Title: Low- Dose Propofol Infusion as an Abortive Treatment for Migraine Headaches in Pediatric Patients

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PI: Deryk Walsh, MD

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1. Introduction and Purpose:

Propofol has been used in adult populations to treat migraines as an abortive agent. We plan to investigate its efficacy as an abortive agent in the pediatric population when administered as a safe low-dose infusion. Goals of the study are to:

1. Evaluate efficacy of low-dose propofol infusion as an abortive agent in pediatric migraine headaches
2. Evaluate effective and safe dosing limits in pediatric populations
3. Evaluate duration of effect reached from a low-dose propofol infusion as an abortive agent

Endpoints for the study will be:

1. Number of enrolled patients
2. Safety endpoints reached, including: cardiopulmonary depression, excessive somnolence

Risks of the study are minimal due to the use of sub-anesthetic dosing of propofol under the guidance and supervision of a board certified pediatric anesthesiologist with the appropriate monitoring equipment and readily available emergency equipment. We hope to demonstrate more rapid improvement and decreased side-effect as compared to standard care.

Background:

Headaches make up one of the largest somatic complaints in children and adolescents. Approximately 82% of adolescents report headaches before the age of 15. (8) Migraine headaches prevalence increases as children age. The reported prevalence increases from 3% (age 3 to 7 years) to 4 - 11% (age 7 to 11) and to 8 - 23% (age 11 to 15+). Mean age of onset differs from male to female, 7.2 years versus 10.9 respectively. (2) Migraine headaches, in particular, have significant impact on children. Repeated exacerbations lead to high levels of school absences, decreased participation in extracurricular activities and have been associated with several comorbid conditions. (9)

Migraine headache pathophysiology continues to be researched. There are many models available for discussion involving the presence of spreading cortical depression and regional blood flow changes. There is clear involvement of messenger molecules nitric oxide (NO) and calcitonin-gene-related peptide (CGRP). This involvement in the sensitization of perivascular nerve terminals and the origination of attacks from a central nervous system location continue to garner increasing attention. (10)

Per the American Academy of Neurology (AAN), treatment of migraine headaches in children has remained difficult. There is a lack of controlled data regarding the treatment of primary headache disorders in pediatrics. Acute treatment recommendations are extrapolated from pooled data of many studies. The recommendations from the AAN include the use of non-steroidal anti-inflammatories, ibuprofen in particular, acetaminophen, and sumatriptan. (2)

Acute medical system treatments of acute migraine exacerbations have been wide-spread as well. As currently the standard of care in acute migraine management is ill-defined. Most centers are

proceeding with a combination therapy including: NSAIDs (typically ketorolac), acetaminophen, anti-nausea medications (metoclopramide, diphenhydramine, prochlorperazine). Should this therapy fail, these institutions proceed to hospital admission for further therapy including dihydroergotamine (DHE) and/or triptan therapy.

Dihydroergotamine is an ergot alkaloid. Following the vascular theory of migraine pathophysiology, DHE has vasoconstrictive properties and is marketed for migraine therapy. (11) Although available to be administered via multiple routes, intravenous (IV) DHE is used to abort migraines refractory to the above therapies. Its administration, at this time, requires admission to the hospital or infusion as an outpatient in a clinical setting. As an inpatient, our current protocol requires premedication with anti-emetics and DHE dosing every six hours for up to twenty doses of DHE on a titration schedule. This requires an admission of up to five days for DHE therapy. As an outpatient, the patient will only receive one dose of DHE, which may or may not be efficacious (data show a 60% reduction in headache severity at one hour with no discussion of total resolution). (11) DHE has significant side-effects including: nausea (32%), chest tightness and mild systemic burning (8%), leg cramps (7%), vomiting (6%), increased blood pressure (5%). (11)

5-Hydroxytryptamine receptor agonist "triptan" therapy, also available in multiple modalities, has demonstrated both efficacy and safety. (2) With oral, intranasal and subcutaneous routes available, many migraine sufferers have preparations available to them at home as a component of the migraine exacerbation plan formulated by their physician.

