# Pain Control in Pediatric Oncology: Utility of EMLA Cream vs Lidocaine Injection in Lumbar Punctures

## 1. STUDY FOCUS

The focus is to compare the use of lidocaine injection versus eutectic mixture of local anesthetics consisting of 2.5% Lidocaine/Prilocaine (EMLA) cream for lumbar puncture site analgesia in pediatric oncology patients.


## Abstract

A common procedure in children with cancer is the spinal tap, or lumbar puncture (LP), in which a needle is inserted into the spinal canal. In this population, LPs are most commonly performed to collect cerebrospinal fluid (CSF, the liquid surrounding the brain and spinal cord) for diagnostic testing, and to inject medications including chemotherapy. Local analgesic (pain control medicine) during pediatric LP procedures is underutilized and not standardized. The first local analgesic routinely used for LP procedures was lidocaine injection. The discovery of the topical EMLA (lidocaine 2.5%/prilocaine 2.5%) cream, approved by the FDA for local skin use in pediatric patients, has provided an additional option for local LP analgesia. A comparison between topical EMLA vs lidocaine injection for LP pain control in the pediatric population has not been performed. Pediatric oncology patients often require serial LPs for diagnostics purposes and/or chemotherapy delivery. Due to a lack of standardization of LP analgesia in this population, we have designed a prospective, single-blind, randomized control crossover trial to examine EMLA vs. lidocaine injection in reducing pain associated with LP in children being treated for leukemia or lymphoma. (Word count = 184)


## Specific Aims/Objectives

Primary objective:

To compare EMLA-2.5% lidocaine/prilocaine cream versus lidocaine injection for local site analgesia for LP procedures as measured by post procedure pain scoring and PRN pain medication usage in pediatric oncology patients requiring serial LPs.

*We hypothesize that when compared, one of two examined local site analgesia strategies (EMLA or lidocaine) will provide superior pain control for LPs.*

## Background

Spinal lumbar puncture (LP) is a common procedure in the pediatric patient population. They are frequently performed on emergency department and hospitalized pediatric patients, often to diagnose meningitis. To reduce pain during these procedures, local analgesics are routinely utilized. Optimal local analgesic type and method during LP procedures have been a source of disagreement for several decades, and continues to be underutilized and non-standardized, especially in pediatric patients[1]. Studies show that analgesic use is not universal within the



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pediatric population when undergoing LPs and that utilization of local anesthetic varies by patient age, with younger children less likely to receive local anesthetic[1]. The lack of adequate analgesia may have long term consequences, with recent studies suggesting that painful experiences during infant development may alter subsequent pain pathway development and decrease pain tolerance for future procedures[2].

The first local anesthetic shown to be beneficial for LP procedure pain control was lidocaine injected prior to LP needle insertion[3]. Local anesthesia with lidocaine has been shown to decrease pain in adult and pediatric populations but is often omitted with pediatric LP procedures due to concerns regarding obscuring anatomical landmarks[3,4]. However, Pinheiro et al showed that local anesthesia with lidocaine decreased the degree of struggling and in the absences of lower LP success rates in newborns. Lidocaine use for local LP analgesia did not increase the number of attempts needed to obtain CSF or the number of traumatic LPs (defined as 10,000 x 10(6)/L red blood cells in CSF) in children (< 3 years old).[4] Lastly, lack of local anesthetic use (including lidocaine) associated with increased rates of traumatic or unsuccessful LP in children and adolescents (aged 0-22 years).[17] Thus, withholding local site analgesic for LP is unjustified.

