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Palatal needle-free anesthesia for upper molars extraction. A randomized clinical trial

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ABSTRACT

Background: The aim of this study was to compare the ability of liposomal and non-liposomal lidocaine and prilocaine in hydrogel formulations to promote topical anesthesia in palatal mucosa during upper molar extractions.
Methods: In this randomized, cross over, triple-blinded clinical trial, a liposomal and a non-liposomal formulation of the eutectic mixture of local anesthetics, 2.5% lidocaine and 2.5% prilocaine, were used to promote palatal anesthesia without the local anesthetic infiltration during bilateral upper molars extractions.
Results: From the total of 40 patients included in this study, the non-liposomal eutectic lidocaine-prilocaine formulation failed in 40% of cases, unlike the liposomal formulation, which was effective for all patients (Fisher's exact test, $p < 0.0001$). Furthermore, the liposomal formulation (26.75 ± 7,47 min) induced longer anesthesia duration (t-test, $p < 0.0001$) than the non-liposomal formulation (16.78 ± 4.75 min). No mucosal ulceration or discomfort was reported for both formulations.
Conclusion: The liposomal formulation was able to induce adequate anesthesia in palatal mucosa during dental extraction, avoiding the local anesthetic infiltration. For the first time, a topical formulation allowed upper molars surgical removal without injection of any local anesthetic agent into palatal mucosa in adults.

1. Introduction

Fear of pain is one of the major common reasons for patient phobia. Local anesthesia, which is the most efficient measure to control pain, is commonly related to anxiety and fear (Meechan et al., 2005). The use of topical anesthetics prior to the needle insertion and injection of local anesthetic agents is a helpful strategy to reduce discomfort or pain. The injection of local anesthetics into the palatal mucosa is considered one of the most painful experiences in dental practice due to the tight binding between the palatal mucosa and the underlying periosteum, and its extensive nervous supply (Kravitz, 2006).

Alternative interventions have been also explored to promote comfort in dentistry treatments such as hypnosis (Abdeshahi et al., 2013) and anxiety reduction protocols (Dantas et al., 2017; Hermes et al., 2007). Furthermore, some advances in formulations and techniques for local anesthesia in the palatal mucosa, such as

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pressure-injection (Kravitz, 2006), palatal cooling (Harbert, 1989), low palatal injection rate (Meechan and Day, 2002), and computer-assisted anesthesia systems (Friedman and Hochman, 1997) are considered important (Sharma et al., 2014). The main goal of these strategies is to provide comfort since even needle insertion might cause pain (Munshi et al., 2001). The search for an effective topical agent is continuous, once the most common topical anesthetic agents fail to provide pain reduction during local anesthetic injection, especially in palatal mucosa (de Freiras et al., 2015; Fukayama et al., 2002; Gill and Orr, 1979).

A eutectic mixture of two local anesthetics, 2.5% lidocaine and 2.5% prilocaine (EMLA), indicated for dermal application, has shown promising results when applied on palatal mucosa. Meechan et al. (2005) reported that only a commercial EMLA® cream, used as a topical anesthetic agent, was able to abolish the pain during a palatal puncture.

Liposomes have been proposed as efficient drug carriers, showing promising results in clinical trials (Franz-Montan et al., 2017; Paphangkorakit et al., 2012; Tofoli et al., 2011). First described in 1965 (Grant and Bansinath, 2001), liposomes are formed when dry lipid films are re-suspended in aqueous solution (Fritze et al., 2006). Liposomes consist of polar layers linked to two nonpolar layers, tending to form bilayers spontaneously and structurally similar to cell membranes. Liposomal entrapment allows the controlled release of the local anesthetic, prolonging anesthesia duration, and reducing both cardiovascular and central nervous system toxicity (de Araújo et al., 2003).

