RESEARCH PROTOCOL

A RANDOMIZED CONTROLLED TRIAL TO COMPARE HYDROMORPHONE VS FENTANYL IN CHILDREN UNDERGOING TONSILLECTOMY SURGERY

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SYNOPSIS

Objective - To compare hydromorphone versus fentanyl for pain control following tonsillectomy or adenotonsillectomy surgery.

Study Period - 2 years

Number of Patients - 300 pediatric patients presenting for tonsillectomy or adenotonsillectomy at St. Louis Children's Hospital (SLCH)

Study Treatment - Hydromorphone vs fentanyl dosed per study design

Study Design - This is a randomized clinical trial with masked assessment, comparing recovery indices for patients receiving intermediate acting versus short acting opioid analgesia using hydromorphone or fentanyl as intraoperative analgesics. An otherwise standardized anesthetic and analgesic regimen will be utilized, consistent with routine care at SLCH. Patients will be randomized 1:1 in blocks of 4 within strata. Patients will be randomized to receive either hydromorphone or fentanyl throughout the perioperative period by opening a sealed protocol envelope.

Inclusion Criteria

1. Children ages 2 to 15 years old
2. Presenting for tonsillectomy or adenotonsillectomy surgery
3. American Society of Anesthesiologists Physical Status (ASAPS) Classification 1, 2 or 3
4. Provide Informed Consent / Assent (as appropriate)

Exclusion Criteria

1. Additional Concurrent surgeries, exclusive of myringotomy tubes, minor oral/nasal procedures (e.g. frenulectomy), and endoscopic procedures
2. Revision tonsillectomy or revision adenotonsillectomy surgery
3. Known pregnancy
4. Any condition which would make the participant, in the opinion of the investigator or the attending anesthesiologist caring for the patient, unsuitable for the study.

Measurements - We will compare the incidence of administration of analgesic rescue medication in the post-operative recovery area. We will also compare post-operative pain scores and the amount of opioid pain medications administered to patients postoperatively expressed in morphine equivalents. Optional opioid plasma concentrations will be measured at three time points using mass spectroscopy. Additionally, we will compare the rates of post-operative respiratory complications, PONV, and length of PACU stay between patients administered fentanyl vs. hydromorphone. Finally, we will assess patient and family satisfaction with treatment through a survey sent on POD 3 as well as validated NIH PROMIS questionnaires.

Outcomes - Perioperative analgesic efficacy and side effect comparisons between hydromorphone and fentanyl in children undergoing tonsillectomy surgery.

1. Introduction

1.1. Study Abstract: Every year hundreds of children undergo tonsillectomy surgery at St. Louis Children's Hospital (SLCH) and many of these children experience significant postoperative pain. Severe postoperative pain can delay recovery and hospital discharge if it impedes eating and drinking. This pain can also lead to significant patient and parental anxiety, and may worsen patient anxiety for future health care related experiences. Opioids are commonly used to treat severe pain; however, opioids also have attendant side effects such as sedation, postoperative respiratory depression (e.g. apnea), and nausea and vomiting. Fentanyl and hydromorphone are the primary opioids used at SLCH in the operating theater and the immediate postoperative period. Fentanyl has a shorter duration of action than hydromorphone and is often chosen in the belief that using the shortest-acting opioid will reduce the risks of sedation and apnea. However, there is limited evidence to suggest that this is the case. Interestingly nurses in the SLCH Post Anesthesia Care Unit have noted a subjective difference in pain levels in patients receiving hydromorphone versus fentanyl with the perception that patients administered hydromorphone, on average, require fewer doses of rescue opioid analgesics. In addition, a recently completed prospective study of fentanyl vs. hydromorphone for pain control in patients undergoing eye muscle surgery suggests that hydromorphone provides both lower pain ratings and faster PACU recovery. Our goal is to determine whether there is a difference in post-operative outcomes between patients receiving fentanyl or hydromorphone post tonsillectomy.

1.2. Research Questions

1.2.1. Is there a difference in the rate of administration for rescue opioid analgesic medications in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.2 Is there a difference in the postoperative pain score in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.3. Is there a difference in the cumulative morphine equivalents administered postoperatively in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.4. Is there a difference in post anesthesia care unit length of stay in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.5. Is there a difference in nausea or the number of vomiting episodes postoperatively and 72 hours after discharge in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.6. Is there a difference in pain scores reported by the parent 72 hours after discharge in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.7. Is there a difference in the number of desaturation events, defined as SPO2 < 90% for 2 minutes or less than 85% for 1 minute, postoperatively in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.8. Is there a difference in the number of witnessed apneic events postoperatively or at 72 hours after discharge in children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.2.9. Is there are difference in patient and family satisfaction with care between children undergoing tonsillectomy who are administered hydromorphone as compared to fentanyl perioperatively?