Propofol (Diprivan) is a short acting lipophilic intravenous general anesthetic. Propofol is currently classified as a sedative-hypnotic and is used as an anesthetic agent.
It is marketed as 10mg/ml emulsion. Its mechanism of action is unrelated to any currently used barbiturate, opioid, benzodiazepine, or imidazole. As an intravenous anesthetic agent it causes global central nervous system depression presumably through GABA receptors and possibly by decreasing gluatametergic activity via NMDA receptor blockade.

Propofol is distributed to all tissues in the body rapidly following intravenous administration. Anesthetic results are dose dependent. There is rapid equilibration of the blood and brain concentrations (1 -3 minutes). Propofol is highly protein-bound (>95%) and metabolism is via rapid glucuronide conjugation in the liver. Duration of action of a bolus injection is 3 -5 minutes. Reported side effects include hypotension, arrhythmias (bradycardia or tachycardia) and burning or pain at injection.

Four studies in the adult population have shown efficacy with propofol as an abortive agent when it was administered in sub-anesthetic bolus dosing[1,12].

Krusz et al, found a 95.4% rate of success in treating intractable headaches in the adult population with propofol. Eighty-two percent of the patients had complete resolution of their headaches. The remaining patients had a 50-90% reduction in their pain scores. At the sub anesthetic propofol dose administered, there was no incidence of loss of consciousness recorded. The total amount of propofol given averaged 110 mg with no weights given for per kg dosing. Mosier et al recently reported a case series of adults presenting to the ED with failed outpatient treatment of migraine headache. Patients were treated with a sedation dose of 1mg/kg of propofol; all subjects reported dramatic improvement or complete resolution of headache symptoms and had a 50% reduction in length of stay as compared to the average LOS for patients with similar chief complaints. No events of hypotension, hypoxia or apnea were reported in these cases (12).

Data about use of propofol as an abortive agent for pediatric patients with migraine is limited. In a retrospective review of seven patients, Sharidan et al (8) found an 80% efficacy rate in reducing intractable headaches with bolus doses of propofol without noting any adverse effects. The total propofol dose administered was 1.71 mg/kg with a range of 0.81 – 3.72 mg/kg. Since this was a small retrospective study, no data was available on the length of the headache relief or the degree of sedation the patients experienced.

As the pathophysiology of migraine headaches remains unknown, the exact mechanism of action of propofol's abortive therapy is also uncertain. The Krusz study [1] raised questions regarding the GABA system and its mechanism regarding intractable headaches. One possible hypothesis suggested that the GABA system is in a low functional state at the time of the headache. This would lead one to conclude that stimulating the system would lead to resolution of symptoms. Propofol's GABA agonism has been documented. The effects of propofol on the central nervous systems have been well studied, some effects include:

- GABA agonism leading to neuronal hyperpolarization and generalized inhibition of neuronal firing,
- enhanced anti-nociceptive dorsal root potentials, inhibition of sympathetic efferent activity,
- decreased sympathetic muscle nerve fiber activity,
- inhibition of voltage-dependent calcium channels (interesting since Ca channel blockers are well known migraine treatment),
- possible depression of NMDA activity,
- global metabolic metabolism decrease in the central nervous system.

Study Aim

The aim of this prospective study is to evaluate the efficacy and safety of propofol administration in a hospital setting, as an abortive medication for children aged 7-18 with migraines.

Primary outcome:

Based on the adult and the limited pediatric data available we hypothesize that propofol infusion in sub anesthetic dose, will result in either complete resolution or improve the headache pain scores by 50% from the baseline pain scores. Patients will be assessed with a 0-10 Numeric Pain Rating Scale.

Secondary outcomes:

- Time to beginning of effect (from the beginning of the propofol infusion till first improvement in pain score noted)
- Duration of effect (from the end of propofol administration till discharge criteria are meet or if treatment is ineffective, till start of new therapy)
- Total propofol dose based on weight.

