Pediatric Pain Optimization After Tonsillectomy: A Randomized Double Blind Methadone Pilot Study

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Purpose of the Study

There is an unmet need to identify an optimal perioperative opioid regimen for common pediatric surgeries that would reduce postoperative pain to acceptable levels without untoward side effects, reduce post-discharge opioid use, and enable reduced postop opioid prescribing. Such a standardized intra-operative opioid regimen pediatric tonsillectomy is long overdue and will require an innovative approach. Methadone is a cost effective, efficacious, and long-acting opioid with an elimination half-life of 24-36 hours. A single intraoperative dose has been used safely and effectively in multiple adult surgical procedures and populations, reduces both postoperative pain and opioid consumption, and increases patient satisfaction compared with shorter acting opioids. Methadone has been used in major pediatric surgeries with encouraging results, but it has not been studied in pediatric tonsillectomy.

Our central hypothesis is that a single intraoperative dose of methadone provides superior pain control and reduction of postop opioid use compared to current routinely used short-acting opioids. To investigate this, we propose a prospective, double blind, randomized, controlled, dose-finding pilot study of single-dose intraoperative IV methadone, compared with short-duration opioids (fentanyl, hydromorphone) in 60 children >=3 and <18 years old undergoing elective tonsillectomy. The primary research goal is to determine an optimal intraoperative methadone dose, and secondarily to assess pain and postop opioid utilization in PACU and for 7 days after surgery. We will test this hypothesis and accomplish our proposal objective, with the following two specific aims:

1. Determine an optimal intraoperative dose of intravenous methadone. Prior pediatric and adult literature have published dosing regimens between 0.1mg/kg and 0.3mg/kg for various operations. Our working hypothesis is that a single methadone dose of 0.1mg/kg to 0.2mg/kg of age based ideal body weight can be identified, that will result in less postoperative pain and opioid use. This is designed as a dose-escalation pilot, with anticipated need for a cohort to receive a higher dose than the initial 0.1 mg/kg.

2. Analyze post-operative outcomes including post-operative opioid utilization and pain scores in the first 7 days after surgery. Our working hypothesis is that those patients who receive a single intraoperative methadone dose will have statistically less postoperative opioid utilization and pain scores, without a greater incidence in adverse events (respiratory depression or excessive sedation).

Background & Significance

Pain is ubiquitous in pediatrics as every infant, child and adolescent will experience it in early life. Yet, pain in children remains a prevalent concern because it is often under-recognized and

under-treated and has the potential to result in life-long comorbidities. There is strong evidence that untreated pediatric pain incurs a high risk for the subsequent development of persistent pain, disability, and psychological disorders in adulthood. In fact, approximately 20% of adult chronic pain patients report a history of poorly managed pain in childhood or adolescence.

One common source of pediatric pain is a direct result of invasive procedures. Each year in the United States, hundreds of thousands of children undergo elective tonsillectomies. Pain after pediatric tonsillectomy is frequent, severe and often insufficiently treated which can lead to post-operative complications such as poor oral intake, dehydration and prolonged recovery. In 2019, The American Academy of Otolaryngology published a Clinical Practice Guideline which included a strong recommendation for the use of non-opioid anti-inflammatory medications for pain management following tonsillectomy in children. However, there is no further guidance for surgeons about the use of other opioids, including type, dose, duration or frequency. We commonly use short acting opioids (fentanyl and hydromorphone) at the discretion of the anesthesiologist in line with standard of care practices to manage both intraoperative and post operative pain following pediatric tonsillectomy. Intraoperative methadone is also used as standard of care practice in pediatric patients (3-18 year olds) for other routine procedures. Yet anesthesiologists and surgeons have published literature showing significant variability amongst perioperative opioid practices and there is a growing movement to reduce or remove opioids from post-tonsillectomy algorithms entirely.