1.3. Purpose of the Study Protocol. The proposed project will test whether there is a difference in multiple metrics of pain between patients who receive hydromorphone or those who receive fentanyl during tonsillectomy. The results of this study should inform the way anesthesiologists approach the treatment of pain following the most common pediatric surgical procedure at SLCH, and in the United States. If a difference is found, appropriate dissemination of findings could influence the universal approach taken for pain control in the most common pediatric surgery.

2. Background

2.1. Prior Literature and Studies. Tonsillectomy is the most common pediatric operation performed in the United States, with more than 500,000 tonsillectomies performed annually[1]. The primary indication for tonsillectomy is childhood obstructive sleep apnea (OSA), defined by periodic, partial or complete obstruction of the upper airway during sleep. OSA is a common disorder in pediatric patients, with a prevalence of 1-3%[2]. It is as common as childhood asthma and children with OSA often require tonsillectomy surgery to correct their OSA[2]. As mentioned, the treatment of OSA is the primary indication for more than 75% of children undergoing tonsillectomy with or without adenoidectomy[3]. Unfortunately, children at high risk for OSA are three times more likely to have post-tonsillectomy respiratory complications and apneic adverse events than children at low risk for OSA[4,5] and the rate of complications in patients with OSA post-tonsillectomy (16 –27%) is substantially increased compared to that of the general pediatric post-operative population (0 –1.3%) [6-10]. These complications include oxygen desaturation, hypercapnia, obstructive apneas requiring CPAP or airway instrumentation, unexpected ICU admission, and in rare cases, death. Concerns for a heightened risk of opioid induced respiratory depression make the peri-operative use of opioids in children with OSA particularly challenging and controversial.

There is currently not a standard of practice for pain management for tonsillectomy surgery at SLCH. Published guidelines recommend decreasing opioid doses in all patients with sleep apnea, for fear of respiratory depression, however they do not give recommendations regarding the use of short vs. intermediate acting opioids[11]. The nurses in the SLCH PACU have subjectively noted a decreased need for opioid rescue analgesia when hydromorphone is administered intraoperatively as compared to fentanyl. Additionally, a recently completed prospective study of fentanyl versus hydromorphone for pain control in patients undergoing eye muscle surgery at SLCH suggests that hydromorphone results in lower pain scores and faster PACU recovery[12]. There are limited data comparing different opioids in pediatric tonsillectomy surgery published in the literature. As far as we are aware, this will be the first randomized controlled trial comparing the intermediate acting opioid hydromorphone to the shorter acting opioid fentanyl for this patient population.

2.2. Rationale for the Study. Providing safe and effective pain control is important for these patients. Subjective observations indicate that hydromorphone may provide superior pain control as compared to fentanyl. This hypothesis has not been rigorously tested. We aim to ameliorate this deficit.

3. Study Objectives

3.1. Primary Aim. The **primary aim** of our study is to compare the need for rescue opioid analgesic medication between patients receiving fentanyl and hydromorphone following adenotonsillectomy surgery. We will also compare post-operative pain scores between the two groups, and the amount of opioid pain medications administered to patients postoperatively expressed in morphine equivalents. Patients will be randomized 1:1 in the operating room to receive either fentanyl or hydromorphone during the perioperative period. We hypothesize that compared to fentanyl, the use of hydromorphone will result in lower need for rescue opioid analgesic in post-surgical recovery.

3.2. Secondary Aims. The **secondary aims** of our study are to compare pain scores, the rates of post-operative respiratory complications, PONV, and length of PACU stay between patients administered fentanyl vs. hydromorphone. We hypothesize that there will be no differences between patients who receive fentanyl and those who receive hydromorphone.

3.3. Rationale for Selection of Outcome Measures. These are the primary concerns for care of patients following tonsillectomy surgery. Nearly all patients will have postoperative pain, and many will experience some degree of postoperative nausea and vomiting. Respiratory complications are possible after emergence from a general anesthetic, especially after the use of opioids in the perioperative setting, and especially after tonsillectomy surgery.

