Original Article

Comparison of the Emulsion and Liposomal Forms of Lidocaine-Prilocaine Mixture Prior to Topical Anesthetic Injection: A Clinical Trial Study

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Abstract

Introduction: This study aimed to investigate the effect of liposomal and emulsion forms of topical anesthesia on pain reduction during dental anesthesia. **Methods**: The study was a randomized clinical trial with a split-mouth design conducted on 15 patients who were referred to a private dental clinic and needed injectable anesthesia for flap surgery in the posterior maxillary area. First, one of the four concentrations (2%, 5%, 7.5%, and 10%) of the emulsion form of Lidocaine-Prilocaine topical anesthesia was applied on one side of the maxilla, and two weeks later, four concentrations of the liposomal form were applied on the other side. These areas were randomly selected for topical anesthesia before injecting anesthesia into the vestibular area. The amount of pain caused by needle insertion was measured by the Visual Analogue Scale. **Results**: The comparison of the emulsion and liposomal forms of Lidocaine-Prilocaine topical anesthesia indicated that 5% of the emulsion form and 7.5% of the liposomal form demonstrated the lowest VAS scores; however, the comparison of different concentrations of the emulsion (P=0.46) and liposomal forms (P=0.64) did not indicate any significant difference. There was not any statistically significant difference between liposomal and emulsion forms regarding the same concentrations (P=0.75). **Conclusion**: Despite the longer substantivity of the liposomal form of Lidocaine-Prilocaine topical anesthesia on the oral mucosa, compared to that of the emulsion form, the findings of the present study revealed that different concentrations of topical anesthesia did not significantly differ in terms of pain reduction efficacy.

Keywords: Dental pain, Emulsion form, Lidocaine-Prilocaine, Liposomal form, Topical anesthesia

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Introduction

The importance of effective pain management during dental treatment lies in the fact that patients cannot be safely treated without anesthesia. Even though pain is usually easily controlled, sometimes complications, such as fear and anxiety, arise, which have a major role in the effect of intra-oral injection of anesthetics (1). While it is true that non-pharmacological methods, including distraction and tissue tremor before injection, can reduce pain (2), studies have shown that topical anesthesia is more effective in minimizing pain during needle insertion (3). It should also be noted that treatment without general topical anesthesia can cause numerous medical emergencies during the dental treatment. The use of local anesthesia enables a more effective and ideal treatment experience. It also reduces the patient's pain and anxiety and improves their cooperation, ability to relax, as well as overall patient satisfaction (4).

Topical anesthetics are available in various forms, including ointments, gels, lotions, and sprays, which are used in dentistry to induce anesthesia on the oral mucosa prior to injection (2). There are various local anesthetics, such as Lidocaine, Prilocaine, Benzocaine, and the

Eutectic Mixture of Local Anesthetics (EMLA) for topical usage (5). A 10% Lidocaine-Prilocaine emulsion is usually used as a topical anesthetic to reduce the injection pain.

Nowadays, various types of topical anesthetics are available with high efficiency. However, their neurological effects and systemic toxicity have rarely been reported (6).

