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Original Article

Comparison of the Analgesic Effectiveness of Lidocaine, Diphenhydramine, and EMLA Before Venipuncture: A Cross-Sectional Study

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Abstract

Introduction: Venipuncture is a common emergency department procedure that can cause discomfort and reduce patient satisfaction. This study compared the anesthetic effectiveness of lidocaine, diphenhydramine, and the lidocaine-prilocaine drug combination (EMLA cream) during venipuncture.

Methods: The study included 200 adult patients requiring venipuncture in the emergency department. Adult patients aged≥18 years were included and classified into four groups: 10% lidocaine, diphenhydramine syrup (60 ml bottle, with each 5 ml containing 12.5 mg of diphenhydramine), EMLA cream, and placebo (water). Patients with Glasgow Coma Scale (GCS)<15, severe pain, or requiring rapid vascular access were excluded. All substances, including the oral diphenhydramine syrup, were applied topically to the venipuncture site five minutes before venipuncture. Pain intensity was assessed immediately after the procedure using the Numeric Pain Rating Scale (NPRS). Data were analyzed using SPSS v21, with $P<0.05$ considered significant.

Results: There were no significant differences among the groups in age, sex, indication for venipuncture, or cannula gauge. Pain intensity differed significantly among the four groups ($P<0.001$). After Bonferroni adjustment, all active treatment groups had significantly lower pain scores than the control group (adjusted $P<0.006$), and EMLA was associated with significantly lower pain scores than both lidocaine and diphenhydramine (adjusted $P<0.006$). No significant difference was observed between the lidocaine and diphenhydramine groups (adjusted $P>0.99$). The median (IQR) NPRS scores for the control, lidocaine, diphenhydramine, and EMLA groups were 6 (6-7), 3 (2-3), 3 (2-3), 0 (0-0), respectively.

Conclusion: EMLA was associated with greater pain reduction during venipuncture compared with lidocaine and diphenhydramine, while no significant difference was observed between lidocaine and diphenhydramine. Further large-scale studies are needed to confirm these findings.

Introduction

Venipuncture is a common medical procedure that can cause pain and lead to considerable distress, anxiety, and psychological consequences.[1,2] Needle-related discomfort during venipuncture is a particular concern among needle-phobic individuals and pediatric patients. Therefore, relieving pain and discomfort is beneficial for all patients. Multiple methods have been suggested to alleviate venipuncture pain, including the application of various local anesthetics, ice, ethyl chloride, and distraction techniques.[3-5]

Lidocaine inhibits nerve signaling by acting on nerve endings and interfering with calcium-binding sites that regulate sodium permeability. This causes reduced permeability, depolarization, and a heightened excitability threshold.[6,7] Diphenhydramine is an antihistamine that has been efficiently used as an anesthetic in individuals with allergies to amide or ester local anesthetics, including in dermatologic, dental, and image-guided procedures.[8] Another widely used topical anesthetics is the eutectic mixture of local anesthetics (EMLA cream), which is a topical cream and consists of a combination of 2.5% lidocaine and 2.5% prilocaine. EMLA is considered the "gold standard" for alleviating pain during venipuncture.[9,10]

There is a growing body of literature addressing pain relief prior to venipuncture; however, the effectiveness of different anesthetic agents remains debated. While there is a wealth of data on the assessment of the different

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approaches to reduce the pain associated with venipuncture in the pediatric population,[11-15] there is limited research in adults, particularly regarding venipuncture involving larger-diameter intravenous (IV) line. Therefore, this study was designed to compare the anesthetic effectiveness of diphenhydramine syrup, lidocaine, and EMLA for venipuncture.

Materials and Methods

Study Design and Participants

This cross-sectional study compared the anesthetic effectiveness of lidocaine, syrup diphenhydramine and EMLA before venipuncture in patients requiring IV-line cannulation. A total of 200 adult patients were included in this study. After getting the ethical approvals from the local ethics committee and written informed consent form, adult (18 +) patients were classified into four groups: control, lidocaine 10%, diphenhydramine syrup, and EMLA cream. Patients with a Glasgow Coma Scale (GCS) below 15 or severe pain in anywhere of body and patients who needed rapid vascular access were excluded.

