Study Protocol

Official Title: Use of a Non-Opioid Pain Regimen for Post-Operative Analgesia Following Intracapsular Adenotonsillectomy

ClinicalTrials.gov ID (NCT number): NCT04791761

Protocol Date: 01/16/2022

Scientific Background

In the present climate, there is a significant lack of consensus regarding the optimal management of pain for pediatric patients post-operatively (1). To further complicate matters, the growing opioid epidemic sweeping the United States makes the prescription of opioid pain medications for post-operative pain control after certain procedures subject to scrutiny. Indeed, just in 2015, opioid related drug overdoses were responsible for 33,091 deaths in the United States – of those deaths, nearly half involved prescription opioids (2,3). It has been identified that patients often use less opioids than prescribed, thus leaving an excess of opioids to be potentially abused by others or the patients themselves (4). In fact, in pediatric populations, one study showed that 58% of the opioid doses dispensed upon discharge were unused – only 4% of patients disposed of the remaining dose properly (5). However, it is important to note that under-treatment of post-operative pain has been shown to be an independent and significant predictor of complication in various surgical procedures (6,7). Patients who have found their pain to be unacceptable were 65% more likely to experience a complication within 30 days post-operatively when controlled for other factors and comorbidities (7).

A double blinded study done by Bean-Lijewski, et al. showed that rofecoxib, a non-steroidal anti-inflammatory (non-opioid), was more effective than opioids in the first 72 hours after tonsillectomy in pediatric children. Though rofecoxib has since been withdrawn from the market, it illustrates that perhaps pain in children post-operatively can be managed without the use of opioids - at least in the short term (8). In fact, Kaiser Permanente Northwest in 2016 instituted a new policy restricting the use of opioids in patients younger than 7, requiring physician override in the electronic medical record in order to prescribe narcotics. As a result, opioid prescription post-tonsillectomy decreased by 66% in their system, with no change in ED utilization (9). A smaller study published by Kelly, et al. investigated the use of morphine (opioid) and acetaminophen versus ibuprofen and acetaminophen (non-opioids) for post-operative pain control after tonsillectomy. The trial demonstrated that pain control (measured only on day 1 and 5) was adequate on either regimen, but the use of morphine was associated with complications and was deemed unsafe in certain children (10).

With a previous retrospective review performed here at UPMC, it was found that after November 2016, the average amount of oxycodone prescribed for children post-tonsillectomy was 0.05 mg/kg for an average of 6.7 days. Typically, this dosage would be taken every 4-6 hours or as needed (11). This falls well into the Epocrates recommended 0.05-0.15 mg/kg dosing every 4-6 hours (not to exceed 5 doses in 24 hours) (12). While the average dosage for acetaminophen and ibuprofen was not previously reported, according to Medscape, acetaminophen can be safely given at a dosage of 10-15 mg/kg every 4-6 hours with no more than five doses in 24 hours (13). Ibuprofen can be safely given at 4-10 mg/kg every 6-8 hours. Maximum single dose is 400 mg/dose, and maximum daily dose is 40 mg/kg/day up to 1200 mg/day (14).

While prescription opioids are one of the most effective options for control of post-operative pain, the growing opioid crisis in the United States makes it prudent to study the effectiveness of other non-opioid pain regiments. The goal of this study is to determine if non-opioid pain control is a safe way to manage pain after intracapsular adenotonsillectomy surgery in children. This study is the second part of our randomized clinical trials of assessing pain after

adenotonsillectomy (T&A), the first being total T&A. The investigators will repeat the methodology in the first clinical trial by randomly assigning children aged 3-17 to one of two groups: one group will receive non-opioid pain medication only, and the other group will receive opioid and non-opioid medications for pain control. The investigators will analyze the data and determine if there is a difference in pain control between the two drug regimens, and if there are any other associated complications between the two groups.

If it can be demonstrated that non-opioid pain control after intracapsular adenotonsillectomy does not lead to increased pain or worse outcomes in certain pediatric age groups, a strong argument can be made for the cessation of opioid prescription for these ages following this technique. Given the widespread opioid epidemic, this would be a significant step in curbing the massive opioid problem, as well as reducing the adverse effects of opioid usage in pediatric populations.