4. Study Design

4.1. Overview. This is a randomized clinical trial with masked assessment, comparing recovery indices for patients receiving longer acting versus shorter acting opioid analgesia using hydromorphone or fentanyl as intraoperative analgesics. An otherwise standardized anesthetic and analgesic regimen will be utilized, as consistent with routine care at SLCH.

4.2. Inclusion Criteria

4.2.1. Children ages 2 to 15 years old

4.2.2. Presenting for tonsillectomy surgery or adenotonsillectomy surgery

4.2.3. American Society of Anesthesiologists Physical Status (ASAPS) Classification 1, 2 or 3

4.2.3. The caregiver of the child must be able to provide informed consent and the child must be able to provide assent (as appropriate)

4.3. Exclusion Criteria

4.31. Additional Concurrent surgeries, exclusive of myringotomy tubes, minor oral/nasal procedures (e.g. frenulectomy), and endoscopic procedures

4.3.2. Revision tonsillectomy or revision adenotonsillectomy surgery

4.3.3. Known pregnancy

4.3.4. Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study

4.4. Ethical Considerations. All patients will receive pain medication as well as medication to control for postoperative nausea and vomiting as per routine care at SLCH. The attending anesthesiologist will accompany the child to the PACU, and rescue drugs will be available if additional pain medication is needed or if there is concern for respiratory distress. Both medications (hydromorphone and fentanyl) to be compared are standard of care analgesics at SLCH and on formulary.

4.5. Risks and Benefits. We do not know if patients will benefit from the intervention. For future patients, it is anticipated that investigators may be able to determine whether one of the pain medications has a better potential to reduce the need for rescue analgesia without a concomitant increase in side effect following tonsillectomy surgery. There is a possibility that parents may feel uncomfortable answering some items on the questionnaires.

4.6. Early Withdrawal of Subjects. Patients may be withdrawn from the study if during surgery an additional procedure is required or if the lead study physician (MCM) determines it is not in the best interest of the patient to continue in the study. Caregivers may decide to withdraw their child from the study at any time without penalty. Withdrawn children will be replaced with a new subject to maintain a consistent number of enrolled patients in each group.

4.7. Study Medications, Administration, and Blood Plasma Concentration Measurements

4.7.1. Hydromorphone. Hydromorphone hydrochloride (4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride) is a hydrogenated ketone of morphine. Hydromorphone hydrochloride is a pure opioid agonist with the principal therapeutic activity of analgesia. A significant feature of the analgesia is that it can occur without loss of consciousness. Opioid analgesics also suppress the cough reflex and may cause respiratory depression, mood changes, mental clouding, euphoria, dysphoria, nausea, vomiting and electroencephalographic changes. Many of the effects described above are common to the class of mu-opioid analgesics, which includes morphine, oxycodone, hydrocodone, codeine, and fentanyl. Hydromorphone has been most extensively studied in adults, however it is commonly used in pediatrics both in the perioperative and inpatient settings. At therapeutic plasma levels in adults, hydromorphone is approximately 8-19% bound to plasma proteins. Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites. Only a small amount of the hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone-3-glucuronide along with minor amounts of 6- hydroxy reduction metabolites. The terminal elimination half-life of hydromorphone after an intravenous dose is about 2.3 hours in adult FDA studies[13].

4.7.2. Fentanyl. Fentanyl citrate (N-1-phenethyl-4-piperidyl propionanilide citrate) is a potent opioid agonist with principal therapeutic activities of analgesia and sedation. As with other potent opioid agonists, the most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression, or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, diaphoresis, pruritus, urticaria, laryngospasm and anaphylaxis. Like hydromorphone, fentanyl has been most extensively studied in adults but is commonly used in the pediatric patient population, especially in the perioperative period. In adults, the pharmacokinetics of fentanyl can be described as a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. It accumulates in skeletal muscle and fat, and is released slowly into the blood. Fentanyl, which is primarily metabolized by the liver, demonstrates a high first pass clearance and releases approximately 75% of an intravenous dose in urine, mostly as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes[14].

