Study Protocol

Official Title: Post-operative Course of Dexamethasone to Reduce Tonsillectomy Morbidity

ClinicalTrials.gov ID (NCT number): NCT04879823

Protocol Date: 01/26/2023

Scientific Background

Tonsillectomy is by far the most painful otolaryngological procedure with a mean worst post-operative pain rating of 5.9/10 while most other procedures have mean worst post-operative ratings between 2.3/10 to 4.4/10.[1] Multiple interventions have been shown to decrease post-tonsillectomy morbidity and to limit unnecessary use of opioid prescriptions in children. A retrospective study from our institution found that a mandated opioid consent form significantly decreased opioid prescriptions while not significantly increasing post-operative nursing calls or ED visits.[2] Intracapsular tonsillectomy in which tonsillar tissue is removed while preserving the capsule was associated with less pain post-operatively compared to traditional approaches.[3] Furthermore, intravenous steroids in the perioperative period have been consistently shown in randomized control trials (RCTs) to reduced post-operative pain and complications.[4] However, the efficacy of a post-operative course of oral steroids to decrease the burden of pediatric tonsillectomy is still under question.

To our knowledge, there are currently two published placebo-controlled RCTs of a post-tonsillectomy course of oral corticosteroids with predominately pediatric samples. Palme et al. randomized 50 patients with a mean age of approximately 14 years old to either a one-week course of prednisolone or placebo, however, adults and children were examined together and no difference in pain on a 10-point scale was revealed on any day.[5] Interestingly, there was significantly less nausea/vomiting in the steroid-group on days 4-7 and there was less acetaminophen intake on days two, seven, and eight. Macassey et al. randomized 215 children to a five-day course of prednisolone or placebo and the steroid group did not have a significant improvement in post-operative pain or any other quality of life.[6] On the other hand, Redmann et al. found that a post-operative course of dexamethasone (Dex) significantly decreased the frequency of post-operative phone calls for pain and the frequency of bleeding in a retrospective review.[7] Later, Greenwell et al. showed that Dex increased pain reduction on post-operative days three, four, and five in a non-placebo controlled randomized trial of children aged 3-10.[8]

As Dex has been shown to be efficacious in a RCT and is a safe medication to use in short courses, we present our protocol on a placebo controlled RCT with an estimated enrollment of 300 children aged 3-17. The experimental group will receive oral Dex on post-operative days 2, 4, and 6 (0.5 mg/kg; max dose: 20 mg). The long-term goal is to more definitively determine the potential for a post-operative course of steroids to become standard of care following pediatric tonsillectomy.

1. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013;118(4):934-944.
2. Whelan RL, McCoy J, Mirson L, Chi DH. Opioid prescription and postoperative outcomes in pediatric patients. Laryngoscope. 2019;129(6):1477-1481.
3. Borgström A, Nerfeldt P, Friberg D. Postoperative pain and bleeding after adenotonsillectomy versus adenotonsillotomy in pediatric obstructive sleep apnea: an RCT. Eur Arch Otorhinolaryngol. 2019;276(11):3231-3238.

4. Titirungruang C, Seresirikachorn K, Kasemsuwan P, Hirunwiwatkul P. The use of steroids to reduce complications after tonsillectomy: a systematic review and meta-analysis of randomized controlled studies. Eur Arch Otorhinolaryngol. 2019;276(2):585-604.
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6. Macassey E, Dawes P, Taylor B, Gray A. The effect of a postoperative course of oral prednisone on postoperative morbidity following childhood tonsillectomy. Otolaryngol Head Neck Surg. 2012;147(3):551-556.
7. Redmann AJ, Maksimoski M, Brumbaugh C, Ishman SL. The effect of postoperative steroids on post-tonsillectomy pain and need for postoperative physician contact. Laryngoscope. 2018;128(9):2187-2192.
8. Greenwell AG, Isaiah A, Pereira KD. Recovery After Adenotonsillectomy-Do Steroids Help? Outcomes From a Randomized Controlled Trial. Otolaryngol Head Neck Surg. 2020 Nov 24:194599820973250. doi: 10.1177/0194599820973250. Epub ahead of print. PMID: 33228459.

Study Objectives

Aim: To determine if an oral systemic course of steroids is a safe and effective option in lowering pain and complications following adenotonsillectomy in various pediatric age groups.

