PEDIATRIC EMERGENCY MEDICINE CRITICAL ARTICLE REVIEW (PEMCAR)	
QUESTION	In children ages 3-16 years, is topical LET (Lidocaine-Epinephrine-Tetracaine) superior to topical EMLA (Eutectic Mixture of Local Anesthetics) plus local infiltration of Mepivacaine for pain control after anesthetic application and during laceration repair?
TYPE	Therapy
TOPIC	Painful Procedures: Topical Analgesia
DATE	January 2020
REVIEWER	Ellen Duncan MD PhD, Rebecca Burton MD
CITATION	Königs I, Wenskus J, Boettcher J, Reinshagen K, Boettcher M. Lidocaine-Epinephrine-Tetracaine Gel is More Efficient than EMLA and Mepivacaine Injection During Skin Repair in Children: A Prospective, Propensity Score Matched Two-Center Study. Eur J Pediatr Surg. 2019 Nov 18., PubMed ID: 31739347

STUDY DEFINITIONS	
POPULATION	Inclusion: Age 3 to 16 years Dermal laceration needing suturing Exclusion: Lacerations occurring > 24 hours Lacerations of the digits, nose, ears and penis Bite wounds Children with chronic diseases Pregnancy Known allergy to any of the medications Setting: Two centers in Germany (Children's Hospital Altona, Department of Pediatric Surgery of the University Medical Center Hamburg-Eppendorf), Enrollment period not provided
INTERVENTION	LET: Lidocaine (4%)-Epinephrine (0.05%)-Tetracaine (0.5%), (maximum 5 ml of LET gel) Applied with a syringe and a sterile dry gauze Left on for 20-30 minutes prior to skin repair
CONTROL	EMLA: Eutectic Mixture of Local Anesthetics: Lidocaine (2.5%), Prilocaine (2.5%), (maximum 5 mL of EMLA cream) Applied with a syringe and a sterile dry gauze Left on for 20-30 minutes prior to Mepivacaine infiltration and skin repair AND Subsequent infiltration of Mepivacaine (1%) Injected throughout wound edge using a 30-gauge needle
CO-INTERVENTIONS	Doses chosen to provide less than 5 mg/kg of Lidocaine. Higher doses can result in systemic toxicity if all of the Lidocaine was absorbed Wounds managed as per "standard care protocols" (not described) 6.0 Ethilon for facial lacerations, 5.0 Ethilon for other lacerations
OUTCOME	Primary Outcome: Efficacy Pain Reduction 1. Patient pain a. FACES pain rating scale (ages 3-10)

	b. Visual analogue scale (ages 11-16) 2. Physician reported pain 3. Parent reported pain A. Time of anesthetic application/infiltration B. During skin closure Secondary Outcomes: Procedure 1. Procedure time: Initial application to completion of wound repair 2. Time until pain recurs 3. Necessity of supplemental infiltration of additional local anesthetic Secondary Outcomes: At follow-up in 2 weeks (Visit or by phone) 1. Rates of wound infection a. Follow-up visit: Erythema, edema, pain and/or fever, received antibiotics b. Follow-up phone call: Received antibiotics 2. Overall satisfaction (assessed using German school grade: See Appendix) a. Parents: After procedure and at follow up b. Patients: After procedure only
DESIGN	Prospective, cohort study (propensity score-matched)

CRITICAL REVIEW FORM FOR A THERAPY ARTICLE

HOW SERIOUS WAS THE RISK OF BIAS?

DID INTERVENTION AND CONTROL GROUPS BEGIN THE STUDY WITH THE SAME PROGNOSIS?

Were patients randomized?	Unclear. The methods section states that "simple random allocation to LET or EMLA group was performed." However, in discussing the limitations of the study, the authors describe the study as a "prospective, propensity score-matched cohort study and not as a randomized controlled trial". Simple random allocation was based on the availability of the LET gel", which makes it a convenience sample. Propensity score matching occurred based on age, gender, wound size, wound location (head vs not head) and application time of topical aesthetic.
Was randomization concealed?	Unclear. Not explicitly stated.
Were patients in the study groups similar with respect to known prognostic factors?	Yes. Authors describe patient information that was recorded (demographics, medical history, medications, wound characteristics, and wound preparation) but there is no Table 1. There was no statistically significant difference in any of the parameters presented.

