Study Title: A Randomized, Double Blind Trial of Pediatric Lumbar Puncture under Sedation/Total Intravenous Anesthesia (TIVA) with and without EMLA cream

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Background, Rationale and Context

Pediatric Sedation/Total Intravenous Anesthesia (TIVA) outside the operating room is a growing field, especially in children's hospitals. One particular area of demand for pediatric sedation/TIVA is procedures for patients with hematologic malignancies. These children often require multiple lumbar punctures (LPs) and bone marrow aspirates. For example, an individual patient diagnosed with acute lymphocytic leukemia (ALL) typically undergoes approximately 20 TIVAs for lumbar punctures with intrathecal chemotherapy over a two to three year period. Pediatric intensivists at Brenner Children's Hospital administer approximately 1200 cases of TIVA per year, and recently have trained pediatric hospitalists to do the same. Pediatric TIVA has inherent risks. Many different medications can be used to achieve an appropriate level of anesthesia, all with different side effect profiles that could be potentially harmful to the patient.[1]

Propofol is a widely used anesthetic for TIVA in such patients. Propofol is a general anesthetic administered intravenously. Propofol acts rapidly and is metabolized quickly, providing TIVA for short duration procedures.[2] While generally safe and effective, propofol must be delivered by physicians explicitly trained in its use and able to deal with common side effects like bradycardia, hypotension, and apnea.[3] Coadministration of narcotics such as fentanyl provides analgesia, which propofol does not provide, but also can exacerbate side effects. Decreasing the total dose of propofol shortens recovery time and may be associated with less undesirable side effects.

EMLA cream (lidocaine 2.5% and prilocaine 2.5%) is an FDA-approved local anesthetic indicated for numbing skin prior to injections and other medical procedures. It is commonly used in pediatric patients prior to painful injections. It is sometimes used prior to LPs, but there is no consistent practice among practitioners or institutions. In children undergoing an LP, the level of anesthesia is balanced with the ability of the practitioner to perform the procedure safely with little to no patient movement. We frequently observe patient movement upon needle insertion despite a "standard" loading dose of propofol (2 mg/kg). Such movement appears reflexive, and to eliminate it requires further propofol boluses, leading to longer recovery times and exposing the patient to higher total propofol doses. We have also observed that patients who have EMLA cream applied to the LP site prior to sedation tend to have less movement than those not treated with EMLA. There have been no randomized trials to date, however, assessing EMLA's efficacy for LP.

Hypothesis: The application of a eutectic mixture of local anesthetic (EMLA) cream at least 60 minutes before an LP will lead to less total dose of propofol and shorter, safer TIVA experience, compared to application of a placebo cream. We also hypothesize that parents and practitioners will be more satisfied with the TIVA experience with EMLA cream compared to placebo cream.

Objectives

1. Primary objective: To determine whether the application of a topical anesthetic (EMLA cream) to the LP site will decrease the total dose of propofol administered to pediatric oncology patients who are being sedated for LPs compared to application of a topical placebo cream.
2. Secondary objectives:
    a. To determine whether the use of EMLA cream decreases complication rates from sedation
    b. To determine whether the use of EMLA cream decreases traumatic lumbar punctures.
    c. To determine whether the use of EMLA cream shortens recovery time.
    d. To determine practitioner and parent satisfaction with the use of EMLA cream.

Methods and Measures

Design

- This will be a prospective, randomized, double blind, placebo-controlled trial.
    - Arm 1 = Arm A = Real EMLA cream
    - Arm 2 = Arm B = Placebo cream

Setting

Single site study in the Pediatric Sedation Suite, 8th floor of Brenner Children's Hospital (Ardmore West) at Wake Forest University Medical Center, Winston-Salem, NC.

