ORIGINAL RESEARCH
Dental Materials

Needle-free anesthesia: clinical efficacy of a mucoadhesive patch for atraumatic anesthesia in dental procedures

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Abstract: This study showcases the clinical efficacy of mucoadhesive patches designed for the buccal delivery of lidocaine and prilocaine hydrochlorides (1:1, 30 mg/patch). Such patches were developed for needle-free pre-operative local anesthesia in dentistry, aiming at mitigating the use of infiltrative anesthesia for medium-complexity clinical procedures. The patches were manufactured encompassing drug-release, mucoadhesive and backing layers, all prepared through film casting using biocompatible materials. Fifty-eight (n = 58) adult patients (65% women and 35% men) were randomly selected and included in a one-arm open clinical prospective cohort study. The average age of the subjects was of 50 years. The majority (59%) of the subjects, mostly women (82%), reported needle-phobia or anxiety due to dental procedures, which was assessed through a questionnaire approved by the ethical council for human use in research. The patches were positioned in the gingival region of the teeth involved in the procedure (86% on the maxillary and 14% on the mandibular bone). Two anesthetic patches were applied on each patient: one in the vestibular region and another in the palate/lingual portion, and these patches remained attached to the placement sites throughout the procedures. Concerning the dental procedures performed, 40% were cavity preparations and dental restorations of medium cavities; 29% staple facilities; 10% gingival retractions; 9% subgingival scrapings; 3% gingivalplasties; 3% supragingival preparations; 3% occlusal adjustments; and 2% subgingival preparations. In 90% of the cases, it was not necessary to complement with conventional infiltrative local anesthesia during the procedures. Patients did not report any discomfort or side effect during or after the administration of the patches. Among the cases in which there was the need for complementation, 50% were cavity preparations and dental restorations; 33% supragingival preparations; and 17% gingivoplasties. The complementary anesthesia volume was of 0.63 ± 0.23 mL and women corresponded to 83% of the participants who needed such intervention. Furthermore, in most cases, the patch was capable of initiating the anesthesia within a short time frame (5 minutes) and reaching the maximum anesthetic effect within 15 and 25 min, lasting at least 50 min. Undesirable side effects were not reported either 2 h after the administration or within the 6-month follow-up. Therefore, the anesthetic patches developed provide needle-free, painless, safe, and patient/dentist-friendly advances in performing routine medium-complexity dental procedures.

Keywords: Lidocaine, Prilocaine Drug Combination; Anesthesia, Local; Administration, Buccal; Drug Delivery Systems.

Introduction

Pain is an unpleasant sensation in response to an aggressive stimulus to the organism,[1] which is often associated with dental care.[2,3] Due to the need to minimize or avoid pain, local or regional anesthesia through needle punctures is mandatory during dental procedures. Nonetheless, needle-phobia is the main factor encouraging patients to delay or abandon dental treatments, impairing significantly their general health and quality of life.[4-7]

Typically, medium- and high-level complexity dental procedures, such as cavity preparations; dental restorations; dental extractions; prosthetic interventions; endodontic treatments; periodontal treatments; and oral surgeries; are associated with a greater probability of experiencing pain or anxiety during the visits to the dental offices.[8] Furthermore, it is noteworthy that the manipulation of the gingival needle is the most prevalent factor of accidents due to sharp instruments amongst clinicians and their assistants.[9]

Concerned with the need to achieve substantial improvements in the comfort and safety of patients and dentists in the pre-, trans- and postoperative periods, overcoming these needle-related issues and increasing the duration of the local anesthetic have being the focus of several Brazilian researches.[10-14] In pursuit of this, the suitability of a broad range of pharmaceutical technologies has been investigated and extensively revised in other papers.[15,16,17]

Within this context, over the last decade, our multidisciplinary research group has also been driving towards advances in several needle-free and patient/dentist-friendly anesthetic delivery systems, such as buffered solutions,[18] mucoadhesive gels,[19] oral-dispersible tablets,[20] thin polymeric films[21,22] and multilayered iontophoretic patches[23] containing prilocaine and lidocaine hydrochlorides (PCl and LCl, respectively).

By means of a controlled, randomized, triple-blind crossover clinical survey performed in adult volunteers, we have demonstrated the efficacy of mucoadhesive monolayer films comprised of PCl and LCl (1:1, 22 mg) in the reduction of the pain sensation due to the puncture by a "needle-shaped" device at shallow and deep levels in the mandibular gum. The onset of the anesthesia effect was achieved within 5 min, the peak of the effect within 15 and 25 min and the effect lasted at least 50 min after being placed in the maxillary sites.[21]

Motivated by these remarkable and unprecedented results, our multidisciplinary team kept seeking enhancements in anesthetic delivery from biocompatible and mucoadhesive polymeric systems. Henceforth, we report on the clinical efficacy of a novel pre-operative local anesthesia mucoadhesive tri-layered patch in medium-complexity dental procedures.