The use of EMLA cream (lidocaine 2.5% and prilocaine 2.5%), which was approved by the United States Food and Drug Administration for local skin and genital skin use in all pediatric age groups, has provided an additional option for LP analgesia[5]. The clinical studies supporting EMLA use demonstrated its analgesia benefits in adult IV cannulation, venipuncture, and skin graft harvesting, in pediatric patients for pre-surgical needle insertion, laser treatment of facial port-wine stains, cryotherapy for male genital wart removal, genital mucous membranes for surgical procedures, and pain control in neonates for blood drawing and circumcision procedures[5]. EMLA has been studied in pediatric oncology patients and has shown that EMLA is associated with significantly lower pain scores[6,7] and decreased indirect measures of pain (propofol doses, patient movement, and heart rate changes) when compared to placebo[8]. In one clinical trial, the researchers examined EMLA vs. no EMLA use during repeat bone marrow biopsies and LP procedures in pediatric oncology patients. They found that EMLA was associated with decreased pain ratings for LPs, but this effect was not sustainable with repeat LP procedures[9]. There has been concern in the past for EMLA causing a significant side effect of methemoglobinemia, although recent reports have concluded that correct usage significantly minimizes this risk[5,10].

A comparison between EMLA vs lidocaine in pediatric patients for LP-related pain to our knowledge has not been studied with the exception of needle-free injection lidocaine in neonates, which is a costly and difficult modality to deliver lidocaine[11]. Studies in adult populations for spinal anesthesia have shown that EMLA cream is an effective alternative to lidocaine injections for analgesia with a decrease in pain scores post procedure[12,13], suggesting possible capacity to standardize LP analgesics in pediatric patients.

Pediatric oncology patients will often require serial LPs for disease progression monitoring and/or central nervous system chemoprophylaxis. Patients with leukemia or lymphoma might need up to 50 LPs throughout their 2-3 years of treatment. Topical analgesics for LP procedures are at the discretion of the oncologist and lack standardization. Currently, at Charleston Area Medical Center (CAMC), in the outpatient pediatric cancer center, oncologists use either EMLA



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or lidocaine for local pain control while moderate conscious sedation is used to limit movement during the procedure. The choice of local analgesia is completely operator dependent and the same patient could receive lidocaine on some of his/her LPs and EMLA on the others. Since topical analgesics are at the discretion of the oncologist, a comparison of EMLA vs lidocaine in pediatric oncology patients undergoing serial LPs could help aid clinicians in providing safe and efficacious pain management for LPs a particularly vulnerable pediatric patient population.

## Significance

There is a lack of standardization regarding local site analgesia for LPs in the pediatric population. Both injected lidocaine and EMLA has been demonstrated to provide safe and effective LP local site analgesia. Therefore, comparing EMLA versus lidocaine could assist in developing a protocol to standardize care by utilizing the best analgesic for LP in children without providing futile or ineffective treatment.

## Methodology

### Design

This is a prospective, single-blinded, randomized, controlled crossover study of pediatric cancer patients receiving care at CAMC Children's Cancer Center (CCC) undergoing serial LPs as part of their management. Following study consent and assent (when required), and enrollment, patients will be randomly assigned to receive EMLA or lidocaine for local site analgesia prior to LP. The second LP post study enrollment will be defaulted to the other local site analgesic method (crossover randomization). For each LP, pain will be assessed at baseline, 30 – 60 minutes after waking up after procedure but prior to departure from the CCC, and 24 hours after procedure recorded on a home log and reported to the nurse practitioner (or other study team member) via a follow-up telephone call. Pain will be self-reported by the child using a validated pain scale. PRN pain medication use in the 24 hours following LP will also be obtained via a home log for each LP. Patient and procedure characteristics will be obtained to describe the study sample.

Patients and parents/guardians will be blinded to the randomized local site analgesic group. Since EMLA cream has to be placed prior to procedure up to a maximum of 1 hour to be effective, the patient will be awake and not sedated at that time. Therefore, sham EMLA cream will be applied to patients randomized to receive lidocaine injection. Patient will be sedated during lidocaine injection and therefore will not know if (s)he received injection. Due to their involvement in the LP procedure, it is unfeasible for the study physicians to be blinded to the randomized local analgesic.

