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Eutectic mixture of lidocaine and prilocaine decreases movement and propofol requirements for pediatric lumbar puncture during deep sedation: a randomized, placebo-controlled, double blind trial

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Abstract

Deep sedation/general anesthesia is commonly used in pediatric oncoclogy patients undergoing lumbar puncture (LP). Propofol is often used for sedation, with or without a narcotic. We hypothesized that eutectic mixture of lidocaine and prilocaine (EMLA) would allow for lower cumulative doses of propofol and less movement. We performed a prospective, randomized, double blind, placebo-controlled trial in children undergoing sedation for LP. Standard initial weight-based doses of propofol and fentanyl were administered, with either EMLA cream or a placebo cream applied topically. The primary outcome was the total dose of propofol administered to each patient. We also tracked patient movement and complications. Twenty-seven patients underwent 152 LPs. Patients randomized to EMLA cream (n = 75) were significantly more likely to receive a lower dose of propofol (2.94 mg/kg, SE = 0.25, versus 3.22 mg/kg, SE = 0.19; p = 0.036) and to not require additional propofol doses (probability 0.49, SE = 0.08 versus 0.69, SE = 0.06; p = 0.001) compared to patients randomized to placebo cream (n = 77). In addition, patients with EMLA cream were significantly less likely to demonstrate minor or major movement. EMLA cream results in less movement and less propofol administration in pediatric oncology patients undergoing sedation for LP.

Keywords

EMLA; topical analgesia; lumbar puncture; sedation; pediatric oncology

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Introduction

Deep sedation/general anesthesia outside the operating room is commonly used for painful procedures for pediatric patients. While the benefits are substantial, pediatric sedation has inherent risks including respiratory depression, airway obstruction, hypotension, and neurotoxicity.[1-4] Children with hematologic malignancies require multiple lumbar punctures (LPs) for both diagnostic purposes as well as intrathecal chemotherapy administration, usually performed under sedation.

Propofol, a general anesthetic administered intravenously, is widely used for sedation in such patients. Propofol acts rapidly and is metabolized quickly, providing an ideal agent for sedation during short duration procedures.[5] 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.[6] Coadministration of narcotics such as fentanyl provides analgesia, which propofol does not provide, but also can exacerbate side effects and increase risks such as respiratory depression and airway obstruction.[4] Decreasing the total dose of propofol may shorten recovery time and may be associated with fewer side effects.[7,8]

Eutectic mixture of lidocaine (2.5%) and prilocaine (2.5%) (EMLA) cream is an FDA-approved local anesthetic indicated for numbing skin prior to injections and other medical procedures. Several studies have documented the safety and efficacy of EMLA cream for lumbar punctures in pediatric oncology patients,[9-11] including one which demonstrated that its use allowed for decreased doses of propofol.[12] The study by Whitlow et al. was published during our study period and demonstrated less propofol use in a crossover double blind population of 25 patients who each had two procedures.[12]

Sedation practices for pediatric oncology patients vary considerably across institutions.[13] In children undergoing LP, the level of anesthesia should be balanced with the ability of the practitioner to perform the procedure safely with little to no patient movement. Performing atraumatic LPs is crucial, especially for diagnostic LPs, which if traumatic are associated with an increased risk of relapse in the central nervous system.[14,15] In addition, it is important for an experienced practitioner to perform the diagnostic LP.[16] Historically, our providers observed patient movement upon needle insertion despite our standard doses of propofol (2 mg/kg) and fentanyl (1 mcg/kg). Such movement is reflexive and to eliminate it, additional doses of propofol are often administered, leading to longer recovery times and exposure to higher total propofol doses. We observed that patients who had EMLA cream applied to the LP site prior to sedation tended to have less movement than those not treated with EMLA.

The primary objective of this study was to determine whether the topical application of EMLA cream to the LP site would decrease the total dose of propofol administered to pediatric oncology patients who were being sedated for LPs, compared to application of a topical placebo cream. Secondary objectives were to determine whether the use of EMLA cream decreases patient movement, decreases complication rates from sedation, decreases

traumatic lumbar punctures, shortens anesthesia time, and to determine practitioner and parent satisfaction with the use of EMLA cream.

Methods

This was a prospective, randomized, double blind, placebo-controlled trial performed at a single academic medical center (Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA).