Hypothesis 1: Post-operative pain will be lower in steroids group (experimental) as compared to the group receiving placebo (control).

Hypothesis 2: There will be a decreased rate of post-operative complications in the steroids group as compared to the placebo group. There will be a decreased rate of post-operative complications in the steroid group as compared to the placebo group. Complications include oropharyngeal bleeding, pain, dehydration as evidenced by fewer calls to nurses and ED re-presentations.

Hypothesis 3: There will be a decreased frequency of opioid prescriptions and non-opioid analgesic consumption in the steroids group as compared to the placebo group.

Study Design & Methods

Design: Experimental, placebo controlled double-blinded randomized control trial.

Methods:

Between the time of the pre-operative appointment and the day of surgery, all listed investigators will be involved in the use of the electronic medical record to confirm that patients meet inclusion criteria, and to exclude any patients who meet the exclusion criteria. Upon completion of screening, patients will be randomized using a block randomization algorithm in order to have an equal distribution of Dexamethasone (Dex) and placebo regimens among three age groups -

young children (ages 3-7), preadolescents (ages 8-12), and teenagers (ages 13-17). We will be recruiting 120 patients ages 3-7, 120 patients ages 8-12, and 60 patients ages 13-17 due to decreased frequency of adenotonsillectomy in this age group.

At the day of surgery, the parents will receive the patient pain diary. Along with the standard post-operative information provided for adenotonsillectomy (which includes items such as emergency contact information, contact information for medical questions, and expected post-operative progress), they will also receive a prescription for the pain medications and a pre-packaged "Study Drug" bag, along with instructions on its proper administration. A drug administration instructional video was also made. This video will only be available via the link (ie not searchable on YouTube).

For the Dex group, IV Dexamethasone Sodium Phosphate (to be taken orally as is routinely done for croup and asthma management in CHP Emergency Department) will be prescribed at a dose of 0.5 mg/kg with a max dose of 20 mg to be taken the morning of days, 2, 4, and 6 post-operatively. In the Placebo group, an equal volume of water will be prescribed to patients. Ibuprofen will be prescribed at 10 mg/kg every 6 hours or as needed, and acetaminophen will be given at 15 mg/kg every 4 hours or as needed as part of standard of care. All medications will be prescribed in liquid suspension form for ease of use in pediatric populations. Subjects or parents will purchase non-opioid analgesics while the study drug or placebo will be provided at no cost and dosage will be given to subjects in easy-to-understand language on a parent instruction sheet (eg. x mL every 4 hours or as needed, with maximum allowable amount of y mL in a day). Patients will not be prescribed an opioid prescription on the day of surgery. However, caregivers may request it for their child at any point of the study without affecting participation. It is up to the child's physician to determine whether or not to prescribe the opioid. An instructional drug administration video link will be sent to the families on Day 1 post-surgery to the cell phone number provided to the researchers on the consent form.

A parent instruction sheet for each group was developed with the following information:
Steroid group –
Parents will be advised:
-on mornings of post-operative days 2, 4, and 6, to mix a specified amount (uniquely prescribed based off of weight of each patient) of "Study Drug" into a 5 mL of pre-packaged cherry syrup using the provided oral syringe.
As part of standard of care:
-to give their child acetaminophen every 4 hours and ibuprofen every 6 hours around the clock for the first 3 days post-surgery.
-after the first 3 days, give subject both medications on an as needed basis, depending on the ability of the subject to take liquids by mouth (>32 oz/day) and/or if the child complains or behaves like they are in pain.
-parents may request opioids from the physician at any point during the trial (provided there are no health-related contraindications).

Placebo group -
Parents will be advised:

-on mornings of post-operative days 2, 4, and 6, to mix a specified amount (uniquely prescribed based off of weight of each patient) of “Study Drug” into a 5 mL of pre-packaged cherry syrup using the provided oral syringe.
As part of standard of care:
-to give their child acetaminophen every 4 hours and ibuprofen every 6 hours around the clock for the first 3 days post-surgery.
-after the first 3 days, give subject both medications on an as needed basis, depending on the ability of the subject to take liquids by mouth (>32 oz/day) and/or if the child complains or behaves like they are in pain.
-parents may request opioids from the physician at any point during the trial (provided there are no health-related contraindications).