### Sample

Twenty patients will be invited to participate. A total of 17 patients are require to have a 90% percent chance of detecting a 2-point difference (standard deviation = 2.25) on the Wong-Baker Faces Pain Rating Scale[14,15] (i.e. the difference from a 4 "hurts little more" to a 2 "hurts little bit"), when using paired 2-tail analysis (Wilcoxon signed-rank test). Sample size calculated



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using G*Power 3.1. We will enroll up to 20 patients to allow for patient withdrawals/loss to follow-up prior to the second LP. The accrual goal of 20 patients is comparable to other studies examining LP analgesics[6-9] as well as a feasible goal with CAMC CCC's current patient load. A maximum of 50 patient records will be screened will to determine study eligibility.

*Setting:*
Charleston Area Medical Center, Women and Children's Cancer Center (CCC).

We are also inviting Pediatric Oncology at Marshall University/Cabell Huntington Hospital also to participate in the study. They will obtain approval from their local IRB. They will send de-identified study patient information to our institutions for analysis. All appropriate approvals (and data use agreements) will be obtained prior to their participation.

*Inclusion Criteria:*
- Pediatric cancer patients (aged 3-18) with a diagnosis of leukemia or lymphoma
- Patients are expected to receive serial (i.e. > 1) LP as outpatients in CCC in the course of 12 months for diagnostic and/or treatment purposes

*Exclusion Criteria:*
- Patients not in the age range
- Non-cancer patients
- Allergy to amide anesthetics
- Patients treated with class I and III anti-arrhythmic drugs (eg, amiodarone, bretylium, sotalol, dofetilide)
- Patients with congenital or idiopathic methemoglobinemia

**Procedures/Protocol**

***Pre-LP***

A member of the study team will approach the pediatric cancer patient and parents/guardians (if patient is less than 18 years of age) to present and describe the study during a prescheduled visit at CAMC CCC. If the patient (and parent/guardian, if applicable) agrees to participate and signs the consent/assent, they will be enrolled in the study and be randomized to a local anesthesia arm.

*Randomization:*
A statistician from Outcome Research will prepare the randomization schedule using block randomization maintaining balance between the two treatment arms. The randomization schedule/allocation will be created using IBM-SPSS (Version 19) and completed prior to initiation of any consenting/assenting activities. A member of Outcome Research not active in enrollment will prepare sealed envelopes containing the randomized local analgesic regimen, will be prepared by a research staff member not involved in enrollment. The sealed envelopes will be maintained in the CCC to be pulled consecutively by an investigator after a patient has been consented/assented to be in the study.



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Patients will be randomized to either EMLA group or lidocaine group at initial lumbar puncture post enrollment and default to the other group at the following lumbar puncture. A log will be maintained in the CCC to track enrolled patients' LPs and randomized local analgesics.

*Baseline Pain Level Assessment:*
Pain level will be measured via Wong-Baker Faces Pain Rating Scale.[14,15] A numeric value is to be collected prior to LP on the day of the LP. See Appendix A for scale and directions. The Wong-Baker Faces Pain Rating Scale has been validated in children aged 3 years and older and is a pain scale that shows a series of faces ranging from a happy ,"No hurt" face at 0, to a crying face at 10 "Hurts worst" with the child self-selecting (either verbally or by pointing to) the face that best describes the pain he/she is feeling.

In a systematic review, The Wong-Baker Faces Pain Rating Scale was one of only six pain scales (out of 34 pain scales) meeting criteria for a well-established pain intensity measure adequately supported by psychometric data.[18] Children have indicated preference for the Wong–Baker FACES Pain Scale relative to other pain scales.[14,15,18] We acknowledge the previous finding of young children (< 6 years old) sometimes selecting faces at the extremes of the scale, however it is unknown if this is related to the pain's nature or if it is a scale artifact.[19] Due to the scale having a successful history in young children,[14,19,20-23] we will use the pain scale in our enrollees (aged 3-18 years old). However, we will conduct statistical analyses for pain scale measures with and without young children (<6 years) as described in the *Data Analysis* section**.**