Inclusion criteria included pediatric oncology patients age 0 – 22 years undergoing LP in the Pediatric Sedation Suite. Patients were excluded if they were undergoing additional procedures during the same anesthetic such as bone marrow aspirate or biopsy; if they were allergic to or not tolerant of EMLA cream, propofol, or fentanyl; they were pregnant; or they were having their LPs done by a student or resident. Patients could be enrolled multiple times, one time for each sedation/procedure. Each event was randomized independently. Our target accrual was a total of 200 LPs. Using a two-sided 0.05 level two sample t-test of equal means, with 100 LPs in each sedation group, we had 80% and 90% power to detect effect sizes of 0.398 and 0.461 respectively.

This study was approved by our Institutional Review Board. For eligible patients who agreed to participate, signed consent and assent (for patients age 7-17 years) were obtained. Enrollment and randomization were performed by the Chief Protocol Registrar of our Comprehensive Cancer Center. Only the head clinic nurse (NMS) was notified of the randomization result. On the day of the sedation, the nurse applied the appropriate cream (EMLA or placebo) without informing anyone else (patient, parent, practitioner to perform the LP, or the sedation team) which cream was applied. The cream was applied to the patients' lumbar spine area at least 60 minutes prior to the LP (maximum 4 hours) and covered with a clear adhesive dressing. The placebo cream was a generic moisturizing skin cream which has the same color (white) and consistency as EMLA cream. Prior to the LP, the cream was removed and the skin prepped in the usual sterile fashion.

Sedation was provided following a standardized protocol including intravenous fentanyl (1 mcg/kg) and propofol (2 mg/kg). Additional doses (1 mg/kg) of propofol were administered at the discretion of the physician performing the sedation based on patients' clinical parameters (primarily movement, but also perceived pain, vital signs, and oxygen saturation). LPs were performed by experienced providers from the pediatric oncology clinic (physician, physician assistant, or nurse practitioner). A 22 gauge needle was used for every LP.

After each sedation, a study staff member recorded data and surveyed the practitioners providing sedation and performing the LP. Satisfaction was measured using a non-validated 5-point Likert scale with 1 = not satisfied, 3 = neutral, and 5 = very satisfied. Recovery procedure was the same for all patients. If feasible, patients were instructed to lie supine or in the Trendelenburg position for at least 20 minutes after each LP. Following recovery, the parent(s) and/or patient were surveyed as to their satisfaction using the same 5-point scale. If a parent did not witness the sedation and procedure, the parental survey was omitted.

The primary outcome measurement was the total dose of propofol administered to each patient. Other outcomes measured included the level of movement at the time of LP needle insertion, the cell count and differential of the cerebrospinal fluid (CSF), blood pressure, duration of the LP (needle insertion to removal), total anesthesia time (induction to awakening time), and practitioner and parent satisfaction. Complications included any change in vital signs that required intervention by the sedation team, post-LP headache, and post-LP back pain. Each patient's parent (and/or the patient) was contacted by telephone within one week of the LP (or in person if the next clinic visit was within one week) to ask if the patient had any headache or back pain after the LP, and if they had any other complications. Traumatic LP was defined as an LP in which CSF contained 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.

Descriptive statistics were used to summarize demographic and procedure characteristics by subject and by event (sedation with lumbar puncture). Because the events were correlated within an individual, we used generalized estimating equation models to estimate differences by arm in propofol dose, anesthesia time, lowest blood pressure, and patient and provider satisfaction using an identity link. Differences by arm for additional propofol administration, post-LP headache, and post-LP back pain used a binomial link. The Rao-Scott chi-square test with patient as the cluster was used to compare patient cooperation, movement level, and lumbar puncture trauma by arm.

Results

Thirty-three participants were registered. Five did not receive a lumbar puncture prior to study closure or their end of chemotherapy, and one was ineligible, leaving 27 participants who underwent 152 procedures (range 1 – 14 procedures per patient; median = 5). Seventy-five (49.3%) procedures were randomized to EMLA cream, and 77 (50.7%) procedures were randomized to placebo cream. Demographic characteristics are shown in Table 1.

After 152 LPs, the study was routinely reviewed by our institution's Clinical Research Oversight Committee. We decided to analyze the data at that time, even though we had not reached our goal of 200 LPs. When the results were available we decided to stop accrual.

