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RESEARCH ARTICLE

Pilot Randomized Clinical Trial Study: Comparative Study of 10% Lidocaine Hydrochloride Solution with Lidocaine Prilocaine Emulsion Prior to Local Anesthetic Injection

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Abstract:

Background:

The pain caused by the injection of local anesthetic has been reported as one of the main complaints of dental patients. Topical anesthetics are widely used drugs in dentistry, mainly to control pain associated with the needle penetration in the administration of local anesthesia.

Objective:

The present study aimed to evaluate (5%, 7.5% and 10%) concentrations of lidocaine/prilocaine agent, compared to the common 10% lidocaine hydrochloride spray in the oral cavity.

Materials and Methods:

This was a split-mouth double-blind, randomized clinical trial pilot study. We randomized 15 patients, ages 35 to 64 years, with American Society of Anesthesiologists I and II with severe chronic periodontitis who were referred to the dental clinic for surgery, to receive 4 topical anesthetics (5%, 7.5%, and 10%) lidocaine prilocaine emulsion and 10% lidocaine hydrochloride topical anesthetic agent before local infiltration. Primary outcomes were assessing drug safety and pain level that measured by assessment of visual analog scale (VAS) scores of pain during LA injection in the first premolar and second molar in each maxillary quadrant in 15 patients corresponding to the posterior superior alveolar nerve (PSA) and secondary outcome was the relationship between age and gender regarding pain perception, and a total of 60 regions were analyzed.

Results:

Results revealed that there was no statistically significant difference between lidocaine hydrochloride and (5%, 7.5% and 10%) lidocaine prilocaine in terms of pain reduction when the 4 different compounds were compared. According to Spearman's rank correlation coefficient and Friedman test, the age and gender of the patients had an insignificant correlation with the anesthetic effects of the four studied solutions.

Conclusion:

Based on these results, age and gender have insignificant effects on the pain scores and it can be said that the four solutions do not have significant differences regarding their anesthetic effects; also, we did not find any adverse reactions by using 7.5% and 10% lidocaine/prilocaine agent.

Keywords: Topical anesthesia, Local anesthesia, Lidocaine hydrochloride, Lidocaine Prilocaine emulsion, Chronic periodontitis, Pain.

Article History

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1. INTRODUCTION

The pain caused by the injection of local anesthetic has been reported as one of the main complaints of dental patients.

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Topical anesthetics are widely used drugs in dentistry, mainly to control pain associated with the needle penetration in the administration of local anesthesia. Topical anesthetics can also be used to relieve discomfort caused by lesions in the mucosa, periodontal treatment, restorative treatments, and biopsy [1]. In the study by P Koppolu, VAS score in the direct needle group was 6.07 ± 1.09 [2]. For this reason, most of the dentists prefer

painless administration of LA injection using topical anesthetics prior to the injection. Various LA are available for topical use, such as lidocaine, prilocaine, benzocaine and EMLA [2]. It is very common to use the lidocaine hydrochloride spray as a topical analgesic to relieve toothache or reduce the pain of the injections. However, despite its popularity, it is not very effective in reducing pain. This could be attributed to its unfavorable bio adhesion and the poor possibility of the solution to confine at the preferred site [2]. There are various anesthetics available today that provide quick and long-lasting anesthesia, which have rarely been reported to cause neurological and systemic deficits [3]. According to studies, EMLA is more effective in this regard in comparison to lidocaine gel after Argon laser stimulation and increased the pain thresholds [4]. Moreover, it has been reported that EMLA cream can sometimes lead to regional pallor, flare, edema, an early burning sensation, and rare itching. In addition, it may also induce allergic and anaphylactic reactions, including hives, vascular edema, bronchospasms, and shock. Although rare, EMLA may result in methemoglobinemia in children. On the other hand, topical anesthetics have little side effects with easy administration and reduce pain caused by needle injections and can thus generate positive responses towards dental treatment in patients [1, 5].

Few studies have been conducted with the aim of evaluation and comparison of the effects of local anesthesia on patients. Furthermore, most of these studies address the general effects of anesthetics. Therefore, due to the role that anesthesia plays for patients and lack of information in this regard, the present study aimed to investigate and compare the efficacy of (5%, 7.5%, and 10%) topical EMLA and 10% lidocaine hydrochloride spray in mucosa prior to anesthesia injection.