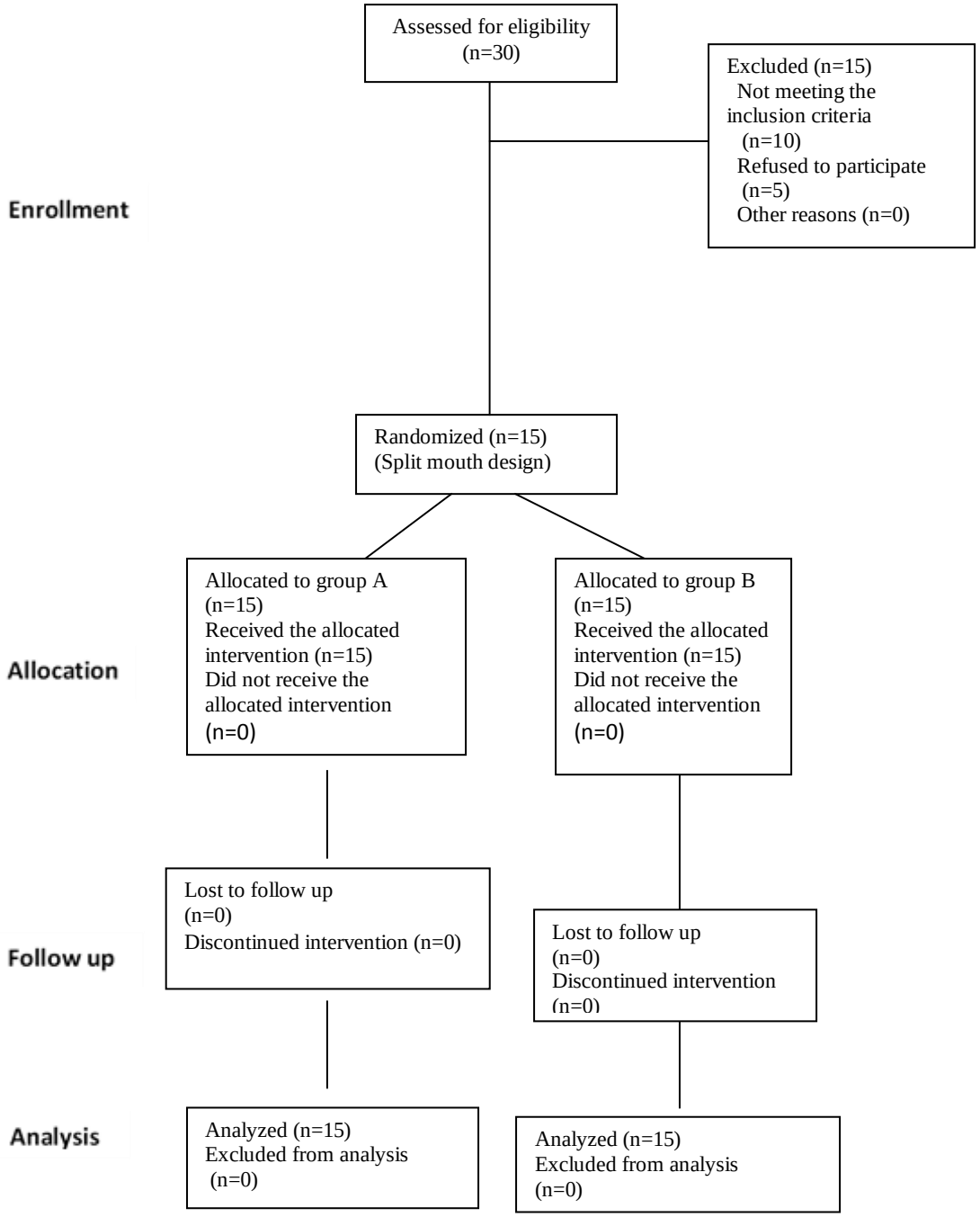
Nayak R et al. indicated that the Lidocaine-Prilocaine mixture was more effective than the Lidocaine gel (7)Different concentrations of the Lidocaine-Prilocaine mixture have been investigated in human studies and revealed no side effects (7,6). Despite its great popularity among dentists, this type of topical anesthesia (i.e., Lidocaine-Prilocaine) has minimal anesthetic effects (8). Due to the prevalence of dental pain, formulating a topical product with a higher potency seems necessary.

There are very few studies on the evaluation and comparison of the effect of different topical anesthetics in dental treatment for pain reduction before needle insertion (10,9). Due to the lack of strong evidence in this field, the present study aimed to evaluate and compare the efficacy of applying topical Lidocaine-Prilocaine in the emulsion and liposomal forms at different concentrations, in reducing the pain of injecting local anesthesia in the oral cavity.