It's widely recognized that standardization of a perioperative opioid regimen for pediatric tonsillectomy pain is long overdue. The lack of guidance both intraoperatively and post operatively results in a haphazard approach to analgesia which directly results in the inadequate treatment of moderate to severe pain. There are also unique considerations for pain management in children that must be considered. Most notably, the task of providing sufficient analgesia to a child often becomes the task of the parent or caregiver. There is a well-documented tendency for parents to under-treat despite pain behaviors for a variety of reasons. Conversely, studies have shown that teenagers are more likely to receive refills on their initial post-operative opioid prescription which places them at risk for opioid misuse, abuse or diversion. This is supported by evidence that shows that millions of 12 to 17-year-olds self-report prescription opioid misuse annually, and at least 25% of these adolescents initially receive their opioids from their medical provider. Commonly left-over opioids are typically not locked in storage, not returned or disposed of and remain available for misuse by patients, families or diversion.

Therefore, it is conceivable that the use of a long-acting opioid such as methadone could have multiple benefits in pediatrics including 1. significantly decreasing pain after surgery, 2. reducing barriers to adequate analgesia in young children, 3. reducing surgeon over-prescribing of discharge take-home opioids, 4. reducing the pool of left-over opioids available for misuse or diversion, and 5. mitigating risks associated with opioid use in the adolescent population.

Design & Procedures

Study Design: Single center, randomized, double blind, parallel-group dose escalation investigation. All patients will receive standard monitoring for anesthesia and postoperative care. Surgical and anesthesia care (except for intraoperative opioid management) are not altered for study purposes. Subjects are randomized 2:1 to either long-duration (methadone) or short-duration opioid (fentanyl, hydromorphone). The use of any short acting opioid (ie: fentanyl, hydromorphone or both) is considered the control group and total dose, timing of administration, frequency of administration, and dose per administration of either/both short acting opioids will be administered at the discretion of the anesthesiologist as per standard of care practice. Because methadone analgesia for pediatric tonsillectomy has not previously been studied, this pilot study will use escalating dose groups to determine the optimal dose for this procedure. In order to achieve this, our trial design will include two periods. In the first period, we will randomly assign 20 patients to methadone 0.1 mg/kg and 10 patients to typical short-duration opioid (controls). An interim analysis will be conducted to determine if we should escalate to the higher dose of methadone. Methadone dose escalation to 0.15mg/kg age ideal body weight will occur if there is no difference in non-methadone PACU opioid use and no increased adverse events. If proceeding to the second period, we will recruit 20 patients for 0.15 mg/kg methadone and 10 patients as controls. Sample size for this pilot investigation was based on prior studies.

Defining an optimal dose of methadone is a crucial aim of this study, which will allow for future investigations, but is not a primary or secondary outcome. The dose finding nature of this study requires interim assessments after each methadone dose cohort. After the first 20 methadone subjects at 0.1mg/kg age ideal body weight, there will be a planned partial analysis of PACU opioid use. Methadone dose escalation to 0.15mg/kg age ideal body weight will occur if there is no difference in non-methadone PACU opioid use and no increased adverse events. Sample size for this pilot investigation was based on prior studies.

Pre-operative, Intra-operative, Post-operative Care: Anesthesia and surgical care are not altered for this study except for randomization to the study drug. Oral or IV midazolam for anxiolysis may be given at standard dosing. Anesthetic induction via inhaled sevoflurane or intravenous agents are to be given at the anesthesiologist's discretion.

Patients in the short-duration opioid group receive short-duration opioids (IV fentanyl and/or hydromorphone), given as needed throughout the intraoperative period, per usual practice at practitioner's discretion. Patients in the long-duration opioid group receive IV methadone HCl at 0.1mg/kg. These subjects receive methadone as their only intraoperative opioid, given as a single bolus at anesthetic induction. If needed, a second cohort will receive or 0.15mg/kg of age-based ideal body weight. Following extubation, patients may receive incremental doses of

0.1mg/kg up to a maximum of 0.5mg/kg of dexmedetomidine (dosed at age-based ideal body weight) for sedation if needed, contingent upon adequate ventilatory rate.