Liposomal lidocaine 5% was similar to a commercial EMLA® formulation in promoting effective dermal anesthesia (Friedman et al., 2001). A liposomal 2% ropivacaine topical formulation was effective to prevent pain during needle insertion on palatal mucosa, but it did not prevent the pain during the local anesthetic injection (Franz-Montan et al., 2012b). Despite that the commercial EMLA® presented superior anesthesia during both needle insertion and local anesthetic infiltration, it was associated with ulcerative lesions on palatal mucosa (Franz-Montan et al., 2008).

Therefore, the aim of this study was to compare the ability of liposomal and non-liposomal lidocaine and prilocaine in hydrogel formulations to promote topical anesthesia in palatal mucosa during upper molar extractions.

2. Methods

2.1. Inclusion and exclusion criteria

The present study selected healthy patients who had an indication of two upper-molar extractions on opposite sides due to unrestorable caries. All volunteers signed a written informed consent form. Subjects with a history of allergy to any of the formulation components, methemoglobinemia, addiction to alcohol or recreational drugs, pregnancy, or phobia were not included.

2.2. Formulations

The liposomes were prepared as previously described by de Araujo et al. (2008). The entrapment of the anesthetic formulation was obtained by an ultrasonic dental scaler (Paphangkorakit et al., 2012). The same operator prepared both lidocaine/prilocaine (lido/prilo) and liposomal-lido/prilo gels, which had equal color, flavor, smell, and viscosity. Lido/prilo was obtained by mixing 2.5% lidocaine and 2.5% prilocaine in a gel matrix prepared using the components listed in Table 1. Liposomal-lido/prilo was obtained by encapsulation of 2.5% lidocaine and 2.5% prilocaine in liposomes suspension and posterior mixing to the same gel matrix (Table 1) (Franz-Montan et al., 2016). Afterward, both gels were stored in coded tubes in order to guarantee the blindness of the study. Both volunteers and the operator (surgeon) were not able to identify the formulations.

2.3. Study design

In this crossover randomized triple-blinded clinical trial, after the randomization procedure performed with sealed envelopes, the patients were randomly allocated into two groups according to the first topical anesthetic used in the first section: hydrogel of 2.5% lidocaine and 2.5% prilocaine (lido/prilo) as first protocol; or liposomal of 2.5% lidocaine and 2.5% prilocaine hydrogel (lipo-lido/prilo) as the first protocol for palatal topical anesthesia. Each patient was subjected to two surgical procedures, on two separate days with a minimum interval of two weeks between the two procedures, to remove upper molars from each side. The second procedure was carried out with a different topical anesthetic gel from the one used on the first procedure, as the previous randomization. The local anesthesia was performed by infiltration in the buccal fornix area of the tooth to be removed by injection of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine. Then, after drying the area with gauze, 0.3 g of the assigned formulation was applied directly on the palatal mucosa, approximately 1 cm from the cervical gingiva of the tooth to be extracted. Both formulations were applied for 2 min (Malamed, 2019) before surgery began and they were left on mucosa until the end of the dental extraction procedure.

The surgery began immediately after 2 min of topical anesthesia application, and the total duration of surgery was recorded. The duration of successful palatal anesthesia was assessed by a blinded third investigator using a blunt-needle insertion every minute after the end of the surgery until any pain was verified (Franz-Montan et al., 2017). Therefore, the total anesthesia duration was the sum of surgery duration and the post-surgery anesthesia duration.

Patients reporting pain during any time of the procedure received a palatal injection of 0.6 mL of 2% lidocaine with 1:100,000 epinephrine. The moment of pain complaint was recorded, being considered as topical anesthesia failure.

2.4. Sample size

This crossover randomized triple-blinded clinical trial had anesthesia success as the most important objective. A proportion of 99% success for one group and 80% success for the other group would need a sample of 40 volunteers to provide 80% of power, assuming a significance level of 5% for an equal proportion of the samples since it was a crossover clinical trial.

2.5. Statistical analysis

Statistical tests were performed according to the data distribution (Shapiro–Wilk test). The anesthesia success was observed by the Fisher's exact test. Duration of both surgery and anesthesia was analyzed by t test. The influence of surgery duration on the success

Table 1
Gel matrix composition used to prepare both EMLA formulations (adapted from Franz-Montan et al., 2016).