	LET	EMLA+MEP	p
Age (years)	8.78	9.57	0.42
Gender (male)	24/37 (65%)	16/22 (73%)	0.54
Wound			
Length (cm)	3.31	3.79	0.40
Shape	Not provided	Not provided	NS
Margin	Not provided	Not provided	NS
Extremity (%)	19/37 (51%)	9/22 (41%)	0.45
Severe Contamination	3/37 (8%)	3/22 (15%)	0.51

	Foreign Body	1/37 (3%)	0/22 (0%)	0.45
	Exposure Time (minutes)	29.49	28.72	0.80

WAS PROGNOSTIC BALANCE MAINTAINED AS THE STUDY PROGRESSED?	
To what extent was the study blinded?	None of the groups (patients, parents, or physicians) were blinded during this study.
WERE THE GROUPS PROGNOSTICALLY BALANCED AT THE STUDIES CONCLUSION?	
Was follow-up complete?	Yes. Follow up was completed at 2 weeks after initial presentation to assess for wound infection and satisfaction of treatment. No patients were lost to follow up. The proportion of patients having a visit compared to those that follow up by phone is not presented..
Were patients analyzed in the groups to which they were randomized?	Unclear. There is no mention of whether the analysis was intention-to-treat or per-protocol, and the authors do state that 13.5% of patients in the LET group required anesthetic infiltration. It would be helpful to know how the analysis was performed and a subanalysis of pain during the repair in the LET group that did and did not receive Mepivacaine.
Was the trial stopped early?	No. It does not appear that the trial was stopped early. However, the anticipated sample size based on a power analysis was not reported.

WHAT WERE THE RESULTS?

HOW LARGE WAS THE TREATMENT EFFECT?

N = 59 patients (73 patients, 14 patients excluded due to propensity score matching)
LET: n=37
EMLA+Mepivicaine: n=22

Primary Outcome

Figure 2 (see appendix) provides graphic representation of the differences in pain after anesthetic application and during laceration repair. Absolute risks and risk differences with 95% confidence intervals were not provided. This makes evaluating the clinical significance of the differences difficult. In addition, the authors did not provide the effect size that they considered to be clinically significant

a. Pain Intensity After Study Medication Application (See Appendix: Figure 2):
Significantly less pain for LET group as assessed by patients, parents, and practitioner
Patients report significantly more pain compared with parental or practitioner assessment.
This was also true in a sub-analysis of patients over 10 years of age using a VAS scale
Parents significantly underestimated patient pain. Physicians to a lesser extent.

b. Pain Intensity During Laceration Repair (See Appendix: Figure 2):
No difference between LET and EMLA groups for pain scores during treatment (wound closure, including debridement)

Secondary Outcomes

MORE ANESTHETIC	LET	EMLA+MEP	P Value
Additional Mepivacaine Given	5/37 (13.5%)	1/22 (4.5%)	0.28
WOUND INFECTION	LET	EMLA+MEP	P Value

Signs of Infection*	3/37 (8.1%)	1/22 (4.5%)	0.99
Received Antibiotics	1/37 (2.7%)	0/22 (0.0%)	0.51
*Swelling, redness or color change			
SATISFACTION*	LET	EMLA+MEPI	P Value
Parents: Immediate After	1.51 [0.55]	1.69 [0.59]	0.62
Parents: At Follow up	1.51 [0.55]	1.69 [0.59]	0.62
Patients: Immediate After	1.59 [0.60]	2.04 [0.90]	0.02
A lower score indicates more satisfaction. These values are graded as excellent or very good (See appendix 2) *Patients satisfaction at follow up was not assessed			
GREEN = Statistically Significant, RED = Not Statistically Significant			

HOW PRECISE WAS THE ESTIMATE OF THE TREATMENT EFFECT?

95% confidence intervals were not provided for any of the differences

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to my patient?	Unclear. Very little demographic information is provide about patients, but as far as patients aged 3-16 with lacerations requiring repair, our patients may be similar.
Were all patient important outcomes considered?	No. The authors considered satisfaction and signs of infection. It would have been helpful to see a breakdown of satisfaction into different factors (duration of ED experience, anxiety, cosmesis). Secondary efficacy outcomes of procedure time (initial application to completion of wound repair) and time until pain recurs are described in the methods section but are not reported in the results section.
Are the likely treatment benefits worth the potential harm and costs?	It is unclear what the relative costs are of LET and EMLA. However, since starting with topical application of LET may facilitate repair without intradermal injection of local anesthetic, it would be beneficial to start with topical anesthetic only.