The Pain Diary is a questionnaire which caregivers will use to assess variables of interest such as amount/frequency of medications taken, pain level, socioeconomic factors, side effects, and satisfaction with pain relief. The diary will be completed by post- operative day 14. The Wong-Baker FACES Pain Rating Scale instructions will be included in the study folder for data integrity.
Families can return the pain diary in multiple ways:
1.) in person at the post-operative appointment:
-A post-operative appointment at CHP Main only can be scheduled and the patient and caregiver will return the diary in person in order to receive the compensation for participating in this trial. A post-operative appointment can be scheduled at CHP Main and the family can return the diary to receive compensation for participation in person.
If the family does not schedule a post-operative appointment at the main hospital, has forgotten the diary at the appointment or for convenience, the pain diary must be emailed to the research team by scanning the diary or taking pictures on their phone.
2.) By mail using the provided post-marked envelope in the study folder
-The $50 compensation will then be mailed to the family when the paper copy is received.
3.) By email:
-For families that have a post-operative appointment at locations other than the main hospital or do not want a post-operative appointment, they can return the pain diary by scanning the diary or taking pictures of the diary on their phone and emailing an electronic copy to the research team. The $50 compensation will then be mailed to the family when the electronic copy is received.

Dexamethasone is sometimes given when children return to the hospital post-operatively, are seen at express/urgent care, or utilize telemedicine, and they receive another dose of steroids for bleeding, severe pain, or edema. Families will be encouraged to continue participation in our study with little increased risk of short-term side effects (ie irritability). Language of continued participation is in the consent and on the "healthcare provider script" provided in the study folder. We will ask families to make note on the pain diary of details of any additional steroids given during the study period.

Follow-up communication:
We will be using REDCap to send out a follow-up text message the day after surgery and on day 8. We will enable a third party web service named Twilio. Twilio is able to be enabled through

REDCap and sends SMS texts to cell phones. We will be sending a web link to YouTube for video drug administration instructions in the first follow-up text.

If the family did not make a post-operative appointment at the main hospital by 2 weeks post-surgery, the research team will call the caregiver 2-6 weeks after surgery to remind them to return the study diary. At this time, participants may request an additional post-marked envelope sent to their home address instead of scanning the diary electronically.

Finally, further research activities will include viewing medical charts of the included subjects, harvesting the data from these medical records, placing these data on a datasheet, and then placing the data in a database for statistical analysis. All listed investigators will work together to obtain the data. Prior to harvesting the data, we will assign subject numbers for all participants so that subjects' names do not need to be recorded on our datasheets or in our database. Data collection and analysis is estimated to be completed in 1-2 years by the listed investigators. Data will not be collected on subjects who turn 18 during the study time period (past the 18th birthdate). We will assure that patients who are eligible and 17 years old are not turning 18 years old within the first 6 weeks after surgery for follow-up data. This would be a rare occurrence and we will exclude these patients rather than obtaining continued consent.

Eligibility Criteria

Inclusion:
Patients age 3 - 17 undergoing adenotonsillectomy meet inclusion criteria

Exclusion:
Patients with Down syndrome
Patients with a history of coagulopathy
Patients with craniofacial abnormalities other than plagiocephaly or submucous cleft palate (SMCP)
Caregivers who cannot speak, read, or write in English proficiently
Patients who take systemic corticosteroids during the enrollment period
Patients who take opioids during the enrollment period
Patients who take chronic opioids
Patients who are pregnant
Patients with allergy to or contraindication for taking any of the study medications (including red dye allergy)
Patients who have the inability to communicate
Patients who have the inability to localize pain
Patients who have type 1 diabetes
Patients who have type 2 diabetes

Statistical Analysis Plan

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Study Outcomes

Primary Outcome

- Average pain burden pre-medication 2-8 days post-operatively. This will be self-reported and measured on the Wong-Baker FACES Pain Rating Scale (0 to 10) before taking pain medication via the study take-home pain diary.

Secondary Outcomes

- Emergency department or urgent care visits 30 days post-operatively from the pain diary and from the patients' medical record.
- Average pain burden post-medication 2-8 days post-operatively. This will be self-reported and measured on the Wong-Baker FACES Pain Rating Scale (0 to 10) after taking pain medication via the study take-home pain diary.

Other Outcomes

- Number of hospital readmissions within 30 days post-operatively
  - Measured via medical record and study take-home pain diary.