Goal of subjects to be consented include: 30 to demonstrate effect
Subjects may receive multiple treatments if propofol infusion is effective in reducing headache symptoms.

Concise Summary: We will be enrolling subjects who are scheduled to undergo DHE infusion for treatment of migraine headaches as part of standard medical care. Subjects will be identified from the investigators' patient list, of children presenting to the Headache Clinic in the Pain Management Clinic for treatment of migraine headache or who have been admitted to the hospital for treatment of migraine headache. Patients who will be treated at the SPU or during inpatient admission by the DHE protocol will be evaluated for eligibility prior to the visit. If the investigator determines that they would be

eligible, the family will be contacted in advance of the visit to discuss possible participation. An investigator will be present at the visit to discuss the study in further detail and answer any questions, and informed consent will be obtained prior to any study procedures are performed.
Prior to initiation of DHE infusion, the subjects will receive sub-anesthetic doses of propofol infusion: 20 mcg/kg/min for 10 minutes, followed by an increase to 30 mcg/kg/min for 10 minutes and then by an increase to 40 mcg/kg/min for 40 minutes. The propofol infusion will be terminated if:

- The patient has no pain, or greater than 50% reduction in pain scores as compared to the pretreatment pain score
- After completing 40 minutes of propofol infusion at 40 mcg/kg/min irrespective of the pain score
- If the anesthesiologist feels cardio-pulmonary depression, airway obstruction or over sedation (Ramsay Sedation Score greater than 3)has occurred

If the propofol infusion is effective in resolving headache symptoms, then subjects will be monitored for at least 30 minutes after termination of infusion. Outpatient subjects would then be discharged home; inpatient subjects would resume standard care treatment.

If propofol infusion is not successful in resolving headache, then the subjects will proceed with DHE infusion per standard of care. If the subject still has no relief, the study investigators will discuss further options with the subject and parents, including hospital admission for further therapy for outpatient subjects.

For all subjects who receive propofol infusion, follow-up will occur at 24 and 48 hours via phone call to evaluate headache status and recover information on headache symptoms and side effects.

METHODS

A. Subject Selection

a. Inclusion Criteria

- Patients with a diagnosis of migraine headache per ICHD – 3 (International Classification of Headache Disorders)
- The subjects will have a history of migraine headaches with a presentation consistent with presentations of their headaches in the past with no indication for further investigation for secondary causes of his/her headache.
- Documented pain score greater than or equal to 6 on a 0-10 Numeric Pain Rating Scale.
- Current migraine has a greater than 24 hours duration with a current pain score of 6 or greater on a 0-10 Numeric Pain Rating Scale.
- Subjects will be scheduled for DHE infusion therapy for treatment of migraines per standard medical care
- Patients age 7-18 years old
- Gender: both male and female
- Appropriate fasting interval as per ASA guidelines

b. Exclusion Criteria

- No long acting triptan therapy within 24 hours,
- No shorter acting triptan therapy within 6 hours.
- No ergot alkaloid derivatives within the last 24 hours.
- No opioid within 2 hours.
- No NSAID or acetaminophen within 1 hour of infusion.
- Use of sedative medications within 6 hours of infusion, including opioids, benzodiazepines, barbiturates.
- Headache not consistent with subject's headache history needing further work-up.
- Headache duration less than 24 hours.
- Subjects in which an intravenous line could not be secured
- Subjects with history of significant reflux or hiatal hernia
- Subjects with history of significant cardio pulmonary disorders
- Patient not fasting as per ASA guidelines

B. Protocol

Patients will be recruited from the investigators patients in the headache clinic or from inpatient consults to the pain service.

Patients may be identified once scheduled for DHE infusion at the CMC Special Procedures Unit (SPU) for treatment of migraine headaches, or once the pain team is consulted for inpatient subjects who have been admitted for migraine symptoms.