Methodology

Manufacture of the anesthetic patch

As presented in Figure 1, the buccal anesthetic patch was designed to have three different layers (thin polymeric films), *i.e.*, a) drug release; b) mucoadhesive; and c) backing. All polymeric layers were obtained by film casting.[24] Further information regarding the methods for manufacturing and characterizing the anesthetic patch are presented in sections S1 and S2 of the supplementary materials, respectively. The PCl and LCl were used as model drugs, being combined at a 1:1 ratio with a total drug load of 30 mg/unit. According to the aforementioned, combining these aminoamide salts at this proportion has been presenting enhanced anesthetic effects in simulated buccal needle-puncture clinical studies carried out in adult volunteers.[21]

Evaluation of the clinical efficacy of the anesthetic patch in dental procedures

Ethical approval

This experimental protocol was approved by the School of Dentistry of Ribeirao Preto's Research Council for Human Use in Research, under Brazil's Platform protocol number 88727118.8.0000.5419. All research subjects were invited to participate in the study by signing the free and informed consent form. The study was registered and approved in the Brazilian Registry of Clinical Trials Platform (ReBEC) under number RBR-2jnmv8 and in the Universal Trial Number under the protocol

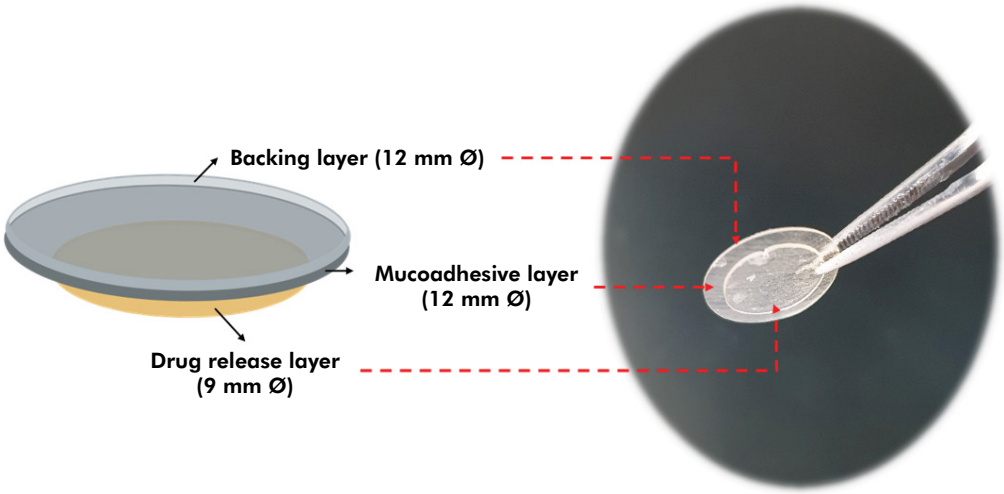

Figure 1. Mucoadhesive patches used in the clinical evaluation of the efficacy of needle-free anesthetic drug delivery systems in medium-complexity dental procedures.

number U11111-1218-7574, which complies with the international use of humans in clinical experiments. The questionnaire for anxiety and needle-phobia self-reporting was approved by these committees with the utmost care due to the incisive questions, to avoid induced responses. The questionnaire was applied to the subjects by a trained operator.

Patients

Fifty-eight (n = 58) healthy individuals that met the defined inclusion criteria were recruited to participate in this clinical study. The sample power was calculated considering the success rate in the pilot study described by Calefi, and the number of patients under clinical care in the public health system at Ribeirao Preto's public university in 2019 (70 patients), using the criteria from epidemiology studies.

The inclusion criteria were individuals with a good systemic condition; no gender distinction; adults (> 18 years old); individuals in need of dental treatment involving medium-complexity procedures and that generated enough discomfort to require local anesthesia in the routine clinical treatment; or with pulp vitality confirmed in thermal tests using the Endo-Frost device (Coltène/Whaledent, Feldwiesenstrasse 209450 Altstätten, Switzerland).

The exclusion criteria were patients with teeth treated endodontically or without pulp vitality confirmed by thermal and cavity tests for procedures involving the dental element; pregnant women; drinkers; smokers; users of illicit and/or legal drugs that act on the central nervous system; and/or those allergic to medications, especially anesthetics; women during their menstrual period.

Study design

The study was developed as a one-arm open clinical prospective cohort study in which the patient is in control of himself, sampled by convenience and considering the significant results of the reports from Calefi.[22] The procedures were chosen randomly, within the inclusion criteria and considering the average time of a consultation in a dental clinic. The authors aimed at evaluating the effectiveness of a non-invasive anesthetic patch in medium-complexity dental procedures, namely decayed tissue removal and Class I, II, III, IV and V restorations in mid and deep cavities; prosthetic moldings using gingival retraction threads; scaling and root planning; preparation of supra and subgingival dental remnants; gingivoplasties; installation of clamps for absolute isolation and occlusal adjustments.

Patch administration and outcome assessment

The anesthetic patch was applied by a qualified professional (L.E.A). The cleaning and removal

of the excess moisture from the mucosa prior to the administration was performed to facilitate the adhesion of the patch placement site. Then, the patch was positioned with a sterile instrument in the gingival region of the teeth involved in the procedure. Two anesthetic patches were applied in the vestibular region and in the palate/lingual portion. Both patches remained attached to the placement sites throughout the procedures.