Subjects selection criteria

- **Inclusion Criteria**
  Pediatric oncology patients (age 0 – 22 years) undergoing a lumbar puncture in the Pediatric Sedation Suite. Patients may or may not be receiving intrathecal chemotherapy.
    - **Exclusion Criteria-**Patients undergoing additional procedures during the same anesthetic such as bone marrow aspirate or biopsy will be excluded because they will likely require higher doses of propofol than those undergoing LP alone.
    - Patients who are allergic to or not tolerant of EMLA cream, propofol, or fentanyl will be excluded.
    - Patients having their LPs done by students will be excluded.
- **Sample Size**

Our target accrual is a total of 200 events (sedation with lumbar puncture). Patients may be enrolled multiple times (one time for each sedation). Each patient may undergo randomization as many times as they are willing to stay on study and they are having sedation for a lumbar puncture. We anticipate enrolling approximately 20 subjects per year, with a mean of 5 events per patient per year. Thus, we hope to have 100 events per year for 2 years, for a total of 200 events. If we enroll 20 subjects per year for 2 years, the total number of subjects for this protocol will equal 40.

We present power calculations for the dichotomous outcome of whether additional propofol was administered (yes/no). With 100 sedations with lumbar puncture in each sedation group (EMLA cream and no EMLA cream), using a two-sided 0.05 level chi-square test of equal proportions the following table presents effect sizes we have 80% and 90% power to detect.

Proportion of additional doses in EMLA cream group	Alternative proportion of additional doses	
	80% power	90% power
5%	17.4%	20.0%
10%	25.0%	27.8%
20%	37.9%	40.9%
40%	59.7%	62.7%
60%	78.2%	80.7%

We present power calculations for the continuous outcome of total dose of propofol administered. Using a two-sided 0.05 level two sample t-test of equal means, with 100 sedations with lumbar puncture in each sedation group we have 80% and 90% power to detect effect sizes of 0.398 and 0.461 respectively.

Interventions and Interactions

- Eligible patients will be approached in the Pediatric Oncology Clinic and offered participation in the trial.
- If they agree, signed consent and assent (for patients age 7-17 years) will be obtained.
- Enrollment and randomization will be done through the Comprehensive Cancer Center
    - Call Lisa Dixon and let her know a patient has signed consent/assent
        - Phone (336) 713-6767
        - Back up phone (336) 713-6929
    - The enrollment form will be emailed or faxed to Lisa Dixon
        - Fax (336) 713-6772
        - Email can be done online at: http://ccc.wfubmc.edu/Reduced-Review-Registration-Form.pdf

    - Ms. Dixon will enroll and randomize the patient, and call the clinic back (713-5940) to tell Nancy Smith, RN or her designee the randomization result
        - Arm 1 = Arm A = Real EMLA cream
        - Arm 2 = Arm B = Placebo cream
    - Nurse Smith or her designee will apply the appropriate cream without telling the patient or practitioner in clinic (who will be performing the LP) which cream is being applied. Both creams should be present in the room before application, so that the patient and the patient's family will not know which one will be used. (They will be instructed not to look while the cream is being applied.) The sedation team will also not be told which cream is being applied.
- Without the patient or patient's family watching, EMLA cream or placebo EMLA cream will be applied to the patients' lumbar spine area at the site of the LP, at least 60 minutes prior to the LP (maximum 4 hours). Patients and their parents will not be told whether real or placebo cream is being used.
- Placebo cream will be a generic moisturizing skin cream which has the same color (white) and consistency as EMLA cream. It will not be labeled, but will be dispensed from a multi-use jar. The placebo cream is a generic Walgreen's Moisture Recovery Lotion. It is hypoallergenic and fragrance free. The ingredients include: Water, Glycerin, Petroleum, Stearic Acid, Glycol Stearate, Isopropyl Isostearate, Dimethicone, Tapioca Starch, Cetyl Alcohol, Glyceryl Stearate, Magnesium Aluminum Silicate, Carbomer, Ethelyne Brassylate, Triethanolamine, Disodium EDTA, Phenoxyethanol, Methylparaben, Propylparaben, and Titanium Dioxide.
- Prior to LP, the cream will be removed by clinic staff and the skin will be prepped in the usual sterile fashion. The practitioner performing the LP and the physician sedating the patient will be blinded.
- Patients mature enough to comply will be positioned appropriately and have their skin sterilized before propofol is administered. For patients not able to do this, propofol will be administered when the patient is in a supine position on the bed, or in their parent's laps or arms (at the discretion of the sedationist).
- Sedation will be provided following a standardized protocol including fentanyl (1mcg/kg) and propofol (2mg/kg). Additional 1 mg/kg doses of propofol will be administered at the discretion of the physician performing the sedation based on the patients' movement, pain, vital signs, and oxygen saturation.
- Lumbar punctures will be performed by experienced staff from the Pediatric Oncology Clinic (physician, physician assistant, or nurse practitioner). A 22 gauge needle will be used for every patient.
- After each sedation, a study staff member will record the data (see Outcome measures, below) and survey the practitioners providing sedation and performing the LP.
- Recovery will be the same for all patients. Patients are instructed to lie supine or in the Trendelenburg position for at least 20 minutes after each LP. Patients