*Application of EMLA cream or Sham-EMLA cream:*
- EMLA group
  - If assigned to EMLA group, the provider will apply ~ 5 grams EMLA at least 60 minutes prior to procedure per standard protocol, covering the site with Tegaderm dressing[16]. Studies show that Tegaderm dressing helps control dose of EMLA administered.
- Lidocaine group
  - If assigned to lidocaine group, sham-EMLA cream (Cetaphil Moisturizing Cream, a fragrance-free hypoallergenic moisturizer cream) will be applied at least 60 minutes per standard protocol with Tegaderm dressing by the provider (study nurse practitioner or physician). Cetaphil Moisturizing Cream will be used as the EMLA-sham for procedures randomized to utilize lidocaine. The Sham-EMLA cream provided by the study PI will be stored, in a secured, locked, normal room temperature area in the CCC.
  - Sham-EMLA cream will be used to reduce patient/parent reporting bias. Participants will be blinded to the type of analgesic used. The sham cream is needed because not applying any cream prior to procedure would automatically mean that the participant will receive lidocaine 1% since a local analgesic is always used.
  - Following conscious sedation, the patient will receive lidocaine 1% injection (~1-2ml) at the appropriate site 30-60 seconds prior to LP needle insertion.



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- In order to maintain patient blinding, the sham-EMLA container or the EMLA tube kept out of sight of patient. We will put the cream on the Tegaderm bandage and then put it on the patien's back.
- The pain medicine (lidocaine 1% and EMLA) are standard for LP associated pain regardless of the study. The pain medicines will be provided by CAMC Pharmacy and secured in the MedStation in the CCC following same processes as non-study LPs.

***LP Procedure***

Procedure will follow the standard protocol used at CAMC CCC for pediatric patients for outpatient LP. Immediately prior to the start of the procedure, a final verification process is to be conducted to confirm correct patient and procedure. The patient will be sedated via anesthesia team. Moderate conscious sedation to limit movement during the LP will be performed with propofol with or without sevoflurane gas with all processes and monitoring adhering to CAMC CCC's standard of care.

Patient will then be positioned for lateral decubitus positioning. Appropriate hand hygiene is to be completed prior to procedure. The operator is to wear a mask and sterile gloves for this sterile procedure. If randomized to lidocaine-obtaining group, Sham-EMLA cream will be removed and an approximately 1 ml of lidocaine 1% is to be injected into the subcutaneous tissue. If randomized to EMLA group, the cream will be removed with no further local site analgesic being introduced.

The lumbosacral area is to be surgically prepped with Betadine or 2% chlorhexidine and draped in the usual fashion. An appropriate needle will be introduced into L3-L4 or L4-L5 interspace and CSF fluid is to be obtained. If applicable, the appropriate dose of chemotherapy per patient's protocol is to be administered into the intrathecal space. The needle is to be withdrawn using standard technique. Sedation will then be stopped by anesthesia team.

***Post-LP***

The patient will be directed to lay still for 30 minutes post-procedure before sitting or standing. Standardized instructions for at home PRN pain control will be provided to the patient, typically acetaminophen (15mg/kg) every 6 hours as needed for pain relief. The post-LP, at home pain medications will not be provided by the study.

*30-60 min Pain Level Assessment:*
Pain level will be measured at 30-60 minutes after waking up from procedure sedation, prior to departure from the CCC, using Wong-Baker Faces Pain Rating Scale. A numeric value is to be collected. The child will self-select (either verbally or by pointing to) the face that best describes the pain he/she is feeling.

*24 hour Pain Level Assessment:*
Pain level will be measured at 24 hours. A paper form of the Wong-Baker Faces Pain Rating Scale will be sent home with the patient and parent/guardian will be directed to complete it 24



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hours following the procedure. The parent/guardian will be directed to have their child to self-select (either verbally or by pointing to) the face that best describes the pain the child is feeling. The patient or parent/guardian will receive a log to document pain score at 24 hours and PRN pain medications; this will be used to record information that will be shared with study personnel during the follow-up phone call.

*24 hour PRN Pain Control Assessment:*
A paper log will be sent home with the parent/guardian. On this log, they will be directed to record all PRN pain control medications, doses, times, the patient used within the 24 hours following the LP. A clinician/study team member will call the patient's parent/guardian within 72 hours to obtain the patient's 24-hour pain rating and PRN pain medicine information.