For illustrative purposes, Figure 2 and Figure 3 depict a summary of the patch administration steps up to the completion of a dental restoration. As an example, the authors have demonstrated an unsatisfactory restoration change in which there

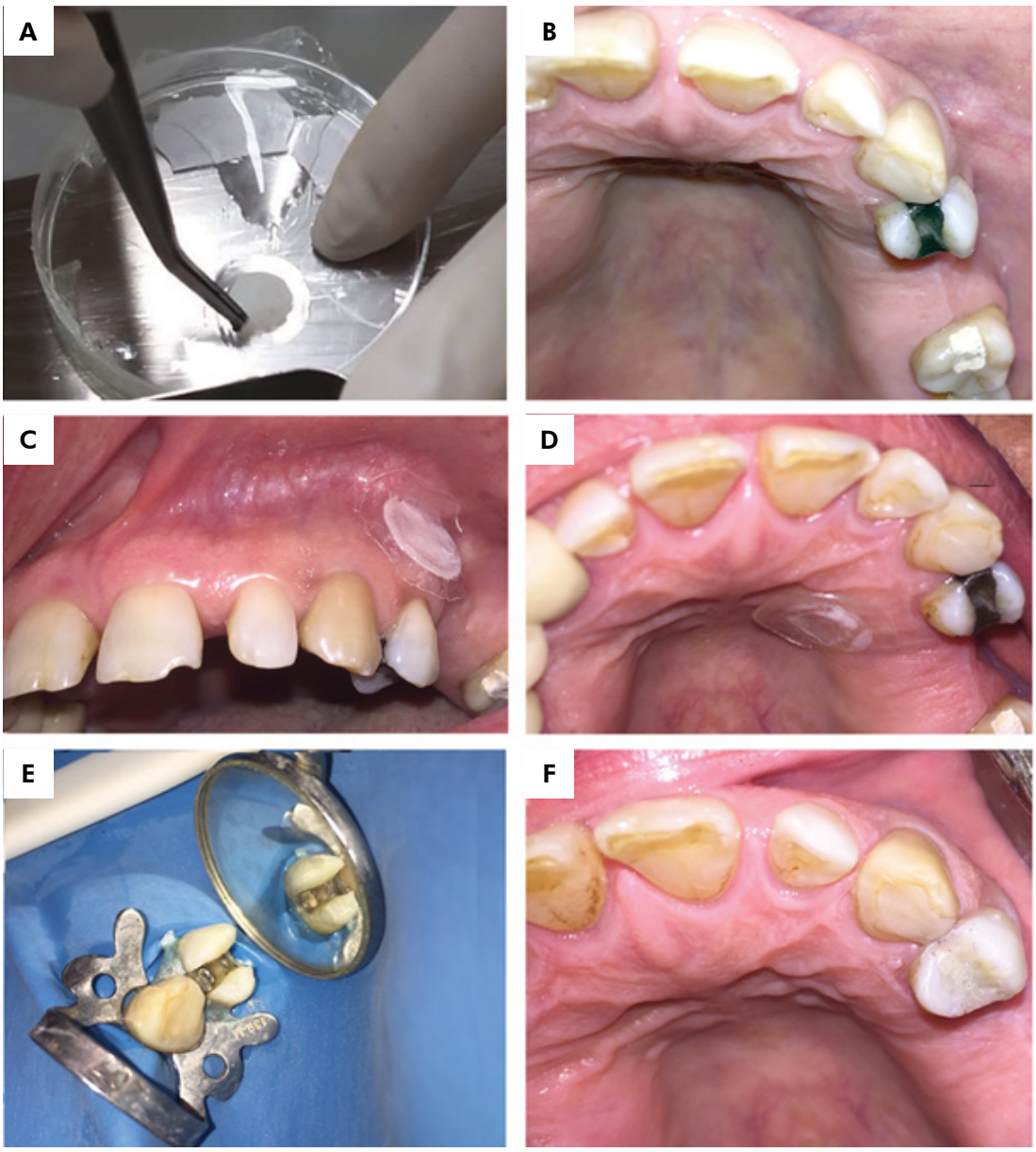

Figure 2. Summarized steps of a dental procedure using the mucoadhesive anesthetic patches. **A-** Handling the mucoadhesive anesthetic patch with a sterile instrument; **B-** Tooth 14 to be restored; **C-** Mucoadhesive anesthetic patch placed on the vestibular mucosa; **D-** Mucoadhesive anesthetic patch placed on the palatine region; **E-** Complete insulation of tooth 14; **F-** Complete restoration.

