Title: Ondansetron as a Strategy for Reducing Propofol Injection Pain in Pediatrics: a Randomized Controlled Trial

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PROTOCOL TITLE: Ondansetron as a Strategy for Reducing Propofol Injection Pain in Pediatrics: A Randomized Controlled Trial

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
Version 2.0	11/13/2023	Removed the endoscopy procedure from Exclusion Criteria.

Table of Contents

1. Study Summary

Study Title	Ondansetron as a Strategy for Reducing Propofol Injection Pain in Pediatrics: A Randomized Controlled Trial
Study Design	Prospective, randomized, controlled
Primary Objective	Determine the effect of ondansetron as a preventative premedication for propofol injection pain
Secondary Objective(s)	Compare the effect of ondansetron to lidocaine in preventing injection pain from propofol.
Research Intervention(s)/Interactions	IV ondansetron prior to IV propofol injection
Study Population	Pediatric patients (≤40 kg) undergoing surgery at CHOA Egleston
Sample Size	120
Study Duration for individual participants	1 day – all study activity will take place in the OR
Study Specific Abbreviations/ Definitions	VRS (verbal rating scale)
Funding Source (if any)	Department

2. Objectives

Our primary aim is to determine the effect of ondansetron as a preventative premedication for propofol injection pain. Our secondary aim will be to compare the effect of ondansetron to lidocaine in preventing injection pain from propofol.

3. Background

Propofol is a rapid onset intravenous (IV) anesthetic drug that is used frequently for the induction of anesthesia. Unfortunately, propofol has a common side effect of causing significant discomfort on injection with an incidence of 70%. (1) This unfortunate complication is not unique to adults and is seen with similar frequency in the pediatric population. Currently, many physicians administer lidocaine intravenously prior to propofol injection to help decrease the severity of pain. While this method is frequently used, a decrease in pain response of only 25% has been seen in children. (2)

Recently, ondansetron has been evaluated as a potential pre-medication for prevention of propofol injection pain. Ondansetron is a frequently used antiemetic that also exhibits opioid agonist and sodium channel blocking properties. Adult literature has shown significant pain reduction when ondansetron has been administered prior to propofol injection. (3) However, there are no pediatric studies we are aware of comparing the effect of ondansetron to lidocaine for the prevention of propofol injection discomfort. In this randomized prospective study, we will determine the effect of premedication with ondansetron on the pain resulting from propofol injection in comparison with the current standard of lidocaine premedication. After consent has been obtained, patients will be randomly assigned to either the ondansetron or lidocaine premedication group. A blinded observer will then monitor the patient's pain response during anesthesia induction with propofol by using verbal rating scale and motor scale specified in appendix A (Singla, 2018). Lidocaine and Ondansetron are both clear solutions and cannot be identified by the naked eye to the observer.

Propofol is the most frequently used IV induction agent for anesthesia in both adult and pediatric populations. However, a common side effect from this medication is substantial pain on initial injection. The quality of pain, as described by adults, is sharp, burning and aching. In a panel of expert anesthesiologists, propofol induced pain has ranked 7th out of 33 clinical problems when considering clinical importance and frequency of episodes.(4) The possible mechanism for this discomfort may be that propofol can activate the kallikrein–kinin system and release bradykinin, resulting in venous dilation and increased permeability, thereby increasing contacts between propofol aqueous phase and free nerve endings.(3) This unfortunate complication is not exclusive to adults and is seen with similar incidence in the pediatric population.

Anesthesiologists have explored numerous techniques to mitigate the pain resulting from the injection of propofol such as local anesthetics, cool fluids and opioids. Currently, the most used technique is the administration of lidocaine prior to the injection of propofol. However, this method has only been shown to reduce the incidence of pain by 20% in adult studies.(5) Of recent, the use of pre-medicating with ondansetron has been evaluated at in the adult population. Ondansetron is a 5-HT3 antagonist that is routinely used as an antiemetic for postoperative nausea and vomiting prevention. Ondansetron also exhibits sodium channel blocking activity and opioid μ agonist activity. As a result of its multifaceted actions, it is not implausible to infer that ondansetron may potentially be used to alleviate pain induced by a drug such as propofol. Ye et al demonstrated that the effect of subcutaneous injection of

ondansetron was 15 times than that of local anesthesia with lidocaine.(6) A recent metaanalysis reviewing 10 randomized control trials showed that ondansetron can effectively prevent propofol injection pain. (3)