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Study Objectives

Aim: To determine if non-opioid pain control is a safe and effective option in the treatment of post-operative pain following intracapsular adenotonsillectomy in various pediatric age groups.

Hypothesis 1: Post-operative pain will not be higher in patients assigned to the non-opioid only group (experimental) as compared to the group receiving both opioid and non-opioid pain medications (control).

Hypothesis 2: There will not be an increased rate of post-operative complications in the non-opioid only group as compared to the group receiving both opioid and non-opioid pain medications.

Hypothesis 3: Those with intracapsular (partial) T&A will not have a lower postoperative pain score than those with a total T&A.

Hypothesis 4: Those with intracapsular (partial) T&A do not require less opioids than those with a total T&A.

Study Design & Methods

Design: Experimental, open-label randomized control trial.

Methods:

Screening can be performed two ways:

1. The otolaryngology nurses will screen patients at the pre-operative appointment based on past medical history that is either in the electronic medical record or elicited from the patient during the appointment to determine if they qualify for the study. They will then inform the otolaryngologists to review the consent form with the family. Between the pre-operative appointment and day of surgery, one of the members of the research team will once again check the patient's eligibility to enroll in this trial using the electronic medical record system.

2. A list of possible qualifying T&A surgery patients will be provided to the research team by the surgery administration. Patients will be screened using the electronic medical record system for inclusion criteria. The family can then be consented the day of surgery. This screening method will be used with telemedicine visits, especially during the COVID-19 restrictions.

The otolaryngology nurses will be responsible for the initial screening of patients at the pre-operative appointment during the standard pre-operative education for adenotonsillectomy surgery. The nurses will then consult the physicians for who qualifies for the study. The physicians will confirm that the patients meet inclusion criteria for the study and they will be responsible for attaining consent from the caregiver. Additionally, they will be responsible for attaining a completed assent form for children, acknowledging their willingness to participate. Girls of reproductive age (13-17) will be counseled on the importance of using contraception if sexually active since pain medication may affect a developing fetus. This will take place in the private medical office exam room. The patient and caregiver will be informed that they will receive a payment of $50.00 for participation in the trial, provided they complete the trial. Families can also be consented the day of surgery. Patients will be screened by the research team using electronic medical records. This will provide all families the opportunity to participate. Oftentimes, a parent is not available at the pre-operative appointment to sign consent or families need time to think about participation. During the COVID-19 restrictions and for future telemedicine visits, the study will be brought up during the pre-operative visit but will be signed the day of surgery. This will help families to discuss the study in more detail after the appointment, as there is no down time in telemedicine appointments. During the restrictions, only one parent is able to attend an appointment as well.

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 opioid and non-opioid regimens among three age groups - young children (ages 3-7), preadolescents (ages 8-12), and teenagers (ages 13-17). Patients or parents will maintain the right to request and receive oxycodone at any point during the trial provided there are no contraindications to their usage.

At the day of surgery, the parents will receive the patient pain diary. A separate sheet with the Wong-Baker FACES Pain Rating Scale instructions will be included in the patient folder. 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 they have been assigned, along with instructions on the dose, frequency, and duration of use.

For the opioid group, oxycodone will be prescribed at a dose range of 0.025 mg/kg to 0.10 mg/kg every four hours or as needed. The total supply will be limited to seven days. This dose range is the standard of care already provided at CHP and will not reflect a change in standard dose prescribed after adenotonsillectomy surgery. This range is necessary for adequate pain management in all age groups. 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. For the non-opioid groups, 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. All medications will be prescribed in liquid suspension form for ease of use in pediatric populations. Subjects or parents will purchase medications and dosage will be given to subjects in easy-to-understand language

on a parent instruction sheet (ig. x mL every 4 hours or as needed, with maximum allowable amount of y mL in a day).

A parent instruction sheet for each group was developed with the following information:
Non-opioid group –

Parents will be advised:
-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. (For example, if pain level is unmanaged). The decision whether or not to prescribe opioids will be up to your child's physician.
Read the directions on the bottle to know how often you are to give this medication. Your nurse will go over this with you before you leave.
Pain peaks at days 5-10. You may want to continue scheduled Tylenol and Motrin during your child's most painful times.