***Subsequent LP***

Patients will be in the study until they have completed 2 LPs, unless if a patient chooses to withdraw. If a patient decides to withdrawal from the study, we will document the date of and reason for the withdrawal.

For the second LP post-enrollment, patients and parent/guardian will be informed of study continuation and be given the opportunity to ask questions to study investigators about the study. The second LP will default to the local analgesic that was not received during the first LP. All procedures described above will be followed for this second LP.

**Data Collection/Instrumentation**
Data will be collected from CAMC Cerner Millennium EMR and CAMC/CAMC Children's Cancer Center records. Collected data variables will include:

- Date of Visit/LP
- Demographic data
  - Name
  - Age
  - Sex
  - Race/ethnicity
  - Weight (kg)
- Valid Telephone number
- Diagnosis
- LP sequential number since study enrollment: first or second
- Randomized to initially received: EMLA or Lidocaine
- For the current LP: received EMLA or Lidocaine
- Time of EMLA / EMLA sham administration
  - Calculated time from EMLA administration to LP
- Amount of Lidocaine
- Number of needle pricks of lidocaine
- Signs of pain with lidocaine



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- Provider that performed LP
- Time of LP
- Number of attempts with LP needle
- Any complications during LP (describe)
- Pain score prior to procedure (baseline)
- Pain score at 30-60 minutes waking up from post LP sedation
- Pain score at 24 hours post LP
- PRN medication requirement within 24 hours post-procedure
- Adverse reaction to local analgesic

**Data Analysis**

CAMC CHERI Outcome Research will perform statistical analysis for the study. Descriptive statistics will be computed. Continuous variables will be presented as means and standard deviations and if non-parametric, as medians and interquartile ranges. Categorical variables will be reported as frequencies and percentages. Each patient will serve as his or her own control; we will compare pain scores and prn medication usage for lidocaine to a patient's pain scores and prn medication usage when receiving EMLA. Tests for carryover and period effects will be conducted prior to treatment effects analyses.

Pain scores between the LPs (lidocaine vs EMLA local analgesia) will be compared using nonparametric test for matched or paired data, Wilcoxon signed-rank test. Nonparametric tests will be for statistical analyses of pain scores, as the Wong-Baker Faces Pain Rating Scale consists of ordinal values. We will analyze pain scores obtained at baseline, 30 – 60 minutes post waking after LP sedation, and 24 hours post-LP separately. Young children (≥6 years) and children/adolescents (6-18 years) pain scale data will be analyzed jointly. In addition, if an age subgroup (<6 years or 6-18 years) has an n >5 then the age subgroup's pain scale measures will be analyzed separately.

We will analyze prn pain medication usage by comparing the amount of acetaminophen (mg/kg) reported as being taken between the two LPs local analgesics (lidocaine vs EMLA). We will compare the prn pain medication amount for each local analgesic via a paired t-test (or Wilcoxon signed-rank test if prn medication data is non-parametric). Other analgesics (if any) will be analyzed separately, in a similar manner.

A p-value of <0.05 will be used to determine statistical significance. The statistical program IBM-SPSS (Version 19) will be used for all analyses.

## 2. HUMAN SUBJECTS

A. Subject Population

i. Study patients will be comprised of children (3-18 years old) with leukemia or lymphoma receiving lumbar punctures as part of their management. It will be clearly described verbally and in writing (in the consent and assent) that choosing not to



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participate will not affect their care at CAMC CCC. Research activity and data collection will only begin after informed consent and if applicable, the assent is signed. Prospective participants will not be vulnerable to coercion or undue influence.

B. Recruitment Method
   i. Cancer patients who receive care at CAMC CCC will be approached regarding possible study participation at a prescheduled CCC visit. A member of the study team will describe the study to the patient and parent/guardian, answer all questions, and obtain the necessary informed consent, if the patient and parent/guardian wish to participate in the research. Written consent will be obtained (from patient if ≥18 years, or from parent/guardian if the patient < 18 years). Written assent will be obtained from patients aged 7-17 years old, verbal assent will be obtained from patients aged 3 to 6 years old. Written consent/assent will be obtained prior to randomization.