Sample size

A formal a priori sample size calculation was not performed. Instead, a pragmatic sample size of 200 participants, with 50 participants in each group, was selected based on the anticipated number of eligible patients during the study period and feasibility of recruitment.

Substances Used Before Venipuncture

In the control group, water was applied topically to the venipuncture site as a placebo.

In the lidocaine group, one puff of 10% lidocaine spray (0.1 mL, corresponding to 10 mg of lidocaine) was applied topically to the venipuncture site.

In the diphenhydramine group, diphenhydramine syrup containing 12.5 mg of diphenhydramine per 5 mL was applied topically.

In the EMLA Group, 1.5-2 g of EMLA cream was applied over an approximately 10 cm^2 area at the venipuncture site and remained on the skin for five minutes before venipuncture. No occlusive dressing was used during this application period.

The assigned substance was applied topically to the venipuncture site using a sterile cotton swab and remained in contact with the skin for five minutes. Immediately before venipuncture, any residual material was gently removed from the skin, after which venipuncture was performed.

Venipuncture and Pain Assessment

All venipunctures were performed by a trained nurse. The venipuncture site was in the antecubital vein in left upper extremity in all patients. Nurse performed venipuncture five minutes after receiving the intervention to the antecubital fossa and after venipuncture, pain intensity was recorded using the Numeric Pain Rating Scale (NPRS). NPRS was assessed through patient self-report.

Statistical Analysis

Results were analyzed using 21st version of SPSS software and the significance level for P value is defined below 0.05 and 95% confidence intervals (CIs) were observed. Data analysis was performed using analysis of variance (ANOVA) when the variables were normally distributed. When the variable was not normally distributed, or for discrete numeric data (like pain scores), the Kruskal-Wallis test was applied. When the Kruskal-Wallis test was significant, pairwise post-hoc comparisons were performed. To account for multiple comparisons (six pairwise comparisons among four groups), Bonferroni correction was applied by multiplying each P value by the number of comparisons; adjusted P values < 0.05 were considered significant. The normality of data distribution were evaluated using the Kolmogorov-Smirnov test. Chi-square test was used for categorical variables.

Results

Total of 200 eligible patients (50 in each group) have participated in this study. The mean age of patients was 55.27 ± 17.48 years (CI 95%; 52.83 - 57.70) and the median age was 56 years. There were 153 (%76.5) males and 47 (%23.5) females. The most common reasons for venipuncture in patients were fluid resuscitation combined with intravenous injection. The most common IV line used for venipuncture in the studied patients was G21. No significant difference was found between the four groups regarding the age ($P = 0.993$), sex ($P = 0.555$), reasons for venipuncture ($P = 0.425$), and cannula gauge ($P = 0.473$) (shown in Table 1).

Pain intensity showed a significant difference between the four groups ($P < 0.001$). In pairwise comparisons with Bonferroni adjustment, all three active treatment groups showed significantly lower NPRS scores than the control group (adjusted $P < 0.006$ for all comparisons). EMLA was associated with significantly lower NPRS scores than both lidocaine and diphenhydramine (adjusted $P < 0.006$ for both), whereas no significant difference was observed between the lidocaine and diphenhydramine groups (adjusted $P > 0.99$) (Table 2, Figure 1).

The median NPRS scores (interquartile range, IQR) were 6 (6-7) in the control group, 3 (2-3) in the lidocaine group, 3 (2-3) in the diphenhydramine group, and 0 (0-0) in the EMLA group.

No adverse effects or local reactions were reported in any group during or after the procedure.

Discussion

Administration of topical anesthetics and analgesics during venipuncture can help alleviate pain. The desirable characteristics of a topical anesthetic include ease of use, quick start of the action, productive analgesia, and minimal complications.[16] This study highlights the effectiveness of lidocaine, diphenhydramine, and EMLA cream in reducing pain during venipuncture, with EMLA cream remaining the most effective in minimizing pain.