Upon identification of potential subjects, if the patients meet inclusion criteria, a study investigator will describe the study details as well as the alternative DHE therapy. Should the patient's guardian consent and the patient assent we will continue with the study protocol. **If consent will be obtained the study will proceed as follows:**

- A urine pregnancy test will be performed for all female of child-bearing potential as standard care in accordance with CMC policy. The patient will have an IV catheter placed as part of standard of care treatment for DHE infusion**.** A peripheral vein will be accessed and an infusion of Ringer lactate will be started. For the intravenous access, a topical anesthetic (i.e. j-tip or synera patch) will be used as per SPU protocol.
- Patients will be continuously monitored as per ASA guidelines to include continuous pulse-oximetry, EKG, respiratory monitoring and heart rate. The attending anesthesiologist (investigator) will be physically present at the start of study drug infusion; he will also be immediately available in the SPU or main hospital for the duration of the infusion period.

- pain scores (Numeric Pain Rating Scale) will be evaluated during study medication titration, before, every 10 minutes throughout infusion and up to one hour after termination of the infusion.
- sedation scores will be evaluated by using the Ramsay Sedation Scale before, every 10 minutes throughout infusion and up to one hour after termination of the infusion.
- The propofol will be delivered through an infusion pump (Alaris) starting at a rate of 20 mcg/kg/min for 10 minutes, followed by an increase to 30 mcg/kg/min for 10 minutes and then by an increase to 40 mcg/kg/min for 40 minutes
- The propofol infusion will be terminated if:
    - The patient has no pain, or greater than 50% reduction in pain scores as compared to the pretreatment pain score
    - After completing 40 minutes of propofol infusion at 40 mcg/kg/min irrespective of the pain score
    - If the anesthesiologist feels cardio-pulmonary depression, airway obstruction or over sedation (Ramsay Sedation Score greater than 3)has occurred

3. Study termination
    - if patient has no pain or greater than 50% reduction in pain scores as compared to the pretreatment pain score, then outpatient subjects will be monitored in the SPU for 1 hour. If no clinically significant side effects are present after one hour, then the IV will be removed and he will be discharged with appropriate instructions from primary headache provider for home care and follow-up. Discharge criteria will follow CMC Perianesthesia Department policy for discharge, Policy Number 1.06. Inpatient subjects who have no pain will resume standard care treatment and will be discharged at the discretion of the attending service.
    - if patient has less than 50% reduction in pain scores, the study investigators will continue with DHE protocol according to standard of care.

4. Follow-up 24 and 48 hours after infusion via phone call to evaluate headache status and recover following information:
    i) pain score (via Numeric Pain Rating Scale) at that time
    ii) if not pain-free, when did the headache return
    iii) side-effects from infusion

C. Consent Process and Documentation

Patients will be prescreened when they schedule an appointment at CMC for DHE infusion, for treatment of migraine headaches; or upon consult to the pain service for inpatients. A member of the study team will contact the family by phone in advance of the visit, or in person when the family is available in the hospital. If the patients express interest in study participation, they will meet with the study investigator to establish eligibility and discuss the risks/benefits of the study. The investigator will emphasize the voluntary nature of participation. The study investigator or research personnel will review the consent form and HIPAA authorization with the patient and their legal guardian. If the family decides to participate, then informed consent will be obtained (and assent if applicable). Copies of the signed forms will be given to the patient, and the consent process will be documented in EPIC.

ETHICAL AND ADMINISTRATIVE SECTION

A. Potential patient benefit

The study aims to show efficacy of a propofol infusion, performed in a controlled and monitored situation with patient safety paramount, will have improved efficacy in providing an abortive therapy for acute migraines in patients refractory to their home regimen. We also aim to show decreased side-effects and sustained headache improvement as compared to DHE infusion. If successful, propofol will be an improvement in treatment and prevent unnecessary emergency center visits and prolonged hospital admission for alternative therapies.

