRB approved phone script. If the patient/parent or guardian indicates interest in study participation, the study coordinator will thoroughly explain the required elements of informed consent and all aspects of the study to the subject including inclusion/exclusion criteria, risks, benefits, and alternative to study participation.

Compensation of $50 will be given to subjects at the end of their study participation.

Risk/Benefit Assessment

The risk of being part of this research study is that the decision on post-operative course of treatment is randomized – the clinical care team will not make that decision. However, both dexamethasone and oxycodone are routinely prescribed for pain management. Common side effects of dexamethasone are nausea, vomiting, stomach upset, swelling, headache, dizziness, mood changes, such as depression, mood swings, or personality changes, trouble falling asleep, anxiety, low potassium levels (causing symptoms such as tiredness), high blood glucose, high blood pressure.

Dexamethasone and oxycodone are known to increase the risk of birth defects and miscarriage in humans when taken during pregnancy and may have risks for breastfed infants. Therefore, females who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in studies using dexamethasone or oxycodone.

If the participant could possibly become pregnant and has a partner who is able to father children, a blood pregnancy test will be performed, and it must be negative to continue in the study.

The participant may benefit from this study if they are randomized to use of dexamethasone as we believe this will reduce the use of oxycodone. Participants randomized to oxycodone alone will not have any benefit beyond standard of care. There may be benefit to society as a whole as we hope this research will potentially reduce opioid use post-operatively and help us to understand the effect that post-operative steroids have on pain control and analgesic use to optimize post-operative pain regimens.

Data Analysis & Statistical Considerations

Statistical Analyses: The primary efficacy endpoint is dose of opioids used post-surgery in the two treatment arms. Secondary endpoints are pain scores, rate of change of pain scores and rate of complications post-surgery. The continuous outcomes will be analyzed using either a two-sample t-test or non-parametric Wilcoxon test, depending on whether the time is normal or non-normal. Associations between treatment arms and categorical variables will be examined using Chi-squared tests. Analysis will be conducted under Intent-To-Treat (ITT), and any missing will be imputed under missing at random (MAR). Statistical significance will be fixed at a two-tailed 0.05 alpha level. The analysis of secondary and exploratory efficacy endpoints and other additional analysis will be described further in the Statistical Analysis Plan (SAP). Secondary endpoints will be examined with and without adjusting for multiple comparisons, using Bonferroni correction. Safety endpoints and other assessments such as readmission/ and presentation to emergency for dehydration, pain or post-operative bleeds, and need for operative intervention as under data & safety monitoring below, will be evaluated descriptively and will include all subjects randomized to the study. In addition, complete case analyses will also be conducted. Analysis will be conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC). The lead statistician for the study is Dr. Kuchibhatla who is responsible for study design, monitoring of the study, and statistical analysis plan (SAP) and the analyses will be conducted by a previously identified BERD statistician.

Power and Sample Size Calculations: No studies exist for this sample where the primary outcome is opioid use post-surgery. Hence, based on the study, Park et al., we use change in pain score in the treatment groups similar to this study as the primary outcome for sample size calculations; the mean change/SD in the non-steroidal and steroidal treatment arms are 2.64(2.6) and 1.4(1.5), respectively. For 70% power to reject the null hypothesis of equal means with the means/standard deviations listed above, and for a significance level (alpha) of 0.15 using a two-sided two-sample unequal-variance t-test, the study requires a sample size of 24 in each treatment, for a total of 48 (PASS-2016, 2018). Accounting for about 20% drop out, we plan to recruit about 29 per arm for a total of 58.

PASS 16 Power Analysis and Sample Size Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Data & Safety Monitoring

The PI will ensure proper data and safety monitoring. Any serious adverse events such as will be reported by the PI to the IRB within 5 business days. Events that are considered both serious and

unanticipated will be reported to the IRB within 24 hours of the PI's knowledge of the event. The PI will reconsider study design and procedures in discussion with the IRB should adjustments be warranted. Adverse events will be monitored from the time of surgery until 14 days post-operatively.

A serious adverse event would be considered bleeding requiring operation and readmission for dehydration.

Adverse Events would include IV fluids given in the ED, bleeding that is not treated operatively, insomnia, nausea, fever and constipation from opioids.