Component	Function
Carbopol (2%)	Gelling agent
Propylene glycol (5%)	Solvent and wetting agent
Methylparaben (0.1%)	Preservative
Deionized water	Solvent
Triethanolamine	Alkalinizing agent (pH = 7.0)

or failure of topical anesthesia was observed by Kruskal–Wallis test. For all tests, the level of significance was set at 5% and all calculations were performed by BioEstat 5.0 (Mamirauá Institute) and GraphPad 7.03.

3. Results

Most of the patients were female (70%) aging from 18 to 60 years. The total duration of the surgical procedure, including suture, did not differ ($p = 0.95$) between lido/prilo (14.0 ± 6.3 min) and lipo-lido/prilo (14.1 ± 7.8 min) groups.

Lipo-lido/prilo provided successful topical anesthesia in all patients (100% of cases), lasting until the end of surgery. Lido/prilo failed in 40% of cases, which presented significantly lower anesthesia success ($p < 0.0001$) than lipo-lido/prilo. In lido/prilo group, anesthesia failure occurred mostly during tissue incision, and in one case, it was reported during tissue detachment. Those patients that reported pain during any time of the procedure, in the lido/prilo group, received a palatal injection of 0.6 mL of 2% lidocaine with 1:100,000 epinephrine so the procedure could be completed. The time spent for the surgical procedure did not influence ($p = 0.74$) the success of the topical anesthesia (Fig. 1).

Fig. 2 shows the topical anesthesia duration according to the groups. Lipo-lido/prilo group (26.75 ± 7,47 min) induced longer anesthesia duration than lido/prilo (16.78 ± 4.75 min).

No intra- or post-operatory adverse effects, such as ulcerations and discomfort, were observed for either formulation.

4. Discussion

An effective local anesthesia without injecting local anesthetics, i.e., using only topical anesthesia for dental procedures, is one of the main goals in pain control in dentistry (Meechan, 2000). Palatal mucosa has been used to evaluate the efficacy of local anesthetics. This tissue is highly sensitive to pain due to its tight adhesion to the periosteum and its numerous free nerve endings (McArdle, 1997). In addition, permeation of lidocaine and prilocaine, free or associated with poly (ε-caprolactone) nanocapsules, in carbopol hydrogels are reduced across porcine palatal mucosal epithelium when compared with porcine buccal mucosal epithelium (Muniz et al., 2018). Therefore, this mucosa was used in the present study due to its histological arrangement, showing a thick layer of keratin that could also influence permeation as shown previously (Meechan, 2002; Muniz et al., 2018).

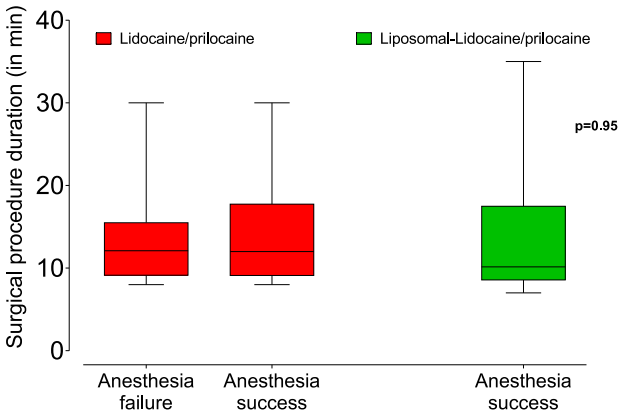

Fig. 1. Duration of the surgical procedure considering the anesthesia success in both groups. Central line = median; box = 1st and 3rd quartiles; whiskers = max and min values.