4.7.3. Administration. The study will be conducted in the operating room and in the PACU. In the operating room, patients will receive a general anesthetic with an endotracheal tube directed by the attending anesthesiologist as per routine care at SLCH. Standard ASA monitors, which include pulse oximetry, non-invasive blood pressure monitoring, telemetry, heart rate monitoring, and end tidal CO2 and oxygen monitoring will be

connected to the patient as per standard of care. Patients will be randomized to receive either hydromorphone or fentanyl in the operating room determined by opening a sealed protocol envelope. Administration and dosing of the randomized opioid to each case will be under the direction of the primary anesthesia team under the direction of the pediatric anesthesiologist caring for the child. In addition to the randomized opioid, patients will receive non-opioid analgesics and PONV prophylaxis as per routine care at SLCH. Blinding will be achieved using syringes prepared by SLCH investigational pharmacy.

4.7.4 Optional opioid Plasma Concentration Assessments. Approximately 3 mls of whole blood will be collected from patients at three time points: 1) within 10 minutes of administration of study drug, 2) within 10 minutes of PACU arrival, and 3) within 10 minutes of PACU discharge. Blood samples will be collected through an additional IV line placed in the surgical suite after anesthesia is given. Opioid (hydromorphone or fentanyl) blood levels will be measured using mass spectrometry. This type of analysis does not require apriori knowledge of the medication administered and will maintain the masking protocol. A Population Pharmacokinetic Analysis will be performed. The patient may decline to participate in the blood draw component of the study and remain in the study for data collection relating to the primary endpoint. Additionally, failed or missed blood draws in individual patients will not adversely affect the population analysis.

4.8. Treatment Regimen. Patients will receive a general anesthetic as per the standard of care at SLCH. Analgesia will include opioids and non-opioid adjuvants for pain in addition to anti-emetics per routine care at SLCH. Airway maintenance will be via an endotracheal tube supervised by the anesthesiologist responsible for the care of the patient in the operating room.

4.9. Method for Assigning Subjects to Treatment Groups. Patients will be randomized to either hydromorphone or fentanyl in the preoperative area prior to presenting to the operating room by investigational pharmacy staff. Randomization will be 1:1 in blocks of 4 within strata. Stratification will be done by age group (2-7, 8-12, and 13-15), and OSA diagnosed using sleep polysomnography within the last year.
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4.10. Preparation of the Study Drugs. Equi-analgesic dose tables poorly accommodate differences in rapid redistribution between drugs. Establishing a definitive therapeutic equivalence between hydromorphone and fentanyl for the patient population, type of stimulus, and duration of procedure is challenging a priori. Previous data gather at SLCH and clinical expertise guide our dosing choices. Hydromorphone, when utilized as the sole opiate intraoperatively is dosed with median 10 ± 4 mcg/kg with16 mcg/kg as the 80th percentile, and fentanyl is dosed with median 0.9±0.5 mcg/kg, with 1.5 mcg/kg at the 80th percentile. We will use these current medians to guide our dosing. We will initiate medication dosing of patients with hydromorphone 10 mcg/kg, and fentanyl 1 mcg/kg. Conveniently, formulary preparation of hydromorphone is at 500 mcg / ml and fentanyl at 50 mcg/ml. Thus, blinding should be achievable as the same volume of medication (ml/kg) can be safely administered for each drug.

Regarding feasibility, we conducted an informal survey of attending anesthesiologists at SLCH. We had an approximately 50% response rate and all were willing to give these two drugs at the proposed doses in a blinded fashion.

5. Study Procedures

5.1. Screening for Eligibility. The patient's medical record will be screened for: age of child, type of surgical procedure planned, history of previous surgery, classification score for anesthesia, whether child is in custody of a legal caregiver, and ability to consent/assent to the study.

5.2. Enrollment. The surgery schedule at SLCH is posted in advance therefore it is straightforward to determine daily if there are eligible subjects to approach for inclusion. The patient's medical history is available to screen for eligibility criteria prior to asking if they would be interested in participating. The day prior to the surgery, a nurse may contact the family to deliver preoperative instructions. At this time, the family may be told a study is being conducted and given details on possible participation. Additionally, the research team will identify potential patients on the day of surgery that may qualify for the study. A member of the research team will then approach the family in the private room in the surgical preoperative area to discuss the study and review the consent form. The study group will consist of 300 patients who are presenting for tonsillectomy surgery or tonsillectomy and adenoidectomy surgery. Enrollment completion will be achieved once consent for up to 360 patients is obtained, assuming a 20% drop-out rate from the study, with an end goal of 300 patients.