Patients randomized to EMLA cream were significantly more likely to receive a lower total dose of propofol (2.94 mg/kg, SE = 0.25, versus 3.22 mg/kg, SE = 0.19; $p = 0.036$) and to not require additional propofol doses to be administered (probability of additional dose 0.49, SE = 0.08 versus 0.69, SE = 0.06; $p = 0.001$; Table 2). In addition, patients with EMLA cream were significantly less likely to demonstrate minor or major movement, with a three-fold reduction in major movement (35.1% with placebo cream versus 10.7% with EMLA cream; $p < 0.001$; Table 3). Of note, patients with EMLA cream were less likely to be cooperative before and during early phases of sedation ($p = 0.016$; Table 3). We observed no statistically significant differences between the two arms for anesthesia time, LP time, lowest blood pressure, traumatic LPs, post-LP headaches and post-LP back pain (Tables 2 and 3). No other clinically significant adverse events were detected in either arm.

Practitioners reported higher satisfaction with LP using EMLA cream compared to placebo (Least squares mean (SE) 4.8 (0.06), N=74 vs. 4.4 (0.11), N=74, p=0.001); there was no statistically significant different in parent satisfaction by arm (Least squares mean (SE) 4.8 (0.11), N=31 vs. 4.6 (0.19), N=24, p=0.428).

Discussion

This study adds to prior reports demonstrating the safety and efficacy of EMLA cream in pediatric oncology patients undergoing sedation for lumbar puncture.[9-12] Our study is notable for its design (prospective, randomized, double blind, and placebo-controlled), relatively large number of events (152), and multiple outcomes assessed (including propofol dose, movement, complications, and satisfaction). Participants randomized to EMLA cream were less likely to move at the time of skin puncture, and were exposed to significantly lower doses of propofol. The study by Whitlow et al.[12] used higher doses of propofol (median 4 mg/kg in EMLA arm and 4.9 mg/kg in placebo arm) compared to our study (median 2.3 mg/kg in EMLA arm and 3.0 mg/kg in placebo arm), likely because in the Whitlow study fentanyl was not used in addition to propofol. Although we did not assess whether EMLA cream could replace fentanyl, it is possible that such a replacement would be safe and effective given that a lumbar puncture creates a brief, sharp, focal pain that may be better suited to local anesthesia than a systemic narcotic.

More patients in the EMLA cream arm were uncooperative prior to induction, compared to the placebo arm. This strengthens our findings that EMLA cream is effective, because even though uncooperativeness was higher in the EMLA arm, movement during sedation was less in the EMLA arm. Interestingly, total anesthesia time was not different between the two arms, despite the placebo arm patients requiring more propofol. This finding could be attributed to the short half-life of propofol, and all patients receiving the same dose of IV fentanyl.

EMLA cream is safe, easy to use, relatively inexpensive, and readily available in the U.S. and most high-income countries. In low-income countries where sedation for procedures may not be currently offered, EMLA cream would likely be cost effective, diminish pain, and improve patient and practitioner satisfaction with LPs.

This study is limited by its single institution setting. In addition, at least six different intensivists/hospitalists administered sedation during this study, and the decision to administer additional propofol was subjective. However, the randomized and blinded design of the study, along with standardized doses of fentanyl and propofol, should have negated biases and diminished inter-practitioner variability. Repeated procedures may attenuate responses to subsequent procedures,[17] and this effect could have influenced the results. When comparing the two groups (EMLA versus placebo), we did not track or analyze the exact age at the time of each LP, the total number of LPs each patient had had, comorbidities, current medications, or immediate complications (such as desaturations or needing additional respiratory support), all of which could have potentially affected the outcomes. We did not track time of topical cream application (range 1 – 4 hours) before each LP, and this could have affected the results. However, the randomized design of the

study should have minimized or negated these potential confounders. Finally, for additional propofol doses we used 1 mg/kg/dose rather than smaller, incremental doses. It is possible that smaller additional doses would have diminished or even negated the differences in total doses between the groups.

Many sedations are now being performed by non-anesthesia providers such as hospitalists.[7] It is crucial for patients to be as still as possible for the provider performing an LP, to minimize movement and the risks of a traumatic or unsuccessful LP.[15] Thus, the most important finding of this study may be the three-fold reduction in major movement in the EMLA cream group. In conclusion, EMLA cream results in less movement and less propofol administration in pediatric oncology patients undergoing sedation for LP.