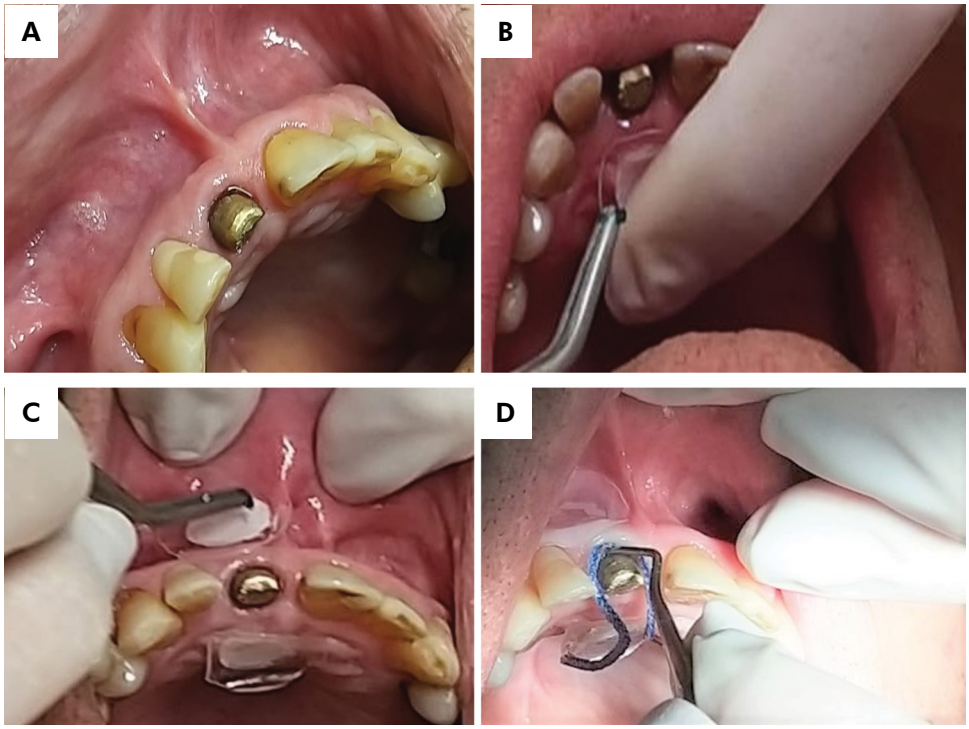

Figure 3. Technical anesthesia sequence with a polymeric anesthetic device: Insertion of the gingival retraction wire to mold the metalloceramic crown coping in the dental element 11. **A-** Tooth 11 with the first retraction wire in position, the patient did not want to be anesthetized initially but in the course of the retractor wire insertion he changed his mind; **B-** Polymeric device being positioned in the palatal region; **C-** Polymeric device being positioned in the vestibular region; **D-** Painless insertion of the second retractor wire.

would be the possibility of reaching some painful sensation (Figure 2), and the use of a gingival retraction wire in order to promote gingival clearance for the metal-ceramic crown coping impression in element 11 (Figure 3).

The authors measured the time interval between the application of the mucoadhesive patch and the beginning of the procedures (onset time), which was given from the moment the patient reported feeling the anesthetic sensation and was checked with a sterile instrument with palpation movements on the gum around the tooth on which the procedure would be performed. As soon as the patient reported the anesthetic sensation, the procedures was started.

The soreness was monitored in real time, and whether the patient reported any pain or discomfort; the type of clinical procedure; the current time and the pain felt following the initial time of the anesthesia were recorded. In the cases in which the patient reported feeling pain or any discomfort, a 2% mepivacaine hydrochloride solution with norepinephrine hemitartarate at 1:100.000 (Mepinor, DFL, Rio de Janeiro, Brazil) was complementarily administered to ensure the completion of the procedure and the end of the service. All quantitative data are expressed as a mean ± standard deviation (SD).

After finishing the procedures, the participants were asked about their general impression concerning the patch. A short-follow-up was done in the present study. All patients were assessed as to the health of the tissues and color of the gingival region where the patches were applied (at least 2 h after the application) and no problems were related to the administration sites for 6 months. The safety of the present patch was assessed using tissue color and the presence (or not) of any ulcerative tissue on the site of the application as parameters. Moreover, criticisms, suggestions, adverse effects and/or any discomfort (*e.g.*, bitter taste, glottis edema, slight prickling or stinging sensation, etc.) were recorded.

Data analysis

The data obtained throughout the dental procedures and the responses collected from the questionnaires underwent descriptive analyses. For the qualitative-variable results, such as the self-reported needle-phobia, type of dental procedures, and the need for complementary anesthesia, we performed absolute and relative frequency (percent, %) calculations. Moreover, for the quantitative outcomes we calculated the average, standard deviation (SD), 95% confidence interval, median, minimum, and maximum values. Herein, the data of two subgroups (gender) were compared using the Mann-Whitney U.test. The p values inferior to 5% ($p < 0.05$) at the 95% confidence interval were considered significantly different. The software used was the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp. Released 2011. Armonk, USA).

Results

All layers revealed uniform thickness and mass throughout. When mounted, the various layers yielded mucoadhesive anesthetic patches with average masses of 42.5 (3.0) mg and thicknesses of 510.0 (45.0) µm. Furthermore, the drug content on the release layer was of 346.0 (7.0) $mg.g^{-1}$ for PCl and 349.0 (6.0) $mg.g^{-1}$ for LCl.

Table 1 depicts the overall information regarding the research subjects included in our investigation. The majority of the patients (65%) were women. The average age was of approximately 50 years for both women and men, thus comprising a homogeneous sample.

Table 1 also shows a great range (800%) between the minimum and maximum onset of the anesthetic effect provided by the patches. While the maximum onset was greater for women, the minimum onset was slightly greater for men. Nevertheless, the anesthetic patches were equally effective for both genders, since there were no statistically significant differences between the average onset times ($p > 0.05$).

As can be seen in Figure 4, the majority (59%) of the research subjects reported some anxiety and needle-phobia regarding dental treatments. Concerning the genders, 74% of women and 30% of men reported being anxious and afraid of anesthesia. Thereby, amongst the self-reported anxious and needle-phobic patients, 82% were women.

Figure 5 presents the general features (absolute frequency) of the dental procedures performed. Detailed information of the procedures is provided in Table 2. The majority (52%) of the procedures were performed in posterior teeth. The premolars accounted for 40% (n = 23) of the treated teeth, incisors 26% (n = 15), canines 21% (n = 12), and molars 13% (n = 8).

Figure 5A depicts that the most prevalent services were cavity preparations and dental restorations of medium cavities (40%); followed by staple facilities (29%); gingival retractions (10%); subgingival scrapings

Table 1. Sample features and onset of anesthesia in the evaluation of the clinical efficacy of needle-free anesthetic patches in medium-complexity dental procedures.

