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A comparison of the impact of time on the analgesic efficacy of emla cream application in children undergoing venipuncture: A randomized controlled trial

Behzad Aliakbari Sharabiani[a,1], Daryosh Sheikhzadeh[a,1,*], Sina Parsay[b,1], Hossein Razmi[a,1], Mahin Seyedhejazi[a,1]

[a] Department of Anesthesiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Pediatric Surgery, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Background: Intravenous catheterization (venipuncture) is a common and relatively painful procedure carried out routinely in healthcare facilities. Topical Eutectic Mixture of Local Anesthetics (EMLA) has been advocated to reduce the pain associated with venipuncture in children. However, it is not precisely understood how long EMLA should be applied prior to the procedure. Some studies recommend the use of EMLA at least 60 min prior to the procedure. This study was performed to evaluate the effectiveness of EMLA when used with a shorter preparation time prior to the procedure.

Methods: In this double-blinded clinical trial, 231 patients aged 2 to 6 years were enrolled and randomly allocated into three groups. Group 1 received EMLA cream 20 min before venipuncture, group 2 received EMLA cream 60 min before venipuncture, and group C received vitamin A ointment as a control group. Pain intensity was recorded in groups based on the FLACC score. Study participants, nurses, and evaluators were blinded to the treatment group.

Results: Pain severity was lower in groups 1 (mean score = 1.96) and 2 (mean score = 1.56) compared to the controls (mean score = 8.7; $P<0.001$). There was no difference in pain severity between groups 1 and 2 ($P = 0.134$).

Conclusion: EMLA cream significantly reduces the pain associated with venipuncture in children. Also, the application of topical EMLA 20 min before venipuncture is as practical as using it 60 min before this procedure.

1.Introduction

The pain arising from medical procedures is one of the most critical problems related to children's health. The fear of painful procedures is far greater in children than adults, which could prevent them from receiving appropriate medical care and diagnostic procedures. Therefore, controlling such pain and reducing the fear of therapeutic and diagnostic procedures is of paramount importance in children.[1-3]

Intravenous (IV) catheterization (also known as venipuncture) is one of the most common and relatively painful procedures that is carried out routinely in health facilities. It can be recognized as one of the unpleasant medical service-related events by kids.[4,5]

Various methods have been presented to reduce the pain caused by venipuncture. One is the subcutaneous injection of local anesthetics such as lidocaine 1% before attempting to venipuncture or inserting an intravenous catheter. However, this subcutaneous injection can be painful by itself. Thus, it can put children in additional distress; it can also cause skin irritation at the injection site, allergic reactions, or a systemic reaction by an unintended injection into the vascular system.[6]

Another method is using topical anesthetic agents, such as Eutectic Mixture of Local Anesthetics (EMLA), prior to the procedure. EMLA is an emulsion that consists of lidocaine 2.5% and procaine 2.5% and can be utilized in the site of the procedure shortly before IV catheterization in order to relieve pain. Regarding its crystalline base nature, EMLA has an ideal cutaneous absorption.[7-9]

While numerous studies have confirmed the effectiveness of EMLA cream in reducing the pain of medical procedures, it is not precisely understood how long the EMLA should be applied prior to the

* Corresponding author.
E-mail address: dr.d.sheik@gmail.com (D. Sheikhzadeh).
[1] The corresponding author submits this statement on behalf of all co-authors.

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Table 1
Demographic characteristics of patients (EMLA: eutectic mixture of local anesthetics).

		Group 1 (EMLA 20 min before the procedure)	Group 2 (EMLA 60 min before the procedure)	Group 3 (control)	total
Mean age		3.54 ± 1.46	3.48 ± 1.53	3.51 ± 1.54	3.51 ± 1.50
Mean weight		15.2 ± 3.29	14.9 ± 3.68	15.1 ± 3.03	15.12 ± 3.3
sex	Male	59	64	65	188
	female	18	13	12	43

procedure.[8-13] Therefore, this study was designed to determine the proper time interval between the application of EMLA and performing the procedure to reach the maximum efficacy. The presumed null hypothesis for this study was "EMLA should be applied at least 60 min prior to venipuncture in order to be effective." The present study was designed to compare the effectiveness of topical EMLA in reducing the pain associated with venipuncture with two different preparation times (20-minutes versus 60-minutes prior to the procedure) among 2 to 6-year-old children.