CLINICAL BOTTOM LINE

BACKGROUND: Lacerations are a common cause of visits to the pediatric emergency department. Laceration repair can be a traumatizing experience, and infiltrating local anesthetic can add to the discomfort and anxiety in patients. The use of topical anesthetics may obviate the need for infiltrative anesthetics. This could result in less patient pain, may improve the rate of successful laceration repair and decrease the need for procedural sedation. The use of Epinephrine results in vasoconstriction which concentrates the anesthetic at the wound site. This may increase the efficacy of the anesthetic and limit potential toxicity due to systemic absorption. In addition, vasoconstriction due to Epinephrine can decrease wound bleeding.

CLINICAL QUESTION: In children ages 3-16 years, is topical LET (Lidocaine-Epinephrine-Tetracaine) superior to topical EMLA (Eutectic Mixture of Local Anesthetics) plus local infiltration of Mepivacaine for pain control after anesthetic application and during laceration repair?

DESIGN/VALIDITY: This was a prospective, propensity score-matched cohort study conducted at

two German hospitals which included 59 children with lacerations. It is unclear how patients were allocated to treatment groups. The methods section states that "simple random allocation to LET or EMLA group was performed." However, in discussing the limitations of the study, the authors describe the study as a "prospective, propensity score-matched cohort study and not as a randomized controlled trial". Lack of randomization may lead to biases. However, propensity score matching was used and it resulted in similar groups with regard to age, gender, wound characteristics, exposure time and the presence of wound contamination or foreign body.

Patients received topical LET gel or topical EMLA cream followed by local injection of Mepivacaine 30 minutes after EMLA application. The choice of the control group is unusual in that it involved the use of a topical anesthetic followed by an injectable anesthetic. However, this was the authors standard practice to which they wanted to compare topical LET alone.

Not all patients returned to the ED for follow up, so parents had to identify signs of infections in some cases. The authors describe follow up being available for all patients but not the proportion with a revisit as opposed to phone follow up.

PRIMARY RESULTS: Figure 2 (see appendix) provides graphic representation of the differences in pain after anesthetic application and during laceration repair. Absolute risks and risk differences with 95% confidence intervals were not provided. This makes evaluating the clinical significance of differences found difficult. The authors also did not give an effect size or sample size on which the sample size determination was based. Generally, a 13-15mm difference in VAS score is considered clinically significant.

LET application was less painful than EMLA and local infiltration as reported by all three groups. Pain during treatment (repair and debridement) was similar between the two groups. Patients report significantly more pain compared with parental or practitioner reporting.

The application time of EMLA may not have been sufficient to reach peak analgesia. The median duration of EMLA application was 29 minutes with a minimum time of 15 minutes. The Food and drug administration states that "satisfactory dermal anesthesia is achieved 1 hour after application" (Web Link). However, some studies have reported successful analgesia at early time intervals.