Participants	Mean	SD*	Median	95%CI		Min	Max
				LB	UB		
Age (years)							
All (n = 58)	50.7	14.4	53.0	46.9	54.5	18.0	78.0
Women (n = 38)	50.3[a]	10.0	50.5	47.0	53.6	30.0	68.0
Men (n = 20)	51.6[a]	20.5	60.0	41.9	61.2	18.0	78.0
Onset anesthesia (min)							
All	13.2	6.3	10.5	11.5	14.9	5.0	40.0
Women	13.5[a]	6.9	13.0	11.2	15.8	5.0	40.0
Men	12.6[a]	5.1	10.0	10.2	14.9	7.0	25.0

*SD: standard deviation; LB: lower bound; UB: upper bound; Min: minimum age; Max: maximun age; Equal letters means not significant statistically difference (Age: p = 0.310; time: p = 0.615).

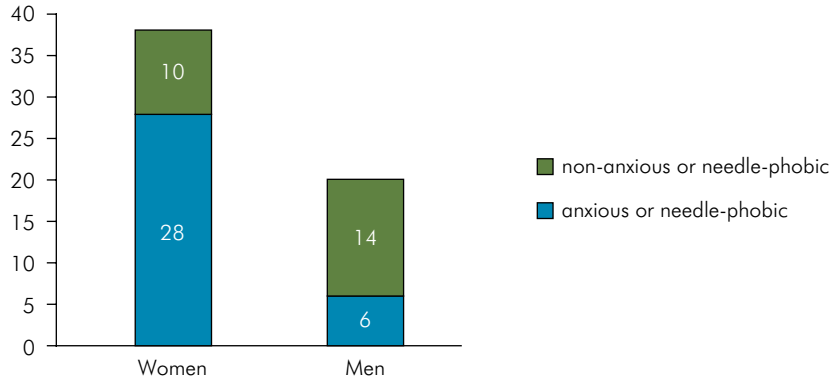

Figure 4. Absolute frequencies of research subjects self-reporting anxiety and needle-phobia before the dental procedures.

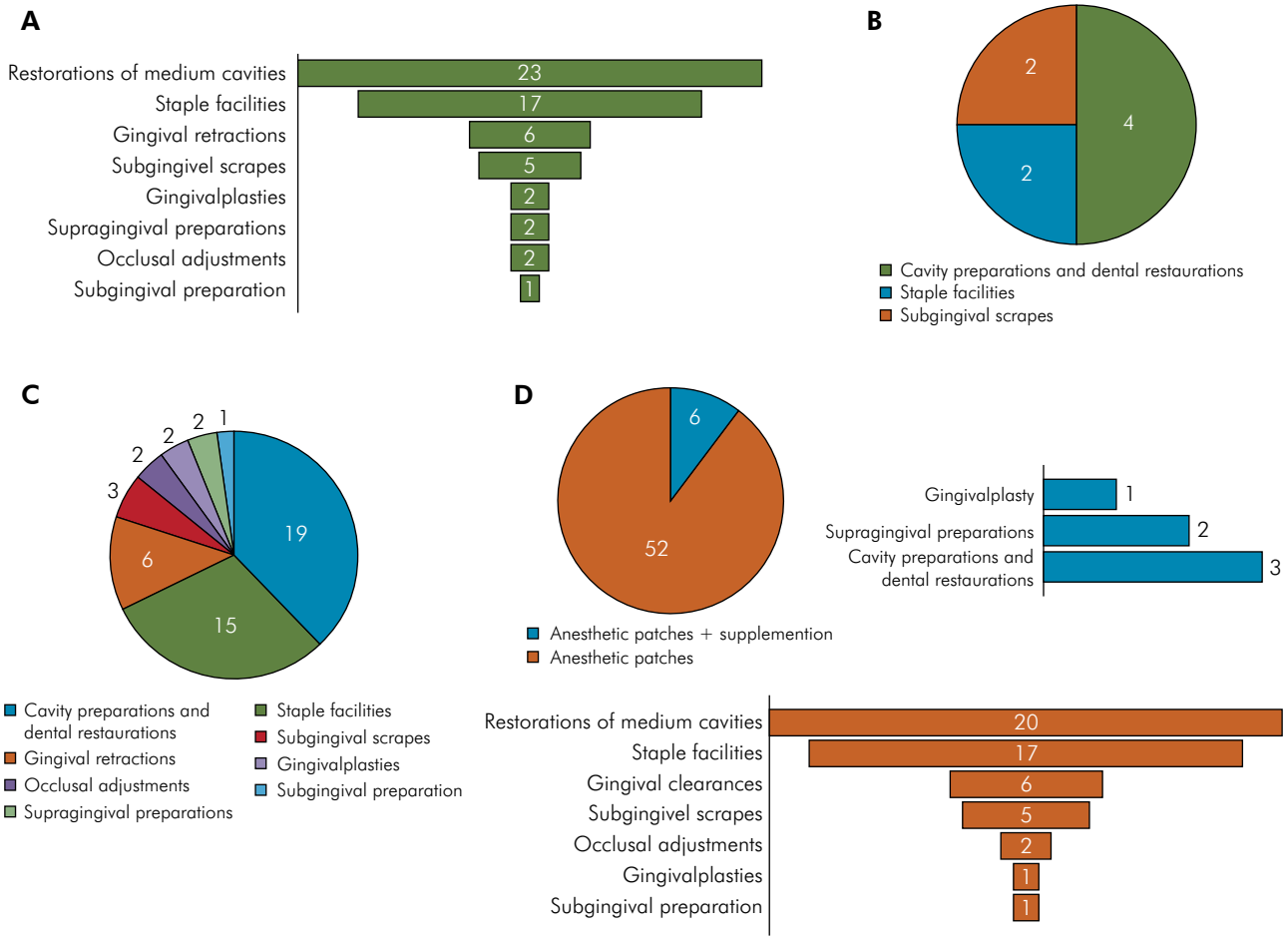

Figure 5. Absolute frequencies of the overall dental procedures **(A)**; procedures performed in the mandible **(B)**; procedures performed in the maxilla **(C)**; and services carried out with or without the need for complementary injectable anesthesia **(D)**.