This investigation is **significant** because, to date, no randomized, controlled trial has examined the effect of ondansetron premedication on propofol injection pain in the pediatric population. A few prospective studies have evaluated the use of lidocaine and ondansetron premedication in the adult population, but these studies are small, adult based and difficult to extrapolate to the pediatric population. As a large tertiary academic center that performs solely pediatric anesthesia, our institution is the ideal environment for this study design. It is imperative that we gain understanding of the most effective way to minimize pain on propofol injection as this method of anesthesia induction is used regularly.

*We **hypothesize** that by administering ondansetron as a premedication prior to propofol injection, we can decrease the pain on injection of propofol for anesthesia induction. We also hypothesize that this method will be more effective than the current practice of lidocaine premedication. This study will provide a more comprehensive understanding of the best way to provide prophylaxis against the pain incurred on injection of propofol.*

4. Study Endpoints

The primary endpoint will be the observed pain from injection of propofol, measured by 1 of 5 trained, blinded observers.

5. Study Intervention/Investigational Agent

Ondansetron (Zofran) is a 5-HT_3 receptor antagonist commonly used to treat postoperative nausea and vomiting. It will be compared to a common standard-of-care treatment, Lidocaine.

The Investigational Drug Pharmacy at Children's Healthcare of Atlanta will prepare the drugs. The operating room pharmacy will dispense these to the treating anesthesia team or study team according it the subject's randomization. The treating anesthesiologist will be blinded at the time of administration, then un-blinded after induction.

6. Procedures Involved

After written informed parental consent (and patient assent when appropriate) has been obtained, patients will be assigned to ondansetron group or lidocaine group by a computerized random number generator. The investigational drug pharmacy will prepare the study drug, either Ondansetron or Lidocaine. Prior to procedure the IV will be flushed with 10cc normal saline to ensure patency and that there is no baseline pain with injection. If the IV is not patent or there is significant pain with flushing the IV, the patient will be withdrawn from the study.

Patients who meet criteria will then be administered midazolam 0.1mg/kg IV in the preoperative holding area. The protocol limits the patient's weight to be less than 40 kg, because the maximum dose of ondansetron is 4mg or a volume of 2cc. The equivalent volume of 2% lidocaine is 40mg, also 2cc. To avoid dilution of the lidocaine, we limited the maximum volume of lidocaine to match the volume of ondansetron.

In the OR, standard ASA monitors will be placed in preparation for induction. The ondansetron group will receive ondansetron 0.15mg/kg IV push followed immediately by propofol 2mg/kg IV for induction. The lidocaine group will receive lidocaine 2% 1mg/kg IV push followed immediately by propofol 2mg/kg IV for induction. A 10cc normal saline flush will follow injection of propofol.

During induction, a blinded observer will measure the pain from the propofol by recording their vocalization (VRS) and motor response to the injection of propofol (appendix A). This pain scale has been used in previous papers (Singla, 2018) studying the use of different agents to mitigate propofol pain. One component of measures the VRS pain scale evaluates how the patient verbally responds to the injection of propofol, from whether the patient has no response versus moaning or screaming. The observer will also measure the motor response, and evaluate for limb movement to measure the patient's response to pain on injection with the propofol.

The anesthesiologist for the procedure will be un-blinded at the end of induction to allow entry of the drug into the electronic medical charting program. Medical records will be reviewed for data relating to induction of anesthesia. No long-term follow-up will occur.

There will be a total of five trained observers—4 physicians and one study coordinator. The number of observers are limited to minimize variability. Each observer will be required to assess a patient with the PI and have a matching score before observing alone.

7. Data and Specimen Banking

Data will not be banked for future use. No specimens will be obtained.

8. Sharing of Results with Participants

No individual results from this study will be shared with participants.

9. Study Timelines

Length of participation for study subjects is one day. It is expected that primary data analysis will be complete by January 2023.