Materials and Methods

The present study was a randomized clinical trial with a split-mouth design conducted on 15 patients who were referred to a private dental clinic and needed injectable anesthesia for flap surgery in the posterior maxillary area (Figure 1. CONSORT flow diagram). The sample size was calculated according to a study by Özkiriş et al. (11) with 80% study power and α=0.05.

Figure 1. CONSORT flow diagram



Sample size formula: $n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\frac{\beta}{2}})^2 (s_1^2 + s_2^2)}{(\tilde{\mu}_1 - \tilde{\mu}_2)^2} = \frac{(1.96+0.84)^2 (1.22^2 + 0.96^2)}{(3.51-1.94)^2} \cong 15$

The protocol of this study was approved by the Research and Ethics Committee of Mashhad Dental School, Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.DENTISTRY.REC.1397.054), and all the included subjects signed a consent form before being enrolled in the study.

Patients diagnosed with periodontitis, whose treatment plan included flap surgery in the posterior sextant of the maxilla, were recruited. Patients were subsequently excluded based on the following exclusion criteria: 1) taking neuroleptics or non-steroidal anti-inflammatory medications 2) a history of systemic disease contraindicating surgery 3) any reported allergies to anesthesia.

The Lidocaine-Prilocaine emulsion and liposomal forms were prepared at Mashhad School of Pharmacy, Mashhad, Iran. To make the emulsion form, Lidocaine and Prilocaine were first weighed and mixed in a porcelain mortar. Afterward, the resulting mixture was mixed with a certain amount of non-ionic surfactant (Tween 80 and Span 80), and then the mixture was diluted with water until reaching the desired volume. Table I shows the values of each component. As for the liposomal form, lidocaine and prilocaine were first weighed and mixed in a porcelain mortar. Afterward, 1.5 ml of alcohol, cholesterol, as well as soy lecithin were added to the resulting mixture, and after heating, as well as melting the mixture, the solvent was removed in a rotary machine. Purified water and glycerin were then added to the resulting mixture and homogenized by a Sonicator. Table II shows the values of each component. After preparing the liposomal form, it was used to prepare products, as shown in Table I.

Table I. Component values of the liposomal form.

Purified Water (g)	Glycerin (g)	Soy listin (g)	Cholesterol (g)	Prilocaine (g)	Lidocaine (g)
Up to 100 ml	5	30	2	14.7	14.7

Table II. Component values of emulsion form and products derived from liposomal form

Products derived from liposomal form			Component values of emulsion form					
Purified Water	Liposome	Concentration (%)	Purified Water	Span80	Tween80	Prilocaine (g)	Lidocaine (g)	Concentration (%)
Up to 60 ml	2.8	2%	Up to 60 ml	0.3	0.7	2.1	2.1	2%
Up to 60 ml	5.20	5%	Up to 60 ml	0.3	0.7	3	3	5%
Up to 60 ml	61.21	5.7%	Up to 60 ml	0.3	0.7	5.4	5.4	5.7%
Up to 60 ml	41	10%	Up to 60 ml	0.3	0.7	6	6	10%

Four concentrations were provided for each of the emulsion and liposomal forms (2%, 5%, 7.5%, and 10%). A total of 30 mm of each of the eight substances were poured into eight identical containers. Allocation concealment was achieved by coding the containers; so that the containers with different anesthetic solutions were indistinguishable from each other (Figure 2). Randomization was performed using randomization.com website.

Figure2. Different concentrations of liposomal and emulsion forms of Lidocaine-Prilocaine topical anesthesia (A: liposomal form, B: emulsion form)

First, one of the four concentrations (2%, 5%, 7.5%, and 10%) of the emulsion form of the Lidocaine-Prilocaine topical anesthesia was applied on one side of the maxilla, and two weeks later, the four concentrations of the liposomal form were applied on the other side. These areas were randomly selected for topical anesthesia before injecting anesthesia into the vestibular area. After drying the injection site, the topical anesthetic was applied by a swab. It is noteworthy that in the present study, the topical anesthesia included 2% Lidocaine containing $\frac{1}{100000}$ epinephrine (Daroopakhsh, Tehran, Iran). After two minutes, the anesthetic solution was injected into the area, and the amount of pain caused by needle insertion and injection in each area was then measured using a visual analog scale (VAS). This study was designed as a double-blinded trial; the outcome assessors as well as the patients, were unaware of the contents of the numbered containers.