(9%); gingivalplasties, supragingival preparations, and occlusal adjustments (3%); and subgingival preparations (2%).

From the total interventions (Table 2), 14% were carried out in the mandible, which were distributed as demonstrated in Figure 5B: 50% were cavity

Table 2. Procedures carried out with the research subjects included in the evaluation of the clinical efficacy of needle-free anesthetic patches in medium-complexity dental procedures.

Subject	Procedure	Teeth	Time to completion (min)
1	Supragingival preparation*	15	≤ 90
2	Cavity preparation and dental restoration	13	≤ 60
3	Cavity preparation and dental restoration	44	≤ 60
4	Cavity preparation and dental restoration	23	≤ 60
5	Staple facility	13	≤ 60
6	Cavity preparation and dental restoration	22	≤ 60
7	Staple facility	44	≤ 60
8	Cavity preparation and dental restoration	35	≤ 60
9	Cavity preparation and dental restoration*	11	≤ 90
10	Staple facility	35	≤ 60
11	Staple facility	13	≤ 60
12	Staple facility	23	≤ 60
13	Cavity preparation and dental restoration	23	≤ 60
14	Staple facility	24	≤ 60
15	Cavity preparation and dental restoration	24	≤ 60
16	Staple facility	27	≤ 60
17	Subgingival preparation	11	≤ 60
18	Cavity preparation and dental restoration	16	≤ 60
19	Cavity preparation and dental restoration	12	≤ 60
20	Cavity preparation and dental restoration	13	≤ 60
21	Staple facility	23	≤ 60
22	Cavity preparation and dental restoration	34	≤ 60
23	Cavity preparation and dental restoration	35	≤ 60
24	Cavity preparation and dental restoration*	21	≤ 90
25	Staple facility	14	≤ 60
26	Staple facility	24	≤ 60
27	Cavity preparation and dental restoration*	15	≤ 90
28	Gingival retraction	11	≤ 60
29	Staple facility	13	≤ 60
30	Gingival retraction	21	≤ 60
31	Subgingival scraping	31	≤ 60
32	Subgingival scraping	18	≤ 60
33	Subgingival scraping	27	≤ 60
34	Subgingival scraping	41	≤ 60
35	Subgingival scraping	28	≤ 60
36	Staple facility	14	≤ 60
37	Cavity preparation and dental restoration	13	≤ 60
38	Staple facility	16	≤ 60
39	Staple facility	24	≤ 60
40	Cavity preparation and dental restoration	24	≤ 60
41	Gingival retraction	21	≤ 60
42	Gingival retraction	23	≤ 60

Continue

Continuação

43	Cavity preparation and dental restoration	27	≤ 60
44	Gingivalplasty	24	≤ 60
45	Gingivalplasty*	11	≤ 90
46	Cavity preparation and dental restoration	13	≤ 60
47	Cavity preparation and dental restoration	14	≤ 60
48	Staple facility	24	≤ 60
49	Cavity preparation and dental restoration	11	≤ 60
50	Cavity preparation and dental restoration	21	≤ 60
51	Supragingival preparation*	27	≤ 90
52	Cavity preparation and dental restoration	11	≤ 60
53	Gingival retraction	11	≤ 60
54	Gingival retraction	21	≤ 60
55	Staple facility	24	≤ 60
56	Staple facility	15	≤ 60
57	Occlusal adjustment	14	≤ 60
58	Occlusal adjustment	15	≤ 60

*Required complementary anesthesia by injection

Table 3. Time required for complementary injectable anesthesia in the evaluation of the clinical efficacy of needle-free anesthetic patches in medium-complexity dental procedures.

Clinical procedure	Time spent until complementary anesthesia (min)
Cavity preparation and dental restoration class III – tooth 11	14
Cavity preparation and dental restoration class III – tooth 21	14
Cavity preparation and dental restoration class II – tooth 15	5
Supragingival preparation – tooth 27	6
Supragingival preparation – tooth 15	4
Gingivoplasty – tooth 11	40
Average	13.8
SD*	13.6

*SD: standard deviation.

preparations and dental restorations, 25% staple facilities, and 25% subgingival scrapings. Dental restorations and clamp installations were performed on posterior teeth (premolars) and the scrapings on anterior teeth (Table 2).

For the services performed in the maxilla, 38% were cavity preparations and dental restorations of medium cavities; 30% staple facilities; 12% gingival retractions; 6% subgingival scrapings; gingivalplasties, supragingival preparations, and occlusal adjustments accounted for 4% each; and 2% were subgingival preparations (Figure 5C).