10. Inclusion and Exclusion Criteria

Patients presenting for surgery to Children's Healthcare of Atlanta at Egleston will be screened for eligibility.

Inclusion Criteria:

- Patients 2 years old through 17 years of age
- Children undergoing surgery at Children's Healthcare of Atlanta Egleston location
- Patient with existing peripheral vascular access in the arm below the antecubital fossa
- Patients with an ASA category score of 1, 2 or 3
- Parent or legal guardian willing to participate, and able to understand and sign the provided informed consent
- No known chronic pain syndrome

Exclusion Criteria:

- Parent or legal guardian unwilling to participate or unable to understand and sign the provided informed consent
- Known chronic pain syndrome

- Patient diagnosed with long QT syndrome
- Patient weighing >40kg
- Documented allergy to study medications
- Pain on injection of pre-operative normal saline flush
- Patient has received an opioid within 30 minutes prior to anesthesia induction Further exclusion criteria may be determined at the discretion of the investigators.

11. Vulnerable Populations

Pediatric patients will be enrolled in this study. This study is intended to improve treatment of this population. Because in many cases only one parent is available in the pre-op clinic or day of surgery, we will require only one parent's consent. Assent will be obtained by patients of appropriate age.

12. Local Number of Participants

One-hundred and twenty participants will be enrolled.

13. Recruitment Methods

Potential participants will be screened by the study team from a list of patients presenting for surgery. Participants may be referred by other physicians, however there will be no incentive for referrals. Potential participants and their parents will be approached by a member of the study team in the pre-op/day surgery clinic room or their hospital room (if inpatient), either during the pre-op appointment or the day of surgery if there is ample time for consideration prior to surgery. Participants will not receive payments.

14. Withdrawal of Participants

Participants may be withdrawn if there are any problems with the IV, including pain or patency. If a participant needs to be withdrawn, the treating anesthesiologist will resume induction per standard of care.

15. Risks to Participants

There may be side effects from the study drug or procedures that are not known at this time. The study drug ondansetron is given routinely after any procedure is completed. In this study, ondansetron will be given at the beginning of the case to minimize pain from the injection of propofol.

The most common risks and discomforts expected in this study are the same if ondansetron is given at the beginning of the case or the end of the case: headache (17%), musculoskeletal pain (10%), constipation (6-11%)

The less common risks and discomforts expected in this study are: shivers (7%), agitation(6%) Rare but possible risks include: injection site reaction (4%), urinary retention (3%), referred pain, pain in lower chest and shoulder (2%), chest pain (2%), painful urination (2%), low blood pressure (2%), fever (2%), cold sensation (2%), itchy or tingling skin (2%)

16. Potential Benefits to Participants

This study may not benefit participants directly but help to reduce pain related to propofol injection. Participants will help to answer the study question and potentially help other patients in the future.

17. Compensation to Participants

Participants will not receive compensation.

18. Data Management and Confidentiality

Descriptive statistics will be calculated for all variables of interest and will include means and standard deviations, medians, ranges, or counts and percentages, as appropriate. Normality of data will be assessed using histograms and/or Shapiro-Wilk tests. Characteristics of subjects who received Ondansetron will be compared to those who received lidocaine using Chi-square tests or Fisher's exact tests for comparisons of categorical variables (i.e. gender, race, adverse events, serious adverse events, etc.) and two-sample tests for continuous variables (i.e. age, etc.). If continuous data is non-normal, non-parametric tests such as Wilcoxon rank-sum tests will be used. Generalized linear regression models will be used to compare differences in the total VRS and motor scores among the cohorts, adjusting for any differences in patient characteristics that may exist between the groups based on initial bivariate analysis. Normality of model residual error will be assessed; if residual error is nonnormal, outcomes will be log-transformed or categorized into a binary outcome (i.e. 0 vs $\geq$1 total score) depending on the distribution of the data. Statistical analyses will be performed using Stata v. 13.1 (College Station, TX) or SAS v9.4 (Cary, NC) and assessed at an alpha level of 0.05.