- Frequency of each analgesic used 14 days post-operatively
  - Measured via the study take-home pain diary.

- Duration of each analgesic used 14 days post-operatively
  - Measured via the study take-home pain diary.

- Overall pain satisfaction over 14 days post-operatively
  - Measured via the study take-home pain diary.

- Frequency of request for opioid medication within 14 days post-operatively
  - Measured via medical record and study take-home pain diary.

- Frequency of post-operative oropharyngeal bleed within 30 days post-operatively
  - Measured via medical record

- Need for follow-up appointment within two months post-operatively
  - Measured via the study take-home pain diary.

- Night-time awakenings within 14 days post-operatively
  - Measured via the study take-home pain diary.

- Post-operative nursing phone calls within 30 days post-operatively
  - Measured via medical record

- Duration of hospital admission
  - Measured via medical record

- Socioeconomic variables at the time of caregivers' filling out the pain diary
  - Measured via the study take-home pain diary.
  - Household income – Check the box that matches income categories
  - Education level – Check the box that matches the highest education level achieved by anyone in the household

- Side effects of medications within 14 days post-operatively, including bleeding from mouth or throat, anxiety, difficulty breathing, nausea or vomiting, stomach pain/discomfort, fever (100.4F and higher), assessed daily.
  - Measured via the study take-home pain diary.

Sample Size Calculation

For the power analysis we used Palme et al.'s data as this is the only placebo-controlled RCT with a predominantly pediatric sample that used a pain scale with a 0-10 range. The mean pain rating in post-operative days 2-8 was 3.43 in the prednisolone group and 3.92 in the placebo group, with an effect size of 0.49. The standard deviation was consistently approximately 2 for both groups across the 8 days. [1]

As we are conducting a placebo-controlled RCT of Dexamethasone (which is a little more than six times as potent as Prednisolone in its anti-inflammatory properties [2]), we are conservatively multiplying the effect size of pain score in Palme et al's study by 1.5, therefore we conducted our power analysis with an estimated average pain of 3.92 in placebo group and 3.18 in the Dexamethasone (Dex) group with a standard deviation of 2 in both groups. To be powered at 0.8 and an alpha of 0.05 with a hypothesis that Dex will decrease pain (one-tailed hypothesis), our total sample size would need to be 182. To be powered at 0.9 and an alpha of 0.5, our total sample size will need to be 250. Therefore we will aim to enroll 300 children and have a minimum retention rate of 83%.

[1] Palme CE, Tomasevic P, Pohl DV. Evaluating the effects of oral prednisolone on recovery after tonsillectomy: a prospective, double-blind, randomized trial. Laryngoscope. 2000;110(12):2000-2004.
[2] Schimmer B, Parker K. Adrenocorticotropic Hormone, Adrenal Steroids, and the Adrenal Cortex. In : Schimmer BP, Funder JW : Goodman & Gilman's - The Pharmacological Basis of Therapeutics 13th Edition. New York: McGrawHill; 2018. p.853.

Analyses

Stata/SE 16.0 will be used for all statistical analysis.
All outcomes will be analyzed between dexamethasone and placebo groups.
P value < .05 will be used for statistical significance.

Primary Outcome
The primary outcome measure 'average pain burden pre-medication 2-8 days post-operatively' will be analyzed with an independent samples, one-tailed t-test if pain scores are normally distributed and Wilcoxon rank-sum tests if pain scores are not normally distributed. Means or medians and 95% confidence intervals (CI) and ranges will be reported.

Secondary Outcome
The secondary outcome measure 'average pain burden post-medication 2-8 days post-operatively' will be analyzed as described above. 'Emergency department or urgent care visits 30 days post-operatively' will be analyzed with Fisher's Exact test.

Other Outcomes
Along with descriptive statistics, univariable and multivariable analyses with tests such as Chi-squared, Fisher's exact, Wilcoxon rank-sum, t-tests, linear and logistic regression, and analysis of variance will be performed.

Cross-Over
Not applicable

Analysis Inclusion
Only those who meet eligibility criteria will be included in the final analysis. Specific outcome measures will be ascertained only in patients who return the pain diary, as indicated.

Missing Data
Data imputation will not be used for missing data.

Harms

Serious Adverse Events and adverse events will be collected up until the post-operative appointment with a maximum of 9 weeks post-operatively.