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Original contribution

Liposomal encapsulation improves the duration of soft tissue anesthesia but does not induce pulpal anesthesia☆

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Abstract
Study Objective: To compare the topical and the pulpal anesthesia efficacy of liposomal and plain benzocaine formulations.
Design: Double-blinded, randomized crossover study.
Setting: University ambulatory dental center.
Patients: 30 ASA physical status I volunteers.
Interventions: Volunteers received, in three different sessions, topical application of liposome-encapsulated 10% benzocaine (LB10), 10% benzocaine gel (B10), and 20% benzocaine gel (B20) in the right maxillary canine mucobuccal fold.
Measurements: Pain associated with the needle insertion was rated by visual analog scale (VAS) and the duration of topical anesthesia was recorded. Pulpal anesthesia was evaluated using an electric pulp tester.
Main Results: VAS values (median, 1st - 3rd quartiles) were 17 cm (11 - 25), 14 cm (3 - 22), and 21 cm (9 – 21) for B10, LB10, and B20, respectively. No differences were noted among the groups (Friedman test; $P = 0.58$). Soft tissue anesthesia was also not different. The LB10 [10 (8 - 12) min] showed longer soft tissue anesthesia (Friedman test; $P < 0.01$) than the other agents [B10 = 8 (5 - 10) min, and B20 = 7 (6 - 9) min]. None of the topical benzocaine formulations tested induced pulpal anesthesia.
Conclusions: The encapsulation of benzocaine into liposome increased the duration of soft tissue anesthesia. However, it did not induce pulpal anesthesia.

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1. Introduction

Injection pain is still a problem in dentistry [1,2]. Topical anesthesia has been widely used to reduce this pain [3,4]. Benzocaine is one of the most used anesthetic agents, especially in pediatric dentistry [4], due to its characteristics of rapid onset of action (30 sec), acceptable taste, lack of systemic absorption, and effectiveness [5,6]. Despite these advantages, adverse reactions such as methemoglobinemia have been documented after topical benzocaine use [7,8].

Pulpal anesthesia induced by topical application of local anesthetics would be of great interest in dentistry. Although Vickers and Punnia-Moorthy [9] observed pulpal anesthesia after topical application of eutectic mixture of local anesthetics (EMLA), no other study was able to show the same result [10,11].

In regional anesthesia, liposome-encapsulated anesthetics have shown better results than the corresponding plain local anesthetic formulation, including longer duration of action, reduced plasma levels, and less toxicity in the cardiovascular and central nervous systems. These actions are probably the result of maintenance of the local anesthetic at the site of injection over a prolonged period of time [12,13]. The encapsulation of both ester and amide local anesthetic agents provided a better overall anesthetic effect on intact skin of humans than did the non-liposomal formulations [14-18].

Several liposomal-benzocaine formulations showed sustained-release properties and an intense anesthetic effect in rabbit conjunctiva [19]. In addition, pain relief was observed after the use of ropivacaine liposomal formulation on oral mucosa prior to a local anesthetic injection [11]. The aim of the present study was to compare the topical and the pulpal anesthesia efficacy of liposomal and plain benzocaine formulations in dentistry.

2. Materials and methods

This study received approval by The Ethical Committee of Piracicaba Dental School, State University of Campinas, Piracicaba, Brazil, and all volunteers provided written, informed consent. The clinical effectiveness of three topical benzocaine formulations on the oral mucosa was evaluated in a randomized, crossover, double-blinded trial. Thirty healthy volunteers (15 women and 15 men), 18 to 26 years of age (21.4 ± 2.4 yrs), were scheduled for three sessions of topical anesthesia tests, spaced at least one week apart. All volunteers were in good health, had no allergic history to benzocaine or any other components of the topical formulations, and were not taking any other medication.

Prior to the experiment, the amount of topical anesthetic used for reducing injection pain in the oral mucosa was estimated. Sixty mg of each topical anesthetic was evaluated: liposome-encapsulated 10% benzocaine gel, 10% plain benzocaine gel, and 20% benzocaine gel (Benzotop; DFL Ind Com Ltda, Rio de Janeiro, Brazil). Liposome-encapsulated 10% benzocaine gel and 10% plain benzocaine gel formulations were prepared at the Department of Biochemistry, Institute of Biology, University of Campinas, Brazil, based on a patented method (required patent INPI #PI0704542-5) [20].

At the beginning of each appointment and before any topical application, the baseline vitality of the right maxillary canine was recorded (6 measures spaced two min apart) using a pulp tester (Analytic Technology Corp., Redmond, WA, USA). The tooth was free of caries, large restorations, periodontal disease, past endodontic treatment, and history of trauma or sensitivity. Fluoride toothpaste was used on the probe tip of the pulp tester as a conduction media so as to measure pulpal response [11].

The topical anesthetics were applied on the canine's maxillary buccal fold using a cotton swab, over two minutes. After this period, the mucosa was gently wiped and rinsed with water.

The following parameters were evaluated right after the removal of each topical anesthetic:

Perception of pain during needle insertion: simulation of local infiltration was performed by inserting a 30 gauge-dental needle until periosteum contact was reached. Volunteers were asked to rate their pain perception on a 10-cm visual analog scale (VAS), with end points 0 ("no pain") and 10 ("unbearable pain").
Duration of soft tissue anesthesia: right after the topical application, the volunteers inserted a sharp explorer into the alveolar mucosa every minute until cessation of numbness [11].
Influence on pulpal response: An electrical stimulus was applied by using the electrical pulp tester every two minutes for 20 minutes, from the time of topical anesthetic application. Pulpal anesthesia was defined as the absence of the volunteer's response to the maximal output (300 V, 0.08 mA) of the pulp tester, indicated as the "80" reading [21].

2.1. Statistical analysis

The results were compared by the Friedman test and Wilcoxon sign-ranked test for pair-wise comparison as

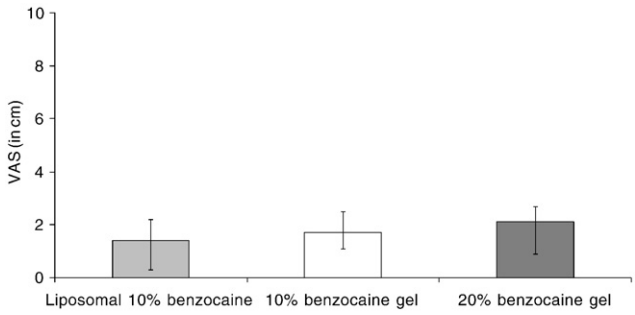

Fig. 1 Visual analog pain scale (VAS) scores, as rated by the volunteer after needle insertion. Bars = medians and error lines = upper and lower quartiles. No statistically significant difference was observed among the groups.