Overall, 90% of the procedures were performed using only the anesthetic patches as presented in Figure 5D and Table 2. Herein, 38% were cavity preparations and dental restorations, 32% staple facilities, 11% gingival clearances, 10% subgingival scrapings, 4% occlusal adjustments, 2% gingivoplasties, and 2% subgingival preparations. All these procedures took no more than 60 min to be fully completed (Table 2).

As presented in Table 3, all procedures with anesthetic supplementation by injection were performed on the maxilla. The number of procedures

performed on anterior teeth was the same of those on posterior teeth (n = 3). Moreover, the majority (50%) were cavity preparations and dental restorations, while supragingival preparations and gingival surgery accounted for 33% and 17%, respectively (Figure 5D). No more than 90 min were spent for the completion of all these services (Table 2).

The average anesthetic volume of solution used for procedures in which there was the need for complementary anesthetic injection was of 0.63 ± 0.23 mL. This corresponds to about one-third of the anesthetic tube (*i.e.*, 1.8 mL) and around 12 mg of drug. All the patients requiring complementary anesthesia reported anxiety and needle-phobia before the procedure. Furthermore, women accounted for 83% (n = 5) of the research subjects in which the complementary injectable anesthesia was necessary. Therefore, it was not possible to determine whether there was a statistically significant difference between the volume of anesthetic solution injected in men and women.

It is important to point out that in the cases in which complementary infiltrative anesthesia was required, the needle puncture was not felt by the patients. This confirms that the developing patches are effective as pre-anesthetics in long-lasting procedures, since their administration markedly mitigated the painful sensation caused by the scary needles used for buccal anesthesia. Interestingly, it was observed that all participants felt comfortable, safe and highly praised the use of the anesthetic patches, especially those patients that did not need the complementary anesthesia and reported not feeling any discomfort, neither during nor after the procedures.

Discussion

Needle-phobia affects almost 20% of the world population.[4] Approximately 5% to 15% of the population avoids dental treatments due to needle-phobia anxiety,[4-7,25] which possibly contributes to the fact that people who are afraid of dental treatments are also those who present the most precarious oral health and require more complex treatments.[26,27,28] According to the literature,[29] stress originating from fear and anxiety can cause an endogenous release of adrenaline up to 40-fold over normal levels, and this would be the cause of syncope and complications that occur in dental-clinic treatments.

In order to predict possible behavioral and organic reactions that could result in accidents and/or impairments in the treatment outcomes, the use of dental anxiety assessments has been quoted.[30] The Modified Dental Anxiety Scale (MDAS),[31] as well as simple questions such as whether they are afraid of the dentist or anxious about dental treatments and anesthesia are feasible to assess dental anxiety in the offices. Moreover, dental surgeons should be aware of the main symptoms of anxious and needle-phobic patients (*i.e.*, feelings of suffocation, dizziness, sweating, tremors, agitation, nervousness, palpitations and anguish).[32] Altogether, these strategies may contribute to the establishment of a trusting rapport between dentists and their patients towards achieving optimal oral health.[31]

The prevalence of anxiety and fear of dental procedures in this study was 2.6-fold greater than that of a previous investigation with users of the Brazilian Public Health System.[33] Since needles are the main cause of anxiety and fear in dental practices, and needle-phobia increases with the increase of the participants' age,[4] this can explain the difference between the results of these investigations. While in our research the included participants were in average in their 50`s, in the aforementioned study[33] the participants that were most anxious and very anxious were mostly in the 20`s and 30`s group.

Like in the study of do Nascimento et al.,[33] our results demonstrated a greater prevalence of self-reported anxiety and needle-phobia regarding dental procedures for women when compared to men. The trend we have presented corroborate with data of current researches from other countries.[30,31,34] Indeed, a systematic review has demonstrated that irrespective to the type of health intervention involving the use of needles, needle-phobia is more prevalent in women.[4]

This unprecedented research also ratified the clinical efficacy of the mucoadhesive patches in needle-free buccal anesthesia in adult volunteers of both genders and a wide range of age groups during routine services in the office. The procedures performed included Class I, II, III, IV and V restorations, gingival

clearances, supra and subgingival preparations, gingivoplasties, staple facilities, subgingival scrapings and occlusal adjustments. To the best of our knowledge, these are dental procedures of medium complexity, thus requiring local anesthesia for suitable pain management.[35,36]

Herein, the average anesthesia onset was of approximately 13 min, which is slightly greater than the onset often reached by the conventional injections cited for buccal anesthesia.[37,38,39] Moreover, the administration of the patches was outstanding for the intended purpose, since the lasting time of anesthesia was suitable for the successful completion of all clinical interventions (*i.e.*, 50 up to 90 min).

Even though in a few cases (10%) complementary injections were required, this was not considered a failure of the drug delivery systems since the needle punctures did not scare or worry the patients because it was not felt at all. Interestingly enough, local anesthesia is assumed to fail in 7% of the overall cases in dental practice due to factors such as anatomical accessory-innervation variations and patient anxiety[40]. Hence, the need for complementary anesthesia in some of our patients is likely related to their reports of anxiety and needle-phobia; nonetheless this issue was circumvented by the meaningful efficacy of the patches as pre-anesthetics.