For analgesia in the Post-Anesthesia Care Unit (PACU), patients in both groups may receive typical short-duration opioids (fentanyl or hydromorphone) as per usual routine care. It is not necessary that patients receive the same opioid postoperatively as intraoperatively. Post-op opioids orders are written by the pediatric anesthesiologist and opioids are given by PACU nurses per standard practice, based on developmentally appropriate pain scales (FLACC, Wong-Baker Faces, VAS) and institutional practice.

Pain scores via developmentally appropriate and validated pediatric pain scales will be confirmed by a blinded research coordinator OR a blinded secondary pediatric PACU nurse and charted in the EMR prior to administration of opioid analgesics. Adverse events will be recorded by a research coordinator who is blinded to randomization allocation and include: Respiratory depression (respiratory rate <10/min), reintubation, decreased oxygen saturation <85% for 30 seconds, excessive sedation (Pasero Opioid-induced Sedation Scale (POSS) score 3>1 hour, 4>15 minutes), unexpected PICU admission, and vomiting in PACU.

Selection of Subjects

Patient Selection: Patients undergoing tonsillectomy +/- adenoidectomy at Duke University Hospital and Duke Regional Hospital or a Duke Affiliated Ambulatory Surgical Center (including Davis Ambulatory Surgical Center) will be recruited for enrollment. Selection criteria are as follows:

Inclusion Criteria (IC): Children age >=3 and <18 yrs having elective tonsillectomy +/- adenoidectomy with signed, informed consent by parent or legal guardian. Post pubescent females are required to have a negative pregnancy test within 48 hours of surgery. Children >12 years must give assent.

Exclusion Criteria (EC): Patients with any of the following: 1. history of or known liver or kidney disease 2. Consistent daily opioid use for chronic pain (defined as ongoing pain >3 months) 3. severe sleep apnea (Sleep study with Apnea Hypopnea Index (AHI) > 10). 4. planned admission to the Pediatric Intensive Care Unit (PICU) following surgery 5. additional procedures under the same general anesthetic for which outpatient opioids would be prescribed.

Patients undergoing procedures such as PE tubes, nasal endoscopy, Auditory Brain Response tests, imaging studies do not have to be excluded.

Subject Recruitment and Compensation

Patients will be screened and properly identified by the principal investigator or member of the clinical research team assigned to the study through IRB-approved review of the surgical schedule. An IRB-approved phone call may be conducted to introduce the study or patients may be approached on the day of surgery allowing sufficient time for explanation, questions and answers. If interested, legal guardians may provide consent for the study via an IRB approved electronic Informed Consent Form (ICF) in advance or paper consent may be obtained on the day of surgery. For patients 12 years or older, patient assent for enrollment in the study will also be obtained.

Goal recruitment is 60 patients to complete the study. Subjects will be compensated a $10 gift card (mailed) for the time and effort to complete 1-7d daily surveys and the phone call on day 30 following surgery.

Study Interventions

Study Intervention and Randomization: Subjects in each cohort will be randomized 2:1 methadone to short acting opioid using randomization tables generated by The Biostatistics Group within the Department of Anesthesia. Each subject is assigned the next number. To consider children in different age may have different pain tolerance, we will balance the treatment groups by age. That is, we will generate a set of blocked randomization numbers for three age groups, 3-6, 7-12, and 13-17 years old. Anesthesia providers receive a sealed envelope or email with Group (drug) assignment, group-specific instructions, and are advised on study procedures. To ensure full double-blinding, subjects, investigators, and study team members evaluating patients will be blinded to drug treatment. The rationale for 2:1 randomization is to achieve the same sample size for each group since we anticipate 2 methadone cohorts, thus final groups (methadone 0.1 mg/kg, methadone 0.15 mg/kg, controls) would each have 20 subjects.

As clarified above, the use of a short duration opioid in this specific study population (tonsillectomy 3-18 year olds) is a standard of care procedure. Methadone is standard of care in pediatric cardiac surgery, pediatric spine surgery and precuts excavatum surgery (3-18 year olds). Not counting the randomization, the dosing and administration of all 3 of these drugs (methadone, fentanyl, hydromorphone) are in line with standard of care practices for pediatric population of between 3 and less than 18 years and are routinely used both in and out of the operating room environment.