2. MATERIALS AND METHODS

This randomized, double-blind, split-mouth clinical trial pilot study compared the efficacy of four different anesthetic solutions and this study was approved by the Research and Ethics Committee of Mashhad University of Medical Sciences and each participant signed an informed consent form.

The selected solution included 10% lidocaine hydrochloride solution and three different formulations of EMLA with concentrations of 5%, 7.5%, and 10% (2.5 to 5 wt%), which were made using a non-ionic emulsifier. The used mixture of lidocaine and prilocaine bases in this study was a eutectic physical mixture which had a melting point of less than 20°C. Therefore, by physically mixing the two materials and grinding them, a clear, viscous liquid is obtained.

This liquid is converted to thermodynamically and kinetically stable emulsions by non-ionic emulsifiers (tween 80 and span 20). Different concentrations of these emulsions were prepared in water and used as formulations with the desired concentrations. Lidocaine and prilocaine are two compounds that have low water solubility; therefore, a eutectic mixture with non-ionic emulsifiers was used in order to increase their water solubility. This mixture was used in the preparation of an oil-in-water emulsion with concentrations of 5%, 7.5%, and 10%. These three substances and the lidocaine solution were placed in containers which were numbered from 1 to 4 so that

the dentist was unaware of the anesthetic agents.

2.1. Sample Size Calculation

This was a pilot investigation. Our sample size, with the level of significance at 0.05 and medium effect size difference in groups, the inclusion of 15 patients in each group would result in a power of 80%.

2.2. Sample Selection

Fifteen subjects randomly (computer generated table) selected from the patients attending the dental clinics of the Mashhad University of Medical Sciences due to moderate to severe chronic periodontitis, who needed to receive bilateral administration of local anesthesia, were invited to participate in the study.

The inclusion criteria consisted of 1) the need for flap surgery of maxilla on both sides, 2) not afflicted with systemic diseases that prevent surgery, 3) no usage of neuropathic pain medications or NSAIDs, 4) not allergic to anesthesia, 5) possession of the desired teeth. 6) American Society of Anesthesiologists (ASA) physical status I or II.

The Exclusion criteria consisted of known allergy or contraindications to use anesthetic materials (lidocaine and prilocaine), patients taking sedatives, use of analgesics and anxiety medications for 2 weeks before the study, or any other drugs that could have affected pain perception.

Patients were fully informed before the study about the possibility of incomplete anesthesia, adverse effects and their informed consent obtained. Thereafter, eligible participants took part in both of the 3 test groups: test (topical anesthetic, EMLA 5%, 7.5%, and 10% wt.) and 1 control (10% lidocaine hydrochloride) on the first premolar and second molar, the randomization related to the product to be used on each side of the mouth was done, through the toss of a coin, prior to proceeding with the administration of local anesthesia.

2.3. Experimental Procedure

After clinical examinations and asking questions about general and oral health and behavioral characteristics.

The procedure was done by 1 student, in the last semester of the course of dentistry. After randomization, the vestibular mucosa, the first premolars and second molar teeth were dried by dental air-water spray and isolated with gauze. Afterward, 2 of the test solutions were applied to the selected area by a swab in the first premolar and second molar area. Neither the researcher nor the patient knew which topical product was being used, resulting in a double-blind situation. Infiltration was done 3 min later for the PSA nerve, according to the study by Mishra [2]. Subsequently, the pain was measured by a visual analog scale (VAS) in which 0 was no pain and 10 indicated severe pain. In the next session after 4 weeks, the same procedure was carried out on the other quadrant of the maxilla, on the vestibular mucosa of the identical teeth, using lidocaine and remnant EMLA. In all the groups, buccal infiltration of 1.8 mL of 2% lidocaine with 1: 100,000 epinephrine (Darupakhsh, Tehran, Iran) was carried out.