C. Benefits
   i. Our study might help identify which analgesic method, whether EMLA cream or lidocaine injection, prior to lumbar puncture provides the most post-procedural pain relief. This will help future patients of the CAMC CCC by providing the most appropriate pain relief when undergoing lumbar punctures.

D. Risks and Discomforts
   i. Lumbar punctures are routine procedures for childhood cancer patients. Since both EMLA and lidocaine injection are routinely used for this procedure, there is no added risk to their standard care regimen.

E. Privacy
   i. The patients (and parents/guardians) will be consented and assented in an examination room or other private room during their visit at CAMC CCC with the door closed. The study aims, protocol, and goals will be described to them by study personnel.

F. Confidentiality
   i. Privacy interests of the participants in the study will be protected at all times. All identifying patient information will remain in the PI's locked office and on a password protected computer in a password-protected file, if electronic. Identifying patient information will only be accessed by study investigators. Paper forms will be shredded, and electronic files will be deleted at the time publication. All results will be reported with no identifiers. Any study information sent from outlying study sites will be de-identified and sent securely (for example password protected file in encrypted email).

G. Costs to Subjects
   i. The patient/patient's guardian will be responsible for all co-pays and deductibles associated with routine care billable to the insurer. There will be no additional financial burden to the patient for participating in this study. Sham-EMLA cream and Tegaderm will be funded through departmental funds and/or grant support and will not be billed to patients or their insurance.

H. Payments to Subjects
   i. None



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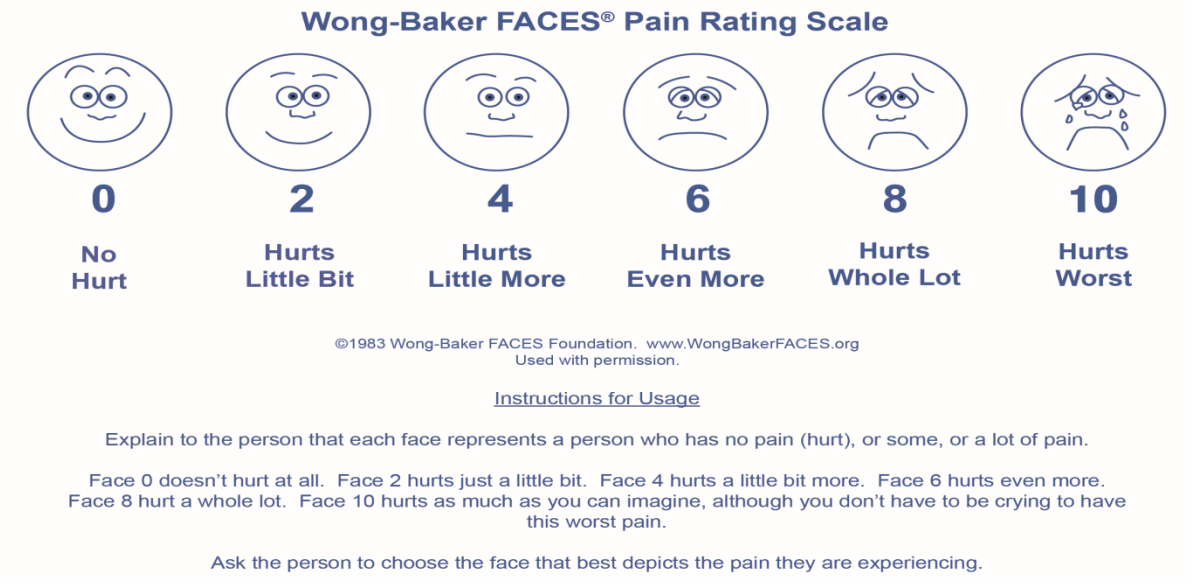
Appendix A




*Obtained from http://www.WongBakerFACES.org*



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