Results

The study population consisted of 15 participants, 9 male and 6 females; with a mean age of 44 years and an age range of 18-82 years. Solutions were classified into groups A (emulsion form) and B (liposomal form). Table III shows the concentrations of each solution.

Table III. Concentrations of the solutions

Solution	Concentration
$A_{1,}B_{1,}$	3%
$A_{2,}B_{2,}$	5%
$A_{3,}B_{3,}$	7.5%
$A_{4,}B_{4,}$	10%

The amount of perceived pain following needle insertion was statistically analyzed in two ways:

A) Comparison of pain between different concentrations of emulsion and liposomal forms:

As displayed in Table IV, Kruskal-Wallis test revealed that there was no statistically significant difference between different concentrations (2%, 5%, 7.5%, and 10%) of the liposomal form of Lidocaine-Prilocaine (P=0.642) and between different concentrations (2%, 5%, 7.5%, and 10%) of the Lidocaine-Prilocaine emulsion form (P=0.460).

Table IV. Comparison of pain reduction between groups

Group	Concentration (%)	Number	Mean	Standard deviation	Kruskal-Wallis test result
Emulsion	2%	15	2.55	2.65	χ^2=0.89
	5%	15	1.14	1.21	P=0.46
	7.5%	15	1.71	1.60	
	10%	15	2.62	2.26	
	overall	15	2.06	2.06	
Liposomal	2%	15	1.5	1.87	
	5%	15	1.75	1.28	
	7.5%	15	1.12	1.72	χ^2=0.68
	10%	15	1.75	2.07	P=0.64
	overall	15	1.48	1.66	

In the emulsion group, the highest mean belonged to solution A_4= 2.62, and the lowest mean was related to A_2= 1.14. In the liposomal group, solutions B_2= 1.75 and B_3= 1.12 demonstrated the highest and lowest mean VAS values, respectively.

B) Comparison of similar solutions (similar concentrations) in each group:

Based on Kruskal-Wallis test results, no significant differences emerged in terms of the recorded VAS parameters between different concentrations (2%, 5%, 7.5%, and 10%) of the liposomal and the emulsion forms of Lidocaine-Prilocaine.

C) General comparison of emulsion and liposomal forms

According to **Error! Reference source not found.**and the results of Kruskal-Wallis test, there was not any statistically significant difference between the total concentrations of the emulsion and liposomal forms of Lidocaine-Prilocaine (P=0.750).

Table V. General comparison of emulsion and liposomal forms

	Group	Number	Mean	Result
VAS	A	30	31.20	P=0.750
	B	30	29.80	Z=3.19
	Total	60		

Discussion

There are various local anesthetics for topical anesthesia, such as Lidocaine, Prilocaine, Benzocaine, and the Eutectic Mixture of Local Anesthetics in a 1:1 weight ratio (EMLA) (5). The efficacy of EMLA has been evaluated in previously conducted studies, with most of them demonstrating its superiority over other topical anesthesia formulas (12). However, Primosch et al. observed that in pediatric patients, the oral adhesive form of EMLA was not proven to be superior for reducing pain responses during local infiltration of anesthesia, in comparison with Benzocaine 20% in either oral adhesive or gel formulation (13).