2.4. Statistical Analysis

Statistical analysis was performed using statistical packages for Social Science (SPSS) 15. The Shapiro–Wilk test showed data was not normally distributed, therefore differences on the VAS between the groups were tested using the Friedman test. The significance level was established at 5%.

For the relationship between topical anesthesia and age, we used a nonparametric measurement test; Spearman's rank correlation coefficient and the correlation between the gender of the participants and the efficacy of the anesthetic agents were measured by Friedman test.

3. RESULTS

A total of 15 patients participated in the study, out of which 6 were men and 9 were women with

an average age of 47.73 ± 9.49 years, ranging from 35 to 64 years. A total of 60 sites were included. It was observed that the reported VAS was at least 7.5% EMLA (0.80 ± 1.01) topical anesthesia. However, the four solutions had no significant difference in this regard ($P=0.199$) (Table 1).

Moreover, for the correlation of average age (47.73 ± 9.49) and the anesthetic effect of EMLA and lidocaine topical anesthesia Spearman's rank correlation coefficient was calculated. The findings revealed that no statistically significant difference was observed between the topical anesthetic agents neither EMLA nor lidocaine. It was observed that this correlation was higher with 7.5% EMLA (.490) and least for 5% EMLA (.110) but this relationship was not significant ($p=.120$ and $p=.697$ for 7.5% and 5% EMLA, respectively) (Table 2).

The results of this study revealed that 10% EMLA was the least effective anesthetic solution for male participants. Similarly, 7.5% EMLA was the least effective anesthetic solution for female participants, respectively. In order to determine whether there was a significant correlation between the gender of the participants and the efficacy of the anesthetic agents, the normality of the data regarding the different solutions for both genders was examined. Based on the results of the Shapiro–Wilk test, the distribution of the data was not normal, and despite using different conversions, it remained the same. Therefore, the Friedman test was used and the results indicated that there was no significant difference in the anesthetic effects of the four solutions regarding the gender of the participants ($p=0.270$ and $p=0.439$ for male and female, respectively) (Table 3).

We found no unwanted or allergic complication with lidocaine/prilocaine groups, but the possibility was considered and the surgeon was ready for it.

4. DISCUSSION

In the present study, we evaluated and compared the efficacy of four topical anesthetics efficacy of three topical anesthetics (5%, 7.5%, and 10% EMLA with concentrations of 10% lidocaine hydrochloride spray) before infiltration in altering VAS scores of pain during LA injection during full mouth periodontal flap surgery and its relationship with age and gender. Painless administration of lidocaine anesthesia injection during any procedure is an important consideration. Topical anesthetics have been used for a number of years for reducing pain during injections.

Table 1. Comparison of the anesthetic effect of the four studied solutions.

Friedman Test	Median ±IQR*	Mean±SD**	Emulsion
X ² =4.65 P=0.199	1.00±1.00	1.20±1.37	5% EMLA***
	1.00±1.00	0.80±1.01	7.5%EMLA
	0.00±1.00	0.87±1.46	10%EMLA
	1.00±2.00	1.40±1.59	lidocaine

* Interquartile range. ** standard deviation. ***lidocaine-prilocaine emulsion.

Table 2. Correlation of age with the anesthetic effect of the studied solutions (n=15).

Age		5% EMLA	7.5% EMLA	10% EMLA	Lidocaine
	Spearman's correlation coefficient	0.110	0.419	0.170	0.165
	P value	0.697	0.120	0.544	0.558

Table 3. Comparison of the anesthetic effects of the four studied solutions on different genders.

Gender	Solution	Mean±SD	Median ±IQR	Friedman Test
Male	5% EMLA	0.50±0.55	0.50±1.00	X ² =3.92 P=0.270
	7.5% EMLA	0.83±1.17	0.50±2.00	
	10% EMLA	0.17±0.41	0.00±0.00	
	lidocaine	1.00±1.09	1.00±2.00	
Female	5% EMLA	1.67±1.58	1.00±3.00	X ² =2.71 P=0.439
	7.5% EMLA	0.78±0.97	1.00±1.00	
	10% EMLA	1.33±1.73	1.00±3.00	
	lidocaine	1.67±1.87	2.00±3.00	