who are young or uncooperative may require additional propofol to stay in this position, and these instances will be captured (see data collection form).
- Following recovery, the parent(s) and/or patient will be surveyed as to their satisfaction. If a parent does not witness the sedation and procedure, the survey will be omitted.

Outcome Measure(s)

The primary outcome measurements will be the total dose of propofol administered to each patient.
Other outcomes to be measured will include the level of movement at the time of LP needle insertion of each patient during the procedure based on the following scale:

1. No movement; no additional propofol was administered.

2. Minor movement; no additional propofol was administered.

3. Major movement; additional propofol was administered.

4. Other: Patient had no or minor movement, but additional propofol was administered due to time required to successfully complete the LP (either more than one attempt or a prolonged first attempt).

We will also record the height, weight, blood pressure, time and length of the LP; total dose of fentanyl administered; time to emergence; length of recovery time; total anesthesia time; and practitioner and parent satisfaction surveys. Complications will include any change in vital signs that requires intervention by the sedation team, as well as post-LP headache and post-LP back pain. Each patient's parent (and/or the patient) will be contacted by telephone within one week of the LP (or in person if the next clinic visit is within one week) to ask if the patient had any headache or back pain after the LP, and if they had any other complications (Appendix 4). Traumatic LP is defined as an LP in which CSF contains at least 10 red blood cells (RBCs) per microliter and bloody LP as one in which the cerebrospinal fluid contained at least 500 RBCs per microliter.

Analytical Plan

Sedations for which lumbar punctures are unsuccessful will be excluded from analysis. Results will be analyzed initially using descriptive statistics. Raw mean total dose administered and raw percentage of times additional propofol was administered will be presented by sedation group treating each event (sedation with lumbar puncture) as the unit. T-test and chi-square tests will be performed as appropriate for the outcome. However, since the events may be correlated within an individual, we will also use analyses to take into account the correlated nature. GEE methods will be used when analyzing the percentage of times additional propofol was administered. Mixed model regression methods will be used when analyzing the total dose administered.

Human Subjects Protection

Subject Recruitment Methods

The parents of the subjects will be approached for recruitment into the study during their Hematology/Oncology clinic visit by the attending Hematologist/Oncologist in a private clinic room. All patients receiving a lumbar puncture through the Hematology/Oncology clinic will be approached regardless of race or gender.

Informed Consent

Signed informed consent and assent (for patients age 7-17 years) will be obtained from each subject, who will be identified and approached in the Pediatric Oncology Clinic by health care providers in the clinic.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. Data and records will be kept locked and secured, with any computer data password protected. The data will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed .three years after closure of the study by shredding. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. This study will not have a Data Safety Monitoring Board.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and/or appropriate government agency if indicated.

References

1. Rappaport B, Mellon RD, Simone A, and Woodcock J. Defining Safe Use of Anesthesia in Children**.** N Engl J Med 2011; 364:1387-1390.
2. Cravero JP. Risk and safety of pediatric sedation/anesthesia for procedures outside the operating room. Current Opinion in Anesthesiology 2009;22:509-13
3. 3.American Academy of Pediatrics; American Academy of Pediatric Dentistry, Coté CJ, Wilson S; Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics 2006; 118:2587-602