Regarding the clinical study of an investigational drug that would be IND exempt, the following ARE true for this study (see below):

- The investigation of a drug that is lawfully marketed in the US and the following 5 criteria are met:
the study is not designed to support approval of a new indication or change in labelling: No new indications sought
the study does not intend to support significant change in advertising of the product: No new advertising sought
the study does not significantly increase risks (or decrease the acceptability of risks) associated with the use of drug through route of administration, study population, dosage level, or anything else: No increase risks associated with the use of the drug, purposeful conservative dosage chosen for study with protective and specific dose escalation criteria
the study is conduced in compliance with IRB and consent regulations: true, once IRB application amended and approved to the satisfaction of the IRB reviewers
the study will not advertise or promote the use of the drug for the indication that it isn't approved for: No new indications or promotion of the drug sought.

Risk/Benefit Assessment

Recruitment and Informed Consent: The study will be conducted under appropriate Duke University IRB protocol and consent form approvals. The study will be conducted under the supervision of the PI, who is a Board-Certified pediatric anesthesiologist (Einhorn) with collaboration from a Board-Certified Anesthesiologist (Kharasch) with decades of experience in the conduct of human volunteer studies. Potential subjects will be identified through IRB-approved review of the surgical schedule prior to their surgery, at which time they will be contacted and asked if they are interested in participating. An IRB-approved phone screen will be conducted. Subjects that wish to participate may sign paper consent on the day of surgery when allowing sufficient time for explanations, questions and answers. If interested and willing, subjects may also be fully consented using IRB approved eICF. Informed consent must be given and signed by parents and/or legal guardian. Children greater than or equal to 12 years of age must provide verbal assent to be in the study.

Protections against Risk:
i) Eligibility criteria exclude patients with known renal or hepatic disease, which may affect opioid disposition, pregnant females, those with severe sleep apnea with apnea hypopnea index > 10 and those who require planned ICU admission post operatively.

ii) Methadone dosing is fixed, using age based ideal body weight, rather than actual body weight, to obviate risk of excessive dosing due to obesity.

iii) Dose escalation will only occur if there are no adverse events in the initial dosing group

iv) If nausea and/or vomiting occur, patients will be treated using the standard of care for all post-anesthesia nausea and vomiting. Respiratory depression with a respiratory rate <10 breaths/minute or hypoxia with oxygen saturation less than 85% for > 30 seconds will be monitored closely. If treatment is required, naloxone will be used. Patients will be routinely monitored by pulse oximetry, and receive supplemental oxygen if dictated, according to standard anesthesia practice.

v) Research subjects will receive pre-operative, intra-operative and post-operative routine monitoring by anesthesiology and nursing staff.

vi) The risk of breach of protected health information will be minimized by limiting the number of people within the research group who have access to identified data which will be described in the data monitoring safety plan.

Potential Benefits:
Long-duration (vs short-duration opioids) may decrease the need for additional opioids in the immediate postoperative period, decrease possible side effects of opioids, improve immediate postoperative pain relief and may decrease the occurrence of chronic postoperative pain.

Successful completion of this research is expected to result in improved pediatric surgical care, enhanced patient recovery and pain management requiring less post-operative opioids. Anesthetic risks associated with long-duration and short-duration opioids are similar, and, in light of improved pain relief demonstrated in adult studies, there is sufficient clinical justification to conduct this research in children.

Data Analysis & Statistical Considerations

Descriptive statistics for each treatment group will be computed for patient demographic and characteristic variables. Since our randomization scheme will have balanced the age effect between treatment groups, we anticipate the demographic and patient characteristic variables will be balanced across groups. For the continuous outcome measures (primary and most of secondary outcomes), we will conduct two-sample t-test to test the outcome difference (e.g., total OME difference) between treatment groups. For categorical outcomes (e.g., PACU side effects and adverse events), chi-square or Fisher exact tests will be applied as appropriate. Considering this is a pilot study for dose finding, we will relax the significance threshold to 0.1 for the interim analysis. Using the primary outcome, total OME/kg as an example, a two-sample t-test will be performed for comparing total OME difference between 20 methadone (0.1mg/kg) treated patients to 10 controls based on significance threshold of 0.10. If methadone showed significant effect on the outcome measure, the higher dose arm (0.15 mg/kg age ideal body weight) will be pursued. In the final analysis, similarly, two-sample test