2. Methods

2.1. Ethical consideration

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the registry code of 92/1–10/48. It was also registered in the Iranian Registry of Clinical Trials (IRCT) with the registration reference of IRCT2015051822309N1.

No additional intervention or cost was imposed on patients in this study. Informed consent was obtained from the parents or legal custodians of each participant, and they were ensured that they are able to leave the study at any time if they feel reluctant. The patients whom their parents or legal guardians did not sign the informed consent form were excluded from the study. It was also assured to the parents that all personal information would remain confidential, and the results of the study would be published in general.

2.2. Patients

In this double-blind, randomized clinical trial, 231 children aged 2–6 years old presenting for elective surgery and managed to undergo general anesthesia were enrolled and randomly assigned to one of the three treatment groups of EMLA 20 min before the procedure (group 1), EMLA 60 min before the procedure (group 2), and Control group with using Vitamin-A cream prior to the procedure (group 3). Any individual with established prior history of an allergic reaction to lidocaine or EMLA, children who were prescribed analgesics or sedative drugs before the procedure, and patients with a decreased level of consciousness were excluded from the study. Patients, operating nurses, and observers were blinded to the groupings throughout the study course.

In the first group, EMLA cream with the brand name of Xyla-P (a mixture of lidocaine 2.5% and prilocaine 2.5% produced by Tehran Chemie Pharmaceutical Co.) was used 20 min prior to IV catheterization. In group 2, the same drug was used 60 min prior to IV catheterization. In group 3, as the control group, vitamin A cream (as the placebo) was used 20 min prior to IV catheterization. According to the manufacturer's instruction, a precise amount of the cream was applied to the dorsum of the subject's hand (the selected spot for cannulation) in an area of 5 cm2. The area was then dressed with an occlusive dressing to maximize the absorption of the drug. All catheterizations were performed by either one of the two trained nurses using a 24 G catheter. The participant was excluded from the trial in case the catheterization failed. The severity of pain was measured by either one of the two trained observers using the FLACC behavioral pain assessment scale, during the procedure.[14] Blood pressure, heart rate, respiratory rate, and blood oxygen saturation level of participants were also recorded before and after the procedure.

2.3. Statistical analysis

All Data were analyzed by SPSS version 23.0. (IBM Corp., Armonk, N.Y., USA) and reported by frequency and percentage for qualitative variables and with mean and standard deviation in quantitative variables. Independent t-Test and ANOVA were used for analyzing continuous variables. Discrete variables were compared by the chi^2 and fisher exact test. The p-value ≤ 0.05 was considered as statistically significant. Inter-observer reliability was also evaluated by Cohen's Kappa coefficient.

3. Results

EMLA and placebo cream were applied to 231 individuals. The demographic data of patients are demonstrated in Table 1. As depicted, there were no statistically significant differences in the patients' demographic status among the three study groups.

Regarding the pain intensity measured by the FLACC score, the acquired data demonstrated a significant difference in the mean pain intensity of the patients between the three groups ($p = 0.001$). However, pair-wise analysis of the groups revealed that this difference was only significant while comparing each study group with the control group. Meanwhile, no statistically significant difference was found in the severity of pain between the two intervention groups. Fig. 1 demonstrates the mean FLACC score and the interquartile range for each group using a stem and leaf plot. Inter-rater agreement was also measured by Cohen's Kappa coefficient, which revealed an excellent level of agreement between the observers ($\kappa = 0.812$).

Table 2 shows a comparison between the vital signs of patients, as an indicator of catecholamine surge, before and after the procedure within each group. As demonstrated in Table 2, changes in some of the vital signs were not statistically significant, while others showed statistically significant differences such as changes in heart rate and respiratory rate in all the groups ($p < 0.001$).