5.3. Schedule of Measurements. Consenting families will be evaluated with the YPAS-m scale prior to surgery. At the time consent is obtained, parents will also be asked to complete a brief demographic data form. Any preoperative sleep studies (also known as polysomnograms) that subjects had previously received will be reviewed. After surgery, the post-operative recovery nurse will evaluate the patient's pain using rFLACC scale on arrival to the Post Anesthesia Care Unit (PACU), and then every five minutes during the patient's stay. This is standard of care.

After transferring from Phase I recovery, a member of the research team will continue to evaluate patient's pain using the same scale on arrival and before discharge. The patient's level of pain (rFLACC) and need for any additional analgesic medications will also be evaluated. rFLACC is standard of care at SLCH and all personnel are well versed in its application. After discharge, the patient will receive a telephone call or text at 24 hours after surgery to evaluate post-operative nausea and vomiting and the level of pain at home. The need for additional pain medication will also be assessed. This is standard of care at SLCH and performed for all patients who are discharged the day of surgery, regardless of type of surgery. Respiratory events will be assessed initially using SpO2 monitoring immediately after arrival to the PACU, followed by clinical assessment after PACU discharge. Postoperative nausea and vomiting is assessed using observation and patient verbalization.

Patient and family satisfaction with care will be assessed using a survey on postoperative day 3, as well as the validated NIH PROMIS questionnaires for Pediatric Self-Report (ages 8-17) and Parent Proxy Report (ages 5-17). We will use the following NIH PROMIS questionnaires: Pain Behavior, Pain Interference, and Pain Quality. PROMIS questionnaires will be sent to patients via e-mail through the REDCap server on postoperative day 7 (± 1 day).

5.4. Safety and Compliance Monitoring. All patients will be monitored by an anesthesiologist for the first 5 minutes in the PACU and then every 5 minutes by a registered nurse until discharged from the PACU to the Same Day Surgery unit. Monitoring is continuous until the patient recovers from anesthesia and then every 5 minutes x3, then every 15 minutes until PACU discharge. The same tool, the rFLACC, is used throughout the hospitalization to assess pain. Postoperative nausea and vomiting is assessed using observation and patient verbalization.

5.5. Medical Monitoring. The PI will be monitoring all unblinded data as it is collected throughout the study and share the information with the anesthesiologists and the surgeons. In general, the Department of Anesthesiology has developed a specific set of Standard Operating Procedures (SOPs) for clinical research. All individuals working on study are required to read and be familiar with and compliant with the SOPs. The SOPs are in part developed from and are compliant with the Institutional Guidelines, including those for a) Interactions with the Washington University Human Subjects Review Committee, b) Informed Consent Development and Implementation, c) Subject Recruitment and Screening, d) Subject Management While on Study, e) Adverse Event Reporting. The potential risks of this study are attributable to the use of opioids in the perioperative period.

As already per routine care at SLCH, there will always be a non-study team attending anesthesiologist available both in the operating room and in the PACU to care for the patient in the event of any potential adverse event. This includes the availability of any resuscitation medications and/or equipment including but not limited to naloxone and emergent airway equipment.

5.6. Data Collection Procedures for Adverse Events. An adverse event would be evident as the study data on pain control, respiratory events, and PONV are collected as per routine standard of care.

5.7. Reporting of Adverse Events. Any adverse event will be reported to the IRB within 7 days as required. Any occurrences of serious adverse events or death will be reported within 24 hours.