will be used to test the total OME difference between methadone and control groups for both dose levels. To correct for multiple testing, the significance threshold in the final analysis will be set at 0.025. If there are covariates showing significant difference between treatment groups, we will perform multivariable linear regression analysis to test the treatment effect after adjusting for one selected covariate and examine if the treatment effect remains the same as that found in the two-sample t-test. The reason to restrict to one covariate in the model was to avoid model overfitting considering there will be only 20 samples per group. Similar analysis strategy will be applied to other outcome measures.

Power calculation: Two-sample t-test with an assumption of equal variance between groups was used to estimate statistical power. For the interim analysis based on 20 methadone 0.1mg/kg cases and 10 controls, assuming standard deviation (SD) total OME as 0.3, our proposed sample size will have 80% power to detect 0.3 OME difference at the significance level (alpha) of 0.1. Assuming we can move forward to the higher dose cohort, the final analysis will include two tests to compare 20 cases vs. 20 controls for each methadone dose level. In this scenario, assuming the same OME variability of SD=0.3 and the reduced alpha level to 0.025, our proposed sample size (N=20/group) can detect the 0.31 OME difference between methadone and control groups with 82% power, a similar effect size as the interim analysis. The detectable mean difference will increase if the OME variability (SD) increases.

Unblinding Procedures:

Emergency Unblinding is appropriate in the unlikely situation of a medical emergency (as determined by the PI or treating physicians, APPs) where knowledge of the treatment allocation is likely to have a significant effect on the clinical management of the enrolled subject and would be instrumental in immediate treatment decisions. In an emergency, it may not be feasible to obtain prior approval from the PI. In this case, after the subject is successfully unblinded, there must be clear documentation explaining why unblinding was necessary. The PI, IRB, and Research Practice Manager will be notified as soon as possible.

Accidental Unblinding: If a subject is accidentally unblinded, clear documentation of events must be recorded, as well as communication with the PI and Research Practice Manager. The treatment assignment must not be revealed to any other members of the study staff, pharmacy staff, or to the subject, unless written approval from the study sponsor is obtained. Every effort should be made to maintain what remains of the blind. In this case, a protocol deviation should be reported to the IRB of record.

Interim Analysis: Patients will be unblinded for the interim analysis by a member of the Department of Biostatistics. The interim analysis will determine if a dose escalation is indicated. Once the partial analysis is complete, the study we resume either at the same dose of

methadone (0.1mg/kg age ideal body weight or an increased dose 0.15mg/kg age ideal body weight).

Primary and secondary endpoint data collection will occur while the study team is blinded with exception of the interim analysis. Once all patients have completed the all parts of the study, final unblinding will occur.

Data & Safety Monitoring

Data are collected and stored via REDCap. The REDCap servers are securely housed in an on-site limited-access data center managed by the Division of Biostatistics. All web-based information transmission is encrypted, and the data is stored on a private, firewall protected network. No identifiable data will be stored on personal computers or laptops. Data will be exported from REDCap for statistical analysis with patient identifying information removed. The consent form, medical information, and case report forms will be stored under lock and key (office, file cabinet) and only the PI, physician investigators, and research team will have access.

All patients admitted for observation post-tonsillectomy are monitored on continuous pulse oximetry with q4h vital signs per standard of care with anticipated discharge on post operative day 1. With the use of any opioid following surgery, there are risks of post operative respiratory adverse events. While the half life of methadone is longer than short acting opioids, there is no evidence in pediatric literature that a one-time appropriate weight based dose of methadone (0.1-0.3mg/kg) requires additional monitoring beyond routine standard of care due to its prolonged half life (PMID 22037641). Our initial dose is purposefully conservative (0.1mg/kg) to protect against adverse respiratory events.