The present study compared the effect of the emulsion and liposomal forms of Lidocaine-Prilocaine mixture in four concentrations of 2%, 5%, 7.5%, and 10% in altering the VAS scores of pain during the injection for flap surgery in the posterior maxilla**.** VAS is a simple and frequently used method for the assessment of variations in pain intensity, which has been confirmed to be reliable and valid (14)**.**

In the present study, no statistically significant difference was found in pain perception between patients who received either the emulsion or liposomal form of Lidocaine-Prilocaine as a topical anesthesia prior to injection.

Similar to the findings of the present study, in a previous study by Franz-Montan et al. (15), according to VAS parameters, the liposomal form of ropivacaine was not found to be efficacious in reducing pain during needle insertion, even in double concentration (2%) and with a longer application time (5 min)**.** However, some studies have reported that the liposomal form of anesthetics had an effect equal to or even greater than EMLA in the commercial formula. Paphangkorakit et al. (16) demonstrated that the liposomal Lidocaine encapsulation was able to improve topical anesthetic efficacy in reducing pain during anesthetic injection in the palatal mucosa, in comparison with a commercial formula. This inconsistency may be attributable to a different liposomal formulation used in their study (cholesterol and egg phospholipid 1:1, w:w, prepared by the sonication method).

In another study by Fisher et al. (17), the liposomal form of Tetracaine was shown to have superior effects in terms of reducing the pain of inserting a needle into the skin, compared to EMLA and non-encapsulated Tetracaine**.** Differences, such as the sample size and incorporating a placebo group, can cause differences between the results of the study by Fisher et al. and the findings of the present study. Moreover, they applied topical anesthesia for 30-60 min, which is much longer than the duration topical anesthesia was applied in the present study (2 min). The time interval between topical anesthesia application and injection ranged from 5 to 20 minutes in studies that demonstrated better results; which is much longer than the waiting time in this study (18).

Since liposomal formulas are reported to have a greater ability to penetrate through the mucosa and also their longer shelf-life; they are expected to be more effective in reducing pain. However, the results of the present study did not confirm this hypothesis, which can be due to the following reasons(19): anxiety before surgery, fear of needle injection, unrealistic and various patient responses depending on age and gender **(**women usually express higher levels of pain (20), the presence of saliva that removes medication, the presence of enzymes in saliva that may decompose the medication, and different thickness of the soft tissue that can affect the penetration of the medication.

Despite all the mentioned factors, attempts were made in this study to establish a dry and isolated environment as much as possible by using a compressed air stream and cotton rolls.

In the current study, based on the recorded VAS scores; there was no statistically significant difference the between the four different concentrations formulas (2%, 5%, 7.5%, and 10%) of emulsion and liposomal Lidocaine-Prilocaine in terms of pain reduction. This was similar to the findings of a study conducted by Sargolzai et al. in 2020 (21).

Like other studies, the present study did not report any evidence of allergy to anesthetics (17).

VAS test is only used for measuring pain severity (22)**,** and is not designed to measure the quality of pain since it is not sensitive enough to measure the difference between anesthetics.

Using the VAS method is considered one of the limitations of this study. Other methods should be used to evaluate the mechanisms of anesthetics to measure pain responses in addition to somatosensory effects, such as superficial tactile perception (18).

Based on the findings of the present study and the lack of significant differences between different concentrations of Lidocaine-Prilocaine lotion and different concentrations of liposomal forms of Lidocaine-Prilocaine in mucosal topical anesthesia, these liposomal

forms can be used as topical anesthetics with the same effects as the Lidocaine-Prilocaine lotion (23). It is recommended to conduct further clinical trials with a larger sample size to evaluate the effects of different topical anesthetics, as well as their relationship with age and gender, in other dental treatments (24). The formulation of nanosome forms of the above-mentioned compounds is also suggested.

Conclusion

Despite the longer substantivity of the liposomal form of Lidocaine-Prilocaine topical anesthesia on the mucosa than the emulsion form, the results of the present study indicated that different concentrations of the topical anesthesia did not significantly differ regarding their efficacy in pain reduction.

Conflict of interest

The authors declare there is no conflict of interest

Acknowledgment

None

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