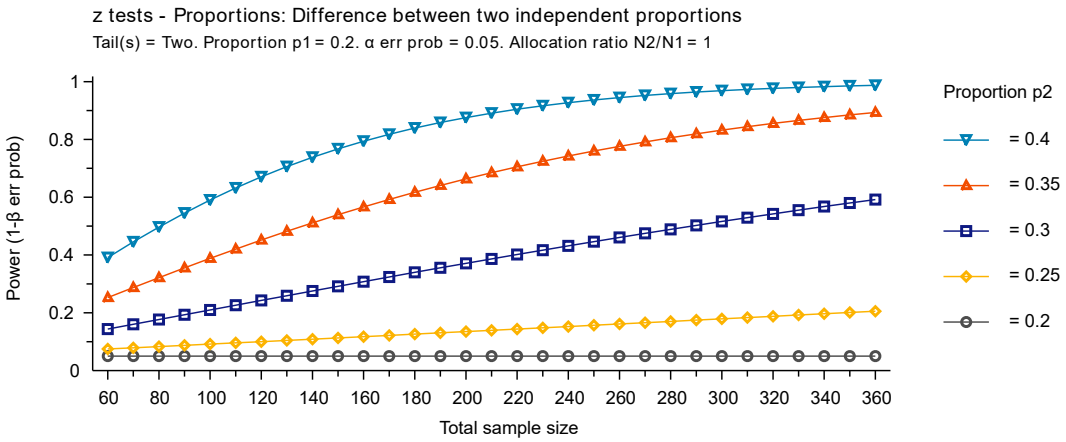
6. Statistical Plan

6.1. Sample Size Determination and Sample Size Estimation. Sample size estimations were performed to determine the number of patients required to see a 50% reduction in the patients requiring rescue analgesia between the group receiving fentanyl and the

group receiving hydromorphone. Each estimation assumed achieving 80% Power, Alpha of 5%, 2 study groups at 1:1 ratio, and 20% attrition (equivalent by study group).

Multiple power curves were calculated. As examples, assuming the proportion using rescue analgesics among patients in the fentanyl study group was 36% compared to a 50% reduction down to 18% for the hydromorphone group, a power analysis comparing independent proportions would require a total sample size of 228 participants. If 50% of the Fentanyl study group utilized rescue analgesics, detecting a 50% reduction down to 25% for the Hydromorphone group, a power analysis comparing independent proportions would require a total sample size of 139 participants (Fig. 1). We selected 300 patients based on an assumed proportion of 0.35 in the fentanyl group requiring rescue opioid analgesia and a goal of 50% reduction in patients requiring analgesia.

Figure 1: Sample size estimation curves. P2 = Fentanyl.



6.2. Analysis Plan. De-identified data will be entered into an excel spreadsheet and then SPSS will be used for data analysis. Demographic data will be summarized using descriptive statistics and the two groups will be examined for baseline differences. Descriptive statistics will include proportions, means, and standard deviation to determine statistically significant differences ($p<0.05$). If the differences at baseline are significant, confounders will be addressed using multivariate adjustment techniques. Alpha level 0.05 will be used.

7. Data Handling and Record Keeping

7.1. Confidentiality and Security. The consent forms and all questionnaires will be collected and stored in a locked file drawer in a locked office. Responses to questionnaires will be entered into a password protected computer. All study data will be entered into a database on a password protected computer. Only study team members will have access to the data. All reporting of data will be in the aggregate.

8. Risks, Study Monitoring and Administration

8.1. Monitoring. Studies conducted in the Department of Anesthesiology follow the Washington University Institutional Review Board Policies and Procedures (last revision January 21, 2019). All individuals working on the study are required to read and be familiar with and compliant with the IRB Policies and Procedures. The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of opioids in the perioperative period. Both drugs of interest are standard of care medications and on formulary at SLCH. Thus, the risk of study participation is nearly identical to that incurred with having a tonsillectomy at SLCH, regardless of study participation. Based on the small size and relatively low risk nature of the protocol, the investigating physicians are involved in the monitoring plan. Additionally, a board-certified anesthesiologist practicing in pediatric anesthesia at SCLH who is not a member of the research team will be included in the monitoring of all adverse events. These individuals will review the annual summary

of adverse events. All reports of a Serious Adverse Event, or an Unexpected Adverse Event will be reviewed and reported to the IRB. The investigators will follow the requirements for principle investigator reporting requirements as outlined in Section X of the IRB Policies and Procedures.

8.2. Funding and Conflicts of Interest. Departmental funding; an intramural ICTS grant is pending. No conflicts of interest for any of the study team members.

8.3. Study Timetable. The study is expected to start immediately after receiving IRB approval. Data collection will take 24-36 months; analysis another 3-6 months.

9. Publication Plan

Publication in a peer-reviewed medical journal is expected following completion of the data collection and analysis of the results. Presentation at regional and/or national meetings is also anticipated. Establishing best practices for the use of opioids in children is a high priority in pediatric anesthesia, and we anticipate national interest in this research.

10. **Management of Intercurrent Events**

10.1. Adverse Experiences: The investigator will closely monitor subjects for evidence of adverse events. All adverse events will be reported and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required.

10.2. Premature Discontinuation: If a subject withdraws from the study, the subject will be replaced to provide the required number of subjects. Subjects will be withdrawn without penalty if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study.

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