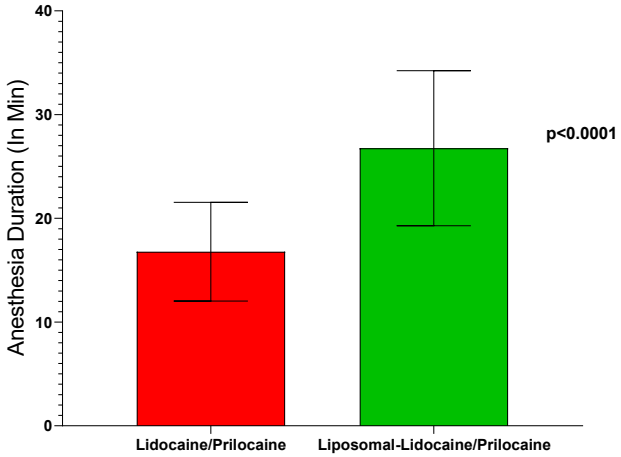

Fig. 2. Anesthesia duration (mean ± SD) in both groups.

Anesthesia of the palatal mucosa without local anesthetic injection is desirable, but there is no evidence to date regarding an effective topical anesthetic agent (Franz-Montan et al., 2017). The present study showed, for the first time, a topical formulation anesthetizing the palatal mucosa for a sufficient time to proceed with dental extractions without local anesthetic injection. Our results also indicated that the proposed liposomal formulation could be effective when used prior to the injection of local anesthetic solution into palatal mucosa.

Despite some conflicting results, the encapsulation of the anesthetic solution into liposome can be a good option by increasing the efficacy of topical anesthesia (Franz-Montan et al., 2017). The anesthetic efficacy of commercial EMLA® in palatal mucosa has been considered superior when compared with traditional topical agents (Franz-Montan et al., 2012b, 2017). Franz Montan et al. (2015) showed similar pain reduction between commercial EMLA® and a liposomal formulation of lidocaine 5% when both were applied for 2 min before needle puncture and injection in palatal mucosa. Usually, commercial EMLA® requires longer application time, varying from 4 to 30 min, which is considered not adequate for clinical procedures in oral mucosa (Franz-Montan et al., 2008; 2012b, 2017, Moragas et al., 2015; Paphangkorakit et al., 2012). Longer periods could cause ulceration of palatal mucosa (Franz-Montan et al., 2008). In the present study, the lipo-lido/prilo has been in contact with the palatal mucosa during the surgery and it did not cause ulceration or other adverse effects. Probably, the vehicle used in our study, i.e., the hydrogel, had an important role to avoid the direct toxicity on palatal mucosa, since the lido/prilo group also did not show adverse effects.

Most of the studies regarding topical anesthesia on oral mucosa did not explore the anesthesia duration. A review on topical anesthesia in Dentistry discussed the pain during local anesthetic injections but did not observe the topical anesthesia duration itself (Meechan, 2000). Probably, the high proportion of anesthesia failure observed when the traditional topical agents were used is the main cause for the small amount of attention on topical anesthesia duration (de Freiras et al., 2015; Franz-Montan et al., 2010b, 2012a,b; Paphangkorakit et al., 2012).

In a clinical trial, Franz-Montan et al. (2010a) compared 20% benzocaine and liposomal 2% ropivacaine applied on the buccal fornix of the lateral incisor. They observed 15 min as the maximum

duration of anesthesia for both formulations. It is very likely that both the local anesthetic used and the drug carrier markedly affected the results. In the present study, the duration of the anesthesia on the palatal mucosa was longer than 25 min when the liposomal formulation was used and allowed painless dental extraction.

Usually, papers on topical anesthesia in dentistry assess pain during puncture or infiltration of the anesthetic solution (Paphangkorakit et al., 2012; Malamed, 2019; Meechan, 2002; Franz-Montan et al., 2012b, 2015, 2010b). From nine studies using commercial EMLA in dentistry, five were described using it as topical anesthesia before the local anesthetic infiltration. The other four studies related its use before scaling and root planing (Franz-Montan et al., 2010a); unlike the present study, none of the aforementioned used the topical anesthetic formulation to tissue surgical manipulation.