In this regard, no statistically significant difference was found in the participants' mean blood pressure before and after the procedure in groups 1 and 2. However, the alteration in the measured values of blood pressure within the control group was statistically significant. Changes in heart rate, respiratory rate, and blood oxygen saturation were also significant in group 3 before and after the procedure. No complications were observed after using the EMLA cream or vitamin A.

4. Discussion

According to our results, there was a statistically significant difference between the groups in which EMLA cream had been used (20 min and 60 min prior to the procedure) in comparison to the control group. On the other hand, neither clinically nor statistically significant differences were found in the EMLA's analgesic effects between the two intervention groups. That iss, using EMLA 20 min prior to a procedure is as effective as using it 60 min prior to the procedure.

Over the last decade, many efforts have been put into action in order to make medical procedures less painful. Pharmaceutical companies have taken an essential step in this path by introducing EMLA.[15] EMLA

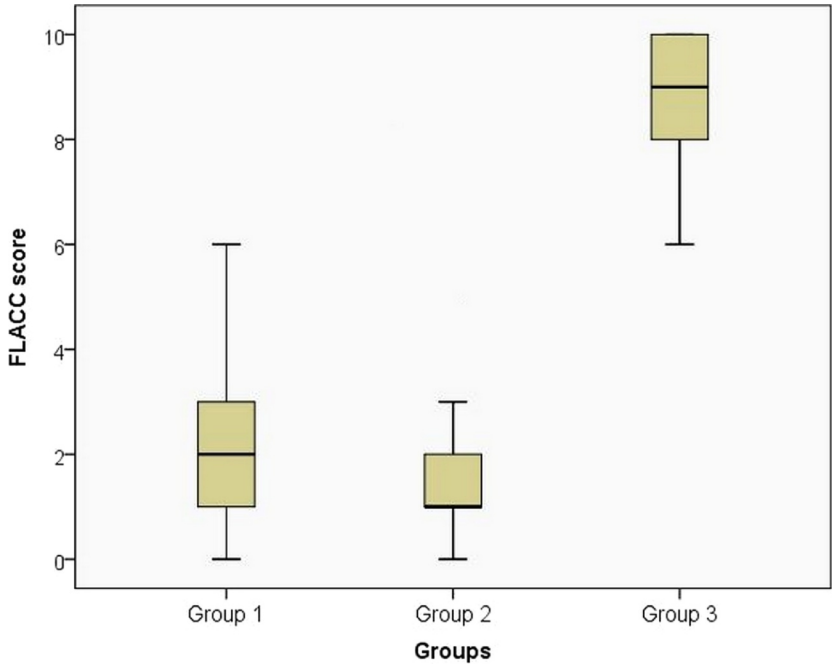

Fig. 1. FLACC Score between study groups.

is a topical eutectic mixture of two anesthetics that blocks the cutaneous pain receptors and causes localized dermal numbness in the affected area. The depth of the induced local analgesia depends on how long the agent is kept on the skin. As a general rule, it usually takes about 60 min for EMLA to reach an acceptable analgesic level following application. The relatively long onset of action of EMLA limits its use in emergency settings.[16,17] However, Selby et al.[10] noted some degrees of numbness within 5 min of application.

On the other hand, in a study carried out by Eichenfield. et al., it was found that using EMLA either 30 or 60 min before venipuncture demonstrated a similar effect on reducing the pain associated with the performed procedure. They also found that ELA-Max (4% liposomal lidocaine) might show the same analgesic effect as EMLA and can be used as an alternative.[18]

Smith et al. found that using EMLA 5 min before IV cannulation can significantly decrease pain during the procedure compared to the control group. However, their sample size was relatively small, including 20 patients within the case and control groups. Furthermore, they conducted their study on an adult population, which might be a reason for our different findings.[19]

Our findings might demonstrate that EMLA cream can be used 20 min before venipuncture to alleviate the pain of this procedure. Twenty minutes is a relatively short time, compared to the previously established 60 min, leading to faster preparation of the patient for a procedure. Thereby, care providers can rely on the 20-minute time gap between applying EMLA and performing a venipuncture, without any concern about waning in drug effectiveness.