EMLA is the most widely applied topical anesthetic since

Table 1. comparison of the groups of the study regarding the possible confounders

Group	Control (n=50)	Lidocaine (n=50)	Diphenhydramine (n=50)	EMLA cream (n=50)	*P* value
Age, years (mean±SD)	56.26±17.6	54.24±17.5	55.38±17.4	55.16±17.5	0.993
Sex, n (%)					
Male	35(70%)	41 (82%)	38 (76%)	39 (78%)	0.555
Female	15(30%)	9 (18%)	12 (24%)	11 (22%)	
Reasons for venipuncture, n (%)					
Blood sampling	2 (4%)	3 (6%)	2 (4%)	3 (6%)	0.425
Fluid resuscitation	5 (10%)	0	2 (4%)	1 (2%)	
Intravenous injection	6 (12%)	4 (8%)	3 (6%)	4 (8%)	
Fluid resuscitation and intravenous injection	37(74%)	43 (86%)	43 (86%)	42 (84%)	
cannula gauge, n (%)					
G14	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0.473
G16	1 (2%)	2 (4%)	1 (2%)	2 (4%)	
G18	3 (6%)	1 (2%)	4 (8%)	2 (4%)	
G21	46(92%)	46 (92%)	45 (90%)	46 (92%)	

Data are presented as mean±standard deviation or n (%). Each *P* value refers to the overall comparison among the four groups for the corresponding variable; *P* value>0.05 indicate no statistically significant baseline difference among the groups. EMLA: Eutectic mixture of local anesthetics; control: water.

Table 2. Pairwise comparisons of NPRS scores between the study groups

Comparison	Median NPRS (IQR)	Difference in medians	Adjusted *P* value
Control vs Lidocaine	6 (6-7) vs 3 (2-3)	3	<0.006
Control vs Diphenhydramine	6 (6-7) vs 3 (2-3)	3	<0.006
Control vs EMLA	6 (6-7) vs 0 (0-0)	6	<0.006
Lidocaine vs Diphenhydramine	3 (2-3) vs 3 (2-3)	0	>0.99
Lidocaine vs EMLA	3 (2-3) vs 0 (0-0)	3	<0.006
Diphenhydramine vs EMLA	3 (2-3) vs 0 (0-0)	3	<0.006

NPRS: Numeric Pain Rating Scale; IQR: interquartile range; EMLA: eutectic mixture of local anesthetics; control: water; *P* values were Bonferroni-adjusted for six pairwise comparisons.

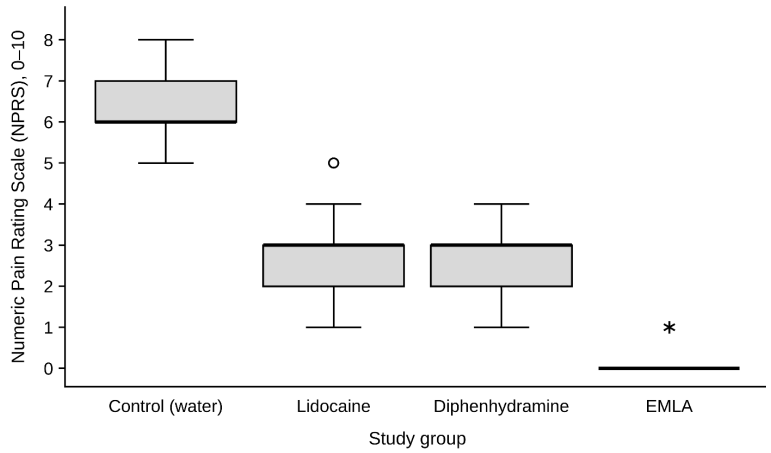


Figure 1. Distribution of Numeric Pain Rating Scale (NPRS) scores across the four study groups. Boxes represent the interquartile range (IQR), the horizontal line within each box represents the median, whiskers extend to the most extreme values within 1.5×IQR of the box, circles indicate outliers, and asterisks indicate extreme values. EMLA: eutectic mixture of local anesthetics

the 1980s.[15] In contrast to its established efficacy, its use has been restricted by a few difficulties. These consist of tendency to cause complications in venipuncture owing to skin blanching, and a risk of methemoglobinemia in infants under 1 year of age.[17] A previous study reported that EMLA cream produced an analgesic effect within 3,5 and 10 minutes of application, with no significant difference observed among these time intervals.[18] However, the maximum analgesic effect is typically achieved approximately 60 minutes after application.[19]