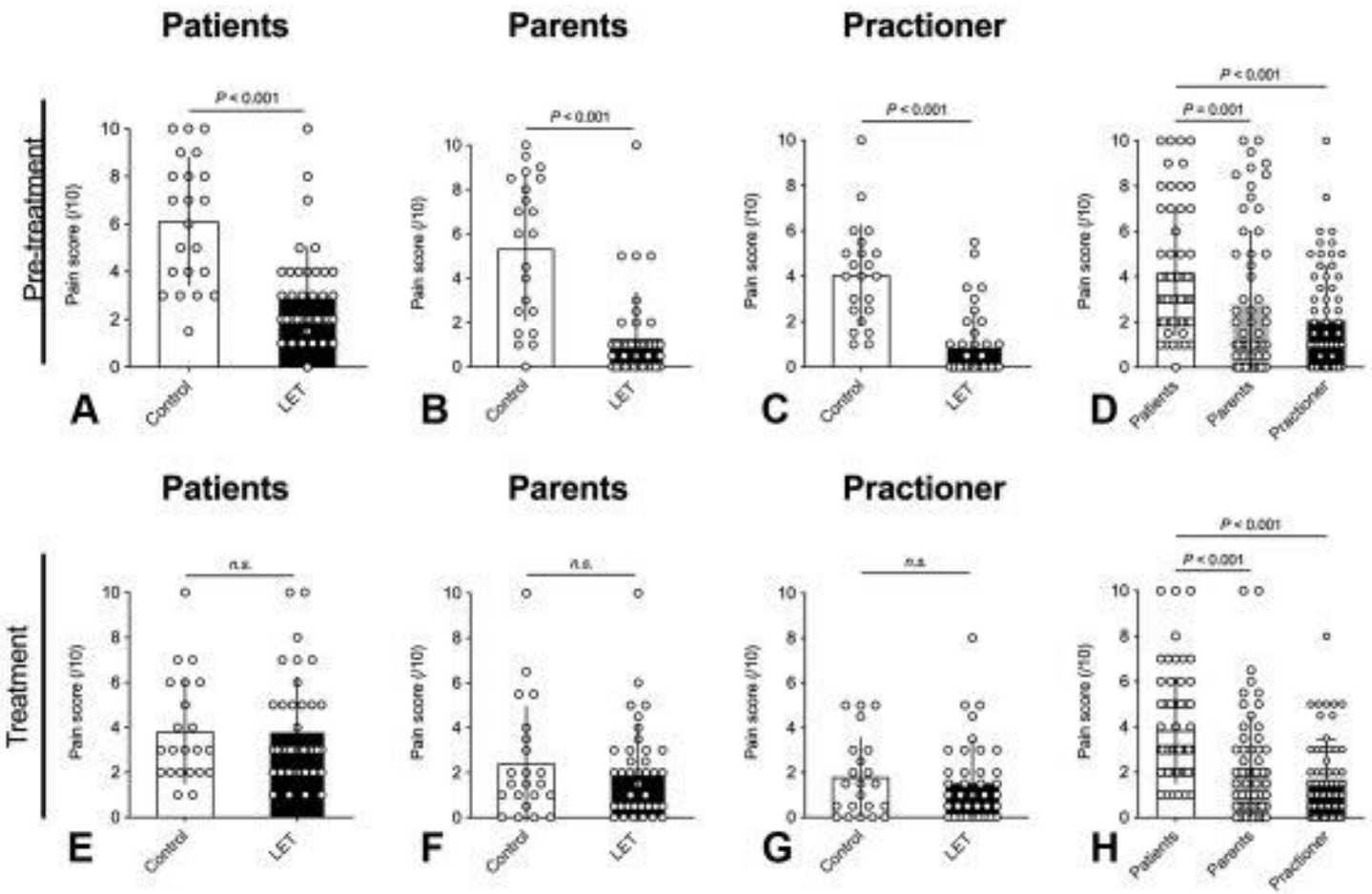
20% (14/73) of patient were excluded due to propensity matching. Patients are excluded if no match can be found. It patients who are excluded have a factor that is not present in those who were matched then the influence of the factors cannot be assessed.

APPLICABILITY: It is unclear what the specific demographics are of patients in this study, but we do see patients ages 3-16 with lacerations requiring repair. Our standard practice has been to apply LET with an occlusive dressing and providing anesthetic infiltration only as needed.

AUTHOR'S CONCLUSION: "In conclusion, it appears that LET is superior to conventional anesthesia including Mepivacaine injection in the pediatric ED. Pretreatment with LET is significantly less painful but equally effective. Hence, we recommend LET as a topical anesthetic in the pediatric ED."

POTENTIAL IMPACT: It may be beneficial to start with topical LET application and then assess the need for local infiltration, as topical application alone may be sufficient to allow for skin repair. This is our current practice. This and other studies have demonstrated that parent and practitioner assessment of pain does not match that of the patient.

APPENDIX 1: FIGURE 2



APPENDIX 2: GERMAN SCHOOL GRADES
(USED FOR ASSESSMENT OF OVERALL SATISFACTION)

GERMAN SCHOOL GRADES		
SCORE	GRADE	ERRORS
1.0-1.5	Excellent	
1.6-2.3	Very Good	Few
2.4-2.9	Good	Some
3.0-3.5	Satisfactory	Many
3.6-4.0	Sufficient (minimum passing)	