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TABLE 1.

Demographic characteristics

Descriptive Statistics	N = 27 subjects	N=152 procedures
Age in years		
Mean	8.1	8.2
Range	1-18	1-18
SD	5.7	5.4
Gender		
Male	17 (62.9%)	108 (71.0%)
Female	10 (37.0%)	44 (29.0%)
Race		
Black or African American	7 (25.9%)	32 (21.0%)
White	19 (70.4%)	116 (76.3%)
More than one race	1 (3.7%)	4 (2.6%)
Ethnicity		
Hispanic	4 (14.8%)	20 (13.2%)
Non-Hispanic	23 (85.2%)	132 (86.8%)

TABLE 2.

Propofol administration comparison by arm

Outcome Measure	EMLA cream N=75	Placebo Cream N=77	P-value[a]
Total Propofol Dose (mg/kg) Least Squares Mean (SE)	2.94 (0.25)	3.22 (0.19)	0.036
Additional Propofol Administered (Yes/No) Mean Probability of Yes (SE)	0.49 (0.08)	0.69 (0.06)	0.001
Anesthesia Time (minutes) Least Squares Mean (SE)	16.1 (1.0)	17.4 (0.9)	0.348
LP time (minutes) Least Squares Mean (SE)	5.6 (0.5)	6.0 (0.7)	0.570
Time from Induction to end of LP Least Squares Mean (SE)	7.9 (0.4)	8.4 (0.7)	0.501
Lowest BP Systolic (mm Hg) Least Squares Mean (SE)	85.1 (1.8)	85.1 (2.0)	0.985
Lowest BP Diastolic (mm Hg) Least Squares Mean (SE)	41.9 (1.3)	42.2 (1.2)	0.834
Lowest BP Percent Systolic (%) Least Squares Mean (SE)	15.8 (3.5)	19.4 (4.2)	0.411
Lowest BP Percent Diastolic (%) Least Squares Mean (SE)	16.3 (2.6)	18.9 (3.8)	0.415
Post-LP Headache (Yes/No)[b] Mean Probability of Yes (SE)	0.19 (0.04)	0.29 (0.06)	0.094
Post-LP Back Pain (Yes/No)[c] Mean Probability of Yes (SE)	0.21 (0.05)	0.25 (0.05)	0.426

EMLA, eutectic mixture of lidocaine and prilocaine; SE, standard error

[a] p-value from Generalized Estimating Equation marginal model

[b] for post-LP headache, N=68 for EMLA cream and N=73 for placebo

[c] for post-LP back pain, N=69 for EMLA cream and N=74 for placebo

TABLE 3.

Patient cooperation, level of movement, and quality of lumbar puncture comparison by arm

	EMLA cream		Placebo cream		
	N	**Percent (SE)**	**N**	**Percent (SE)**	**p-value**[a]
Patient Cooperation [b]					0.016
Cooperative	33	47.1 (10.0)	49	64.5 (9.6)	
Somewhat Cooperative	11	15.7 (6.0)	9	11.8 (4.7)	
Not Cooperative	26	37.1 (7.6)	18	23.7 (7.3)	
Level of Movement [c]					<0.001
No Movement	50	66.7 (6.8)	29	37.7 (5.7)	
Minor Movement	7	9.3 (3.9)	12	15.6 (3.7)	
Major Movement	8	10.7 (3.9)	27	35.1 (4.9)	
Other	10	13.3 (4.9)	9	11.7 (4.5)	
Lumbar Puncture					0.382
Atraumatic	63	90 (3.4)	57	86.4 (3.8)	
Traumatic	6	8.6 (3.2)	5	7.6 (3.5)	
Bloody	1	1.4 (1.4)	4	6.1 (2.8)	

EMLA, eutectic mixture of lidocaine and prilocaine; SE, standard error

[a] Rao-Scott Chi-square test

[b] Cooperation Scale:

1. Patient was positioned and skin prepped prior to propofol

2. Patient was somewhat cooperative but not in position and skin not prepped prior to propofol

3. Patient was not cooperative

[c] Movement 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 (such as more than one attempt or prolonged first attempt).