EMLA is an emulsion containing the oily phase of the mixture of eutectic lidocaine and prilocaine at a 1:1 ratio [2]. The practice of measuring the quantity of pain is extremely difficult, but not impossible. Huskisson has stated that “pain is a psychological and indexical experience and the observer can never directly measure it” [6, 7]. The method used to measure the pain in a randomized clinical trial can directly affect the outcomes obtained in a study. In the present study, we used the VAS, which is an instrument with good clinical relevance; it is frequently used because it has good validity for determining the perceived intensity of pain, it is easily understood by patients, and it is a reliable method for representing pain [1]. The data obtained in this study showed that there was no statistically significant difference in pain perception between the EMLA topical anesthetic and the lidocaine hydrochloride spray groups during the administration of local anesthesia. Svensson P [4], J haasio [8], and Meechan *et al.* [9] found similar results in their studies, showing that the topical anesthetic EMLA is no more effective than lidocaine in reducing pain during injection of local anesthesia in the oral cavity. However, Mishara *et al.* reported that prilocaine gel was more effective than other topical anesthetics based on VAS, since lidocaine and benzocaine were absorbed more slowly compared to other topical anesthetic agents [2, 10]. Moreover, the findings of Bromage PR [11] indicated that the anesthetic effect of lidocaine hydrochloride was insignificant and short, also the study performed by Abu Al-Melh *et al.* concluded that lidocaine/prilocaine topical anesthetic was more significant than placebo [12].

The pain scores in previous studies indicate that the performance of all topical anesthetics increases until a maximum of 30 min after application [4, 13]. Moreover, it is possible for the anesthetic effect of lidocaine to last 10-15 min longer for some patients [14]. Based on the results of recent studies, the onset of action 2.5% EMLA is 3 min, which increases by time if it remains within the mouth [12, 15, 16]. In the present study, differences in VAS ratings by age and gender were not significant. According to the literature review, few studies have investigated the efficacy of the usage of topical anesthetics prior to intravenous injections in children and adults [11]. Therefore, the relationship between age and the efficiency of the anesthetic agents has remained unexplored. The findings of a study that aimed to investigate the efficacy of local anesthetics in children revealed that the results of the usage of topical anesthetics and their placebo did not differ in children [16, 17]. Furthermore, the results of the present study showed that there is an insignificant correlation between the age and the VAS scores for the selected anesthetic solutions.

Various epidemiological studies have indicated an increase in the prevalence of pain in females. Results of clinical and laboratory studies have also shown gender-based differences in pain threshold that could be due to the nociceptors and gonadal hormones [18]. Moreover, the effect of sex hormones on analgesic neurochemical mediators has been controversial [19, 20]. Previous research has indicated that females have lower pain thresholds, and are less tolerant of harmful stimuli and pain compared to males [21, 22]. Findings of a study performed by Gursoy *et al.* on the gender-based differences

regarding the perception of pain indicated that males felt less pain, compared to females in both EMLA and placebo groups [19]. Few researchers have investigated the relationship between gender and topical anesthesia. However, in the present study, using the Friedman test, no significant gender-based difference was observed regarding the VAS score.

Topical anesthetics can present adverse effects such as allergy, methemoglobinemia, plasmatic alterations [1] and even bland taste [23]. In EMLA, the amount of topical anesthetic used must be considered, principally in children [1].

In this study, there were some weaknesses that need to be addressed in future studies. Increasing the sample size with a 1:1 allocation ratio would be advantageous besides facilitating the investigation of the effect of age, gender, ethnicity, and psychosocial factors on the outcome of the subject's response to pain after local anesthesia injection and reducing the possibility of bias, also prior to this study there was no publication using 7.5% and 10% EMLA topical anesthesia, so we recommend to use different concentrations of EMLA in future studies.

CONCLUSION

Based on the results, we conclude that within the limitations of this study, no significant difference was observed in the use and efficiency of 4 anesthetic solutions in the present study. Moreover, there was an insignificant relationship between the age and efficiency of the studied solutions and also no adverse effects were presented.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Research and Ethics Committee of Mashhad University of Medical Sciences, Iran.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

All patients participated on a voluntary basis and gave their informed consent.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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