Oraqix® is an EMLA formulation developed for use in the periodontal pocket (Friskopp et al., 2001) which produces a sufficient anesthetic effect for scaling and root planning (Donaldson et al., 2003). However, the pain reported by patients using or not using Oraqix® in the study by Donaldson et al. (2003) could be considered as mild (Meechan et al., 2005), indicating that the periodontal procedure would be tolerable without Oraqix®. In the present study, all procedures were surgical interventions demanding adequate local anesthesia, as confirmed by the volunteers that needed anesthetic infiltration when the lido-prilo gel failed. In addition, the success of the formulation was considered only in the total absence of pain.

Paphangkorakit et al. (2012) observed anesthesia efficacy to relieve the pain on palatal mucosa after topical anesthesia with liposomal 2% lidocaine by using a pinprick model. They used a liposomal formulation made by simply mixing liposomes and 2% lidocaine with dental ultrasound and reported lower values on VAS for the liposomal formulation compared to a gel of 18% benzocaine plus 2% tetracaine. In the present study, the same mixture methodology was used due to its simplicity and efficacy and our results presented even better since it was used for a surgical procedure and there was no pain reported by the volunteers when using the liposomal formulation.

Liposomal formulations with varied vesicle sizes have been studied since this factor directly affects the anesthesia latency (Franz-Montan et al., 2007a,b, 2010a,b,c, 2012a,b). Other factors, such as surface charges, and the lipid used to prepare the carrier, also influence the latency (Choi and Maibach, 2005). The present study did not focus on laboratory physical-chemical characterization of the liposomal formulation used in the present study, such as rheological, mucoadhesion and kinetics properties. However, the clinical results on lipo-lido/prilo and lido/prilo groups indicated that both formulations differed and the lipo-lido/prilo is clearly more effective, since it resulted in successful anesthesia for all patients.

Despite its good results, our study also brings more questions due to its own limitations, such as the characterization of the formulation. Maybe a laboratory focused study could determine if the liposomal particle size can influence results, analyzing drug delivery kinetics properties of the formulations. Our study also did not explore the stability of the formulation, the encapsulation efficacy or the time of permanence on mucosa. With respect to those limitations, we cannot affirm exactly why the lipo-lido/prilo hydrogel presented those good results.

Considering the limitations of the present study and the aforementioned good results for the liposomal formulation, new questions need to be answered. Further studies are necessary to evaluate both lipo-lido/prilo hydrogel efficacy in other clinical scenarios, such as periodontal procedures and minor soft tissue interventions, and laboratory analysis, which could help to understand what exactly has improved the lipo-lido/prilo hydrogel.

5. Conclusions

The present clinical trial shows a remarkable achievement in topical anesthesia on the oral mucosa. For the first time, a topical anesthetic formulation allowed upper molars surgical removal without injection of any local anesthetic agent into palatal mucosa in adults. The liposomal lidocaine/prilocaine hydrogel proved to be better than non-liposomal lidocaine/prilocaine hydrogel and sufficient to promote anesthesia on palatal mucosa, allowing realization of the full procedure of upper-molar extraction without any pain.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This clinical trial was approved by the Sergipe Federal University Human Health Research Ethics Committee (CAAE: 39185414.0.1001.5546), additionally, it was submitted to the Brazilian Clinical Trials Registration (ReBEC) (registration: RBR-36bxjx; UTN: U1111-1168-7335).

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Conflict of interest

Klinger de Souza Amorim declares that he has no conflict of interest. Michelle Franz-Montan declares that she has no conflict of interest. Francisco Carlos Groppo declares that he has no conflict of interest. Bruno Vilela Muniz declares that he has no conflict of interest. Jaiza Samara Macena de Araújo declares that she has no conflict of interest. José Vânison Ferreira Santana declares that he has no conflict of interest. Anne Caroline Gercina Carvalho Dantas declares that she has no conflict of interest. Eneida de Paula declares that she has no conflict of interest. Liane Maciel de Almeida Souza declares that she has no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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