In another clinical trial performed by Singh S. et al.,[20] the authors evaluated the analgesic effect of EMLA cream compared to the local injection of lignocaine prior to the radiofrequency waveguide wart removal procedure. In this study, warts were harvested 30 min after EMLA cream administration. This study suggests that EMLA cream is a good and effective alternative to lignocaine in reducing pain due to wart removal procedure. Additionally, a topical agent was more acceptable than an injectable medication by the patients.

With this background in mind, EMLA is a topical anesthetic agent which can be used in many conditions and is almost safe with no reported significant side effects. Regarding the literature, in order to reach maximal effectiveness, this product must be applied 60 min before the procedure known as the preparation gap. However, in this study, we showed that the preparation gap could be snipped off by 40 min in case of venipuncture with the preserved analgesic effect of the used material.

Moreover, the comparison of patients' vital signs as a predictor of catecholamine surge before and after the procedure revealed no statistically significant increase in these values within both study groups. When a healthcare provider approaches a child with a needle, the fear of anticipated pain is one of the other major concerns in pediatric healthcare centers, which cannot be addressed with EMLA. Even though indirect measuring of catecholamine surge via vital sign monitoring before and after a procedure could serve as a predictor of the mentioned phobia in children, which was statistically insignificant in

Table 2
mean systolic and diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation of individuals within each group before and after the procedure and comparison of the results within each group (SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HR: Heart Rate, SPO_2: Blood Oxygen Saturation, RR: Respiratory Rate).

	Group-1			Group-2			Group-3		
	Before	After	p-value	Before	After	p-value	Before	After	P-value
SBP	100.06 ± 4.32	100.71 ± 4.91	0.105	98.92 ± 3.59	100.87 ± 3.90	0.107	100.0 ± 2.14	105.26 ± 5.34	0.001
DBP	59.93 ± 3.93	61.29 ± 4.24	0.148	59.87 ± 3.88	59.93 ± 4.01	0.567	59.93 ± 1.90	62.27 ± 3.76	0.001
HR	96.94 ± 7.86	99.48 ± 8.52	0.001	98.16 ± 8.22	99.43 ± 8.63	0.001	97.31 ± 2.81	113.65 ± 3.73	0.001
SPO_2	95.32 ± 1.54	95.27 ± 1.18	0.753	95.44 ± 0.95	95.25 ± 0.92	0.001	95.40 ± 0.94	94.82 ± 0.83	0.001
RR	21.06 ± 2.98	22.09 ± 3.32	0.001	20.35 ± 1.95	21.03 ± 2.36	0.001	19.85 ± 1.02	25.48 ± 1.47	0.001

our study, using indirect predictors might be a potential limitation of this study.

Besides, it should be stated that one of the potential side effects of the EMLA is vasoconstriction, which may result in difficulty in IV catheter placement and increased number of attempts. Unfortunately, data indicating the number of attempts for successful IV catheter placement was not recorded in our study. Another limitation was not addressing the probable difference in the skills and experience of the two nurses who performed the catheterizations.

The possible side effects of EMLA may include pallor or blanching, erythema, edema, burning sensation, itching, and rash on the application site. Also, methemoglobinemia, severe allergic reaction, and shock have been recorded as extremely rare side effects.[21]

In general, we can conclude that EMLA cream might be useful with shorter preparation time, for instance, 20 min prior to a procedure, in order to reduce the pain associated with that procedure. Finally, the presence of different results in various studies can be a consequence of potentially confounding variables. Further research, particularly systematic reviews, seems to be essential to clarify the subject.

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CRediT authorship contribution statement

Behzad Aliakbari Sharabiani: Conceptualization, Methodology, Resources. **Daryosh Sheikhzadeh:** Conceptualization, Methodology, Writing - review & editing. **Sina Parsay:** Software, Writing - original draft, Formal analysis, Validation. **Hossein Razmi:** Data curation, Resources, Investigation. **Mahin Seyedhejazi:** Supervision, Project administration.

Declaration of Compting Interest

The authors declare that they have no competing interests; this manuscript or part of it has not been previously presented in any conference or published in any form.

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