Although EMLA is generally expected to achieve its maximal analgesic effect after a longer application period, we observed a significant reduction in venipuncture pain after only five minutes of application. Previous evidence has suggested that an analgesic effect may begin within the first few minutes after EMLA application, although

this early effect should not be interpreted as comparable to its maximal analgesic effect. Therefore, the greater pain reduction observed with EMLA should be interpreted as an early analgesic response rather than as evidence of its maximum efficacy under standard application conditions.

Studies have shown that EMLA is also safe for use in infants, and this anesthetic cream is recommended for full-term infants in Sweden.[20] Suren et al.[21]examined the effect of the Valsalva maneuver and EMLA cream on reducing the distress of needle puncture during venipuncture in adults. This study showed that both methods considerably reduce the pain without affecting heart rate and arterial blood pressure.

Pourfakhr et al.[22] found that local administration of diphenhydramine (0.5%) provided postoperative pain relief similar to that of lidocaine (1%), with lower pain scores at 18 hours, and lower opioid use, although it caused more sedation. Diphenhydramine may therefore be a potential alternative to lidocaine, which is consistent with the similar pain scores we observed in the lidocaine and diphenhydramine groups. Lidocaine is the most effective local anesthetic which is widely recognized for its rapid onset and medium duration of action. It prevents nerve impulse transmission by inhibiting the activity of voltage-dependent sodium channels and is used for controlling both acute and chronic pains. Moreover, Lidocaine is an amino amide agent that is metabolized in the liver by hepatic enzymes.[23]

Diphenhydramine is a first-generation antihistamine that acts as a competitive antagonist at H_1 receptors by inhibiting histamine binding to the receptor. H_1 receptors are found in respiratory smooth muscle cells, vascular endothelium, cardiac tissue, the gastrointestinal tract, immune cells, the uterus, and the central nervous system (CNS). H_1 receptors are distributed throughout the CNS and are involved in the regulation of alertness and attention. Diphenhydramine readily passes through the blood-brain barrier and causes significant sedative effects. Diphenhydramine is structurally similar to local anesthetics and can block intracellular sodium channels. Therefore, it may be used as an alternative local anesthetic in patients with allergies or sensitivity to amide and/or ester-type local anesthetics.[24]

In this study, diphenhydramine syrup was applied topically rather than administered orally. Given that this formulation is not conventionally used as a topical analgesic, the observed effects of diphenhydramine should be interpreted cautiously and in the context of the specific formulation and application method used.

Matsumoto et al.[25] in a single-center randomized interventional study, demonstrated that EMLA cream was more effective than lidocaine tape in reducing pain associated with venipuncture. Pain was assessed using the visual analog scale (VAS) and verbal rating scale (VRS). Analysis of data from 24 patients showed that both VAS and VRS scores were significantly lower with EMLA cream compared to lidocaine tape. A notable strength of this study was that each patient received EMLA cream on the dorsum of one hand and lidocaine tape on the other, allowing for direct intra-individual comparison. The greater effectiveness of EMLA may be attributed to higher skin permeability and the fact that, unlike lidocaine, it doesn't require a solvent for application, resulting in a higher concentration of local anesthetics. In a prospective, randomized, placebo-controlled study involving 102 adults scheduled for elective surgery, Oluwadun et al.[26] compared the efficacy of 5% EMLA cream, 10% lidocaine, and KY gel (placebo) in reducing pain associated with venous cannulation. The authors concluded that VAS scores were lower among patients who received 10% lidocaine compared to those who received 5% EMLA cream; however, the difference was not statistically significant. Adverse reactions observed in the study included a burning sensation in one patient in the EMLA group and two patients in the lidocaine group, a tingling sensation in one patient in the lidocaine group, and blanching in one patient in each group. other adverse reactions reported with the use of 5% EMLA cream include regional pallor, oedema, flare, itching. Additionally, hives, vascular oedema, bronchospasm have been observed, representing anaphylactic and allergic reactions.[27] Erythema has been reported as a side effect associated with the use of 10% lidocaine.[28,29] the most commonly reported side effects of lidocaine include periorbital numbness, dizziness, vertigo, and dysarthria which are associated with lidocaine accumulation.[30] A review of four randomized clinical trials concluded that needle-free lidocaine is more effective than topical lidocaine in reducing pain associated with venipuncture. needle-free lidocaine was also found to be well tolerated, easy to use, and cost-effective compared to topical lidocaine. Moreover, it provides a faster onset of analgesia than topical lidocaine (1-3 minutes vs > 30 minutes).[31]