B. Risks/Discomforts

1. Risks related to the study protocol

- As propofol will be used at sub-anesthetic dosing, the risk of cardio-pulmonary depression will be very low. Regardless, we will have appropriate monitoring in place and administration will be supervised by a board certified pediatric anesthesiologist. All appropriate rescue equipment and medications will be readily available. The investigator will be certified in PALS (Pediatric Advanced Life Support) and will follow PALS guidelines for resuscitation in the event that the patient experiences adverse cardio-pulmonary outcomes.
- To reduce the risk of medication error, the anesthesiologist and infusion nurse will both verify the correct programming of the infusion pump upon starting the study drug treatment. The Alaris IV infusion pump utilized in the SPU has capability to be programmed for mcg/kg/hr, and each pump is inspected for calibration and proper function by the CMC BioMed department. Each subject will also have a worksheet with the dosing protocol and the dose estimates based on weight (e.g. a patient who weighs 50kg would start at 1 mg/min of infusion, a patient who is 60kg would start at 1.2 mg/min, etc).

Possible side effects associated with propofol include:

- •Decreased heart rate
- •Irregular heart rate
- • Increased heart rate
- •Decreased blood pressure
- •Increased blood pressure
- •Pain at injection site
- •Decreased breathing rate
- •Rash
- •Itchiness
- •Uncontrolled movement
- •Allergic reaction
- Propofol is a known venous irritant and administration may cause localized pain at the insertion site when the infusion is started. Pain will be self-limiting. Subjects and their parent, if applicable, will be informed of the discomfort and we will have distraction techniques in place to assist with the initial pain.
- Allergic reactions to the study medication are rare, however appropriate interventions will be available should this rare event occur.

- Risks to pregnant females or to the embryo/fetus are unknown; therefore we will screen this population for exclusion with a urine pregnancy test.
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- There is always risk of loss of confidentiallity; the study team will protect the confidentiality of all study patients and follow all regulations and policies in place to protect patient confidentiality.

2. **C. Alternatives**

3. **D. Costs to the Subject**

   Subjects will be responsible for all procedures done as standard care, including IV placement, costs associated with use of SPU space, inpatient admissions and related costs of hospital procedures, treatments, medication and DHE infusion therapy. The participants will not be responsible for the cost of the study drug.

4. **E. Reimbursement of the Subjects**

   Patients will not be paid for participating.

5. **F. Confidentiality of Records**

   Information about the patients will be kept confidential. The data will be stored on a password protected database accessible only to the investigators.

5. Sub-Study Procedures:
None

8. Sources of Research Material:
Patient medical charts will be reviewed to assess eligibility criteria and for demographic information. Additional data will be observed and recorded during study treatment, and at the 24 and 48 hour follow up telephone calls.

Data Collection

- Demographic information (age, gender, ethnicity**)**
- Medical history
- Current medications
- Treatment Data
  - Pulse Oximetry (continuous)
  - Respiratory Rate (continuous)
  - Pulse Rate (continuous)

- NRS pain score
- Sedation scores
- Adverse events

11. Subject Safety and Data Monitoring:
As stated above, appropriate monitoring will be in place with appropriate equipment and personnel. Distraction techniques will be available to assist with initial infusion discomfort.

12. Procedures to Maintain Confidentiality:
All institutional procedures regarding collected personal health information will be followed. Subjects will be assigned a study number to minimize the use of identifying information. Consent forms and paper materials will be stored in a locked office in a locked filing cabinet. Electronic data will be stored on a secure, encrypted server on a password protected computer. Only members of the study team will have access to the research files.

13. Potential Benefits:
1. Improved migraine abortive therapy with decreased side-effect profile available to pediatric group
2. Safety profile of propofol infusion therapy at sub-anesthetic dosing confirmed

14. Biostatistics: Statistical analysis will be performed by the statistician within the Department of Anesthesiology & Pain Management at UT Southwestern Medical Center.

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