Sample size calculations were performed using a two-sample independent t-test at an alpha level of 0.05. At 80% power, we will need 60 subjects in each group (120 total) to detect a moderately sized (Cohen's effect size: 0.50) difference in total VRS and motor scores between the lidocaine and ondansetron groups. Power calculations were performed using R version 3.5.1 (R Core Team 2018).

Permuted block randomization with randomly selected block sizes of 2 and 4 will be employed for assigning participants to the two treatment groups.

Data will be recorded in a secure CHOA REDCap database which will be accessible only to the study team.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) is an important aspect of data collection. After enrollment, the principal investigator or designee will collect the adverse experiences from the medical record. The study subjects will be reviewed on a case-by-case basis. The principal investigator will determine the seriousness of each adverse event and whether the event was related to the study. Serious adverse events (life-threatening, requiring

intervention) will be reported to the IRB within the guidelines set by the IRB. AEs will be reviewed by an anesthesiologist not involved in the study within a week of occurrence.

Emory's self-monitoring tool will be used to ensure all requirements are met throughout the duration of the study.

The anesthesiologist for the case will be un-blinded to ondansetron or lidocaine administration after induction. This will allow for the patients to be properly administered ondansetron during the procedure if they did not receive it on induction. It will also prohibit double dosing of ondansetron during the procedure. After fifty percent of patient enrollment, the principal investigator will review the charts to ascertain if adverse events occurred, and to make sure if the study is still safe to continue the study.

20. Provisions to Protect the Privacy Interests of Participants

Participants and their parents will be approached in a private room. No aspects of this study involve sensitive topics.

Confidentiality will be maintained throughout the entire process from obtaining consent to data analysis. Confidentiality will be maintained by only recording information necessary to fulfill the study's objectives. Information directly identifying patients (names, addresses, phone numbers, social security numbers, email addresses, and account numbers) will be excluded from any publication or presentation. In the research database, patients will be identified by their assigned study number. The database, along with the code linking a subject's identity to an assigned number, will be locked in the office of the principal investigator or designee.

21. Economic Burden to Participants

There will be no additional cost to the participants. The drug, either lidocaine or ondansetron, will be funded by the study.

22. Consent Process

The Institutional Review Board will approve informed consent documents prior to commencement of the study. Only those patients who meet the entry criteria will be considered as possible study candidates. A thorough discussion between the parents or legal guardian and the principal investigator, or the study coordinator will occur during the study consent process. No study related procedure will occur prior to obtaining appropriate informed consent. Patients will be enrolled consecutively as they present to Children's Healthcare of Atlanta. The parents or legal guardian of the patient will be approached prior to surgery by the principal investigators, or the study coordinator to discuss the goals, benefits and risks of the project. Written informed consent will be obtained following this discussion. Patients undergoing emergent procedures or when there is insufficient time for the parents to thoroughly consider the goals, benefits and risks of this project will not be approached for enrollment.

Parental permission will be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

If an individual has legal guardianship of a patient and authority to consent for medical care, they will be able to consent for the study. This will be determined by reviewing the medical record.

Assent will be obtained by participants 2-17 years old. If a participant has a developmental delay, this will be documented, and the parent's consent will suffice for the child's participation in the study. **Non-English-Speaking Participants**

For non-English-speaking patients who qualify, an interpreter will be provided to translate the objectives of the study, procedures, and details of the consent form. The appropriate short-form consent will be used per Emory and CHOA policy.

23. Setting

Research will be conducted at Children's Healthcare of Atlanta at Egleston in the operating room. Potential participants will be recruited preoperatively in the pre-op clinic and day surgery. In-patients will be approached in their rooms.

24. Resources Available

Egleston has a busy surgical service, with multiple patients qualifying daily for this study. The study team will recruit as able. Blinded observers will need to be available for induction, but we do not anticipate this being a significant barrier given the number of qualifying patients.

25. References

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Appendix A

Table 1: Pain scale for evaluation of propofol-induced injection pain

Response to propofol injection	Pain score
Motor events	
No movement	0
Slight hand withdrawal	1
Marked withdrawal, rubbing, trying to tear off the line	2
General restlessness	3

Verbalisation scale	
No vocalisation	0
Purposeless moaning	1
Explicit protest	2
Screams, cries	3