Since the pain intensity was self-reported by patients in this study, the potential for placebo effect should be considered here. The placebo effect plays a significant role in regulating clinical outcomes.[32,33] It is Associated with psychoneurobiological alterations and is driven by expectations of patients, caregivers and providers. several mechanisms are correlated with the placebo effect, including: 1) endogenous opioid, endocannabinoid, oxytocin, vasopressin, and dopamine systems. 2) verbal instructions, conditioning paradigms (classical and nonclassical), and social interactions, such as observational and interpersonal learning.[34] To minimize the potential influence of the placebo effect, water was used as the control. In our study, the placebo effect did not appear to have a substantial impact on the outcomes. Nevertheless, we recommend that future studies in this field be designed as Randomized controlled trials (RCTs).

In our study, no significant difference in pain intensity was found between the lidocaine and diphenhydramine groups. Although this finding should not be interpreted as evidence of equivalence, it suggests that diphenhydramine may be worth further investigation as an alternative topical agent, particularly in patients with allergy to conventional

local anesthetics.

This study has several limitations that should be acknowledged. First, this study's single-center design may limit the generalizability of the findings, as variations in practice and patient populations across different settings could affect the outcomes. Second, the sample size was relatively small, and larger, multicenter studies are needed to validate and expand upon these results. Third, potential confounding factors such as patient anxiety, previous needle experiences, and individual pain tolerance were not assessed. In addition, baseline NPRS scores were not recorded; therefore, pre-intervention comparability regarding subjective pain perception could not be directly assessed. Fourth, the relatively short application time of EMLA should be considered when interpreting the findings, as the five-minute interval was substantially shorter than the application time generally recommended to achieve its maximal analgesic effect. Fifth, the absence of an a priori sample size calculation should be considered when interpreting the non-significant findings. In particular, the non-significant difference between lidocaine and diphenhydramine should not be interpreted as evidence of equivalence, as the study may have been insufficiently powered to detect smaller between-group differences. Future well-designed studies with larger sample sizes and appropriate control of potential confounding factors are warranted to better establish the clinical utility of these interventions. Additionally, comparative studies evaluating needle-free lidocaine against other rapid-onset analgesic modalities may further clarify its relative clinical benefits, particularly in time-sensitive settings.

Conclusion

This study compared the anesthetic effectiveness of lidocaine, diphenhydramine, and EMLA prior to venipuncture. All three agents were associated with lower pain scores than the control, and EMLA was associated with significantly lower pain scores than both lidocaine and diphenhydramine. No significant difference was observed between the lidocaine and diphenhydramine groups; however, this finding should not be interpreted as evidence of equivalence. Nevertheless, given the single-center design, relatively small sample size, and potential unmeasured confounding factors, further large-scale, multicenter studies are required to confirm these results and better define their clinical applicability.

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Competing Interests

None.

Ethical Approval

This study (research project no. 63283, approved by the Deputy of Research of Tabriz University of Medical Sciences) was approved by the Ethics Committee of Tabriz University of Medical Sciences (approval code: IR.TBZMED.REC.1398.1060).

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