Opioid group -

Parents will be advised:
-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 patient to take liquids by mouth (>32 oz/day) and/or if the child complains or behaves like they are in pain.
-that if acetaminophen and ibuprofen are both given and the child is still demonstrating the inability to drink and/or complain or behave like they are in pain, oxycodone is advised. The Oxycodone prescription is for 7 days and is prescribed based on weight.
The Opioid group is not required to take any amount of the oxycodone during the trial.
Read the directions on the bottle to know how often you are to give this medication. Your nurse will go over this with you before you leave.
Pain peaks at days 5-10. You may want to continue scheduled Tylenol and Motrin during your child's most painful times.

This 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. Families can return the pain diary in multiple ways:
-A post-operative appointment at CHP Main 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. These families can also email or mail the diary. During COVID-19 restrictions, families will be encouraged to return the Pain Diary via mail or email. As a last resort, families may bring the

Pain Diary to their in-person appointment, however a post-op appointment for T&A may be rare during the restrictions due to the level of urgency of a patient without complications.

-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. They can also mail the diary using the post-marked envelope provided. The $50 compensation will then be mailed to the family when the electronic or physical copy is received. The research team will call participants anywhere from 2 to 6 weeks after surgery for a reminder to return the study diary. At this time, participants may request another post-marked envelope sent to their home address instead of scanning the diary electronically. The research team will call the families after the surgery to see if they have any additional questions about filling out the pain diary. This will occur anywhere from the day after surgery to a week later.

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.

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. 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 email an electronic copy of the pain diary.

For the intracapsular T&A study, we are adding in an opioid disposal pouch arm to the study. This pouch is a drug deactivation system that can be disposed in the trash in a household. We are randomizing the opioid group of 150 patients total to receive education (75 patients) versus education of disposal vs education of disposal plus the disposal pouch (75 patients).

Eligibility Criteria

Inclusion:
Patients ages 3-17 undergoing intracapsular T&A

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 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
Patients who have the inability to communicate
Patients who have the inability to localize pain

Statistical Analysis Plan

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Study Outcomes

Primary Outcome

- Average pain burden 14 days post-operatively. This will be self-reported and measured on the Wong-Baker FACES Pain Rating Scale (0 to 10) before and after taking pain medication via the study take-home pain diary.

Secondary Outcomes

- Emergency department or urgent care visits 14 days post-operatively from the pain diary and from the patients' medical record.

Other Outcomes

- Number of hospital readmissions within 14 days post-operatively
  - Measured via medical record

- 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.

- Post-operative nursing phone calls within 14 days post-operatively
  - Measured via medical record

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

- Non-opioid group switching to opioid group within 14 days post-operatively
  - Measured via the study take-home pain diary.

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

- 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 nausea, vomiting, constipation, stomach ache, difficulty breathing. This is reported by the child's caregiver after all medication administration is completed. The question is check all that apply and assessed via study take-home pain diary.

- Use of the opioid disposal pouch within 8 weeks post-operatively
- Measured via the study take-home pain diary.

Sample Size Calculation

A power analysis was performed with Logistic regression statistical test using G*Power. For preliminary results, those with a total T&A had an average pain score of 5.6 before pain medication and projected those with a partial T&A to have a pain score of 3.5, 1 SD below those that had the total T&A. With an alpha of .05 and a power of .95, we are projected to need 79 total patients in each age group (3-7, 8-12, 13-17). Factoring in the response rate of returned pain diaries, we are going to recruit the same number of patients for this intracapsular study as the total T&A study for a total of 300 patients.

[1] Whelan RL, McCoy J, Mirson L, Chi DH. Opioid prescription and postoperative outcomes in pediatric patients. Laryngoscope 2019;129:1477–81. https://doi.org/10.1002/lary.27614.

Analyses

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

Primary Outcome
The primary outcome measure 'average pain burden 14 days post-operatively' will be analyzed with independent samples t-tests if pain scores are normally distributed and Wilcoxon rank-sum tests if pain scores are not normally distributed. Pain scores will be compared between opioid versus non-opioid groups separately before medication and after medication. Means or medians and 95% confidence intervals (CI) will be reported.

Secondary Outcome
The secondary outcome measure 'emergency department or urgent care visits 14 days post-operatively' will be analyzed with Fisher's Exact test. Odds ratios (OR) and 95% CI will be reported.

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
A sub-group analysis will be performed without those patients who had drug cross-over.

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.