Among the risks inherent to anesthetic injections using syringes and needles, the following can be highlighted: post-anesthesia traumatic ulcers; bruises caused by tissue trauma due to the needle; and allergic reactions.[37] By using these mucoadhesive patches in medium complexity dental procedures, such risks can be minimized. Since needles are supposed to be rarely used and patients do not feel the needle punctures when required, fractures can be avoided; neither the dentist, nor the patient and assistant suffer any accidental punctures during or after the technique; and the risk of hematomas and bites on the lips and cheeks after the anesthesia may decrease markedly.[9]

The efficacy of our product may be justified in the lines of the intrinsic physicochemical and pharmacological properties of the aminoamide salts that therein were rationally combined. Due to their small molecular mass, moderate lipophilicity and ionization degree in the buccal physiological environment, which yield a strict balance between diffusion and partition phenomena, these drugs were capable of permeating through the buccal epithelium; reach the nerve endings; penetrate the nerve cell membrane; bind with specific receptors; and block the influx of sodium ions normally associated with membrane depolarization.[38]

The fast anesthetic onset can be achieved due to the greater lipophilicity and vasodilator properties of LCl, and the rapid peak and long-lasting effect of the anesthetic effect is related to the smaller vasodilator effect PCl.[37] Moreover, these aminoamide salts have been shown to act in a synergic way with each other in buccal local anesthesia. This trend was confirmed by means of *in vivo/in vitro* correlations (IVIVC) which demonstrated that the permeation flux at a steady-state of both these drugs, but mainly LCl, does correlate with the anesthesia onset; the Jss and permeability coefficient of PCl determines the peak of anesthetic effect; and the overall amount of drug retained in the epithelium influences the duration of anesthesia.[21]

The results of the anesthesia onset and duration do corroborate with the IVIVC previously reported by our team.[21] Therefore, the current study also validates both the *in vitro* experimental protocol for assessing the drug permeation and retention through the porcine esophageal epithelium,[18] as well as the *in vivo* clinical survey to assess the painful sensation due to a "needle- shaped" device puncture at shallow and deep levels in the mandibular gum in adult volunteers.[21]

Based on our previous findings,[21,23] we hypothesize that the total anesthetic flux through the buccal epithelium which was suitable for the anesthetic onset was in average around 100 $\mu g.cm^{-2}$. Moreover, the total drug amount retained in the buccal epithelium might be of about 27 $mg.cm^{-2}$ or 17 mg for the two patches. This drug reservoir generated in the epithelium is much lower than the daily maximum recommended dosage for these drugs, *i.e.*, 600 mg and 200 mg for PCL and LCL, respectively.[37]

Routinely, this anesthesia onset can still be enhanced by hydrating the surface of the drug release layer with 50–100 µL (one or two drops) of distilled water a few seconds prior to its attachment to the desired administration site. This previous hydration

can speed up the drug dissolution and facilitate its prompt delivery to the epithelium.

It is noteworthy that the patches remained attached to the placement site throughout the services, proving their enhanced mucoadhesive properties due to the composition, dimension and design, besides being easily withdrawn from the mucosa at the end of the procedures without causing any irritation to the patients' buccal epithelium. At the end of the procedure, none of the patients had any needle-induced anesthesia residual effects. Indeed, the mucoadhesive polymers used for developing the patches have been widely referred to and used by formulation scientists due to their affordability, drug release versatility, attractive mechanical properties, and biocompatibility.[41-44]

In our team's preliminary studies,[22] we obtained great advances with local anesthesia by determining the onset and duration of anesthesia following the administration of a monolayer (drug release) in volunteers. However, the first prototype was rectangular and its edges were not delimited by the mucoadhesive and backing layers used herein. This led some patients to feel an anesthetic sensation in the throat isthmus, without major side effects, but patients reported discomfort and concerns.

Conversely, the current rounded design of the patches, with a core containing anesthetic salts, covered by a thin and moldable mucoadhesive layer and a third insulating layer allows its application on any mucosal surface in the oral cavity. Besides rendering a target drug-delivery flux, this reduces the anesthetic washout through the salivary flow, thus resulting in convenient administration, dosage optimization, absence of side effects and remarkable clinical efficacy, as demonstrated in this study.

A remarkable and unprecedented outcome is that in all procedures performed on the mandible, complementary anesthesia was not necessary. The procedures were performed on anterior and posterior teeth (premolars), a fact that can be justified by the proximity of the mental canal, with dissipation of anesthetic salts via the mental and incisor nerves. This clinical finding is very interesting because the expectation would be the opposite, since the mandibular bone is less porous than the maxillary bone, which would make the diffusion of anesthetic salts more difficult.[37,45]

The limitation of this study is the absence of information concerning the exact time required for the completion of each dental procedure. This was not recorded, since our priority goals were to a) determine what would be the onset time of anesthesia for the patches; b) demonstrate whether it would be possible to carry out the services successfully without the need of injectable anesthesia; and c) assess the safety of the patches during and after the visit to the dental office.

Altogether, our findings enable the assertion that the tri-layered patches fulfilled the most important performance attributes required for a needle-free atraumatic anesthesia: *i.e.*, a) mucoadhesive properties aiming at close contact with the mucosa and maintenance on the administration site for the desired time frame; b) rapid release and permeation of a drug amount capable of reaching the nerve fibers and thus causing a fast onset, maintaining the anesthesia for the desired period (long lasting); c) unidirectional drug release, avoiding the spreading of the composition in the oral environment; d) biocompatibility; and e) safety.

Conclusion

In conclusion, we demonstrated scientific evidences of the needleless pain blockage following the administration of the patches, which was achieved without any harm to the application site or adjacent tissues, reaching suitable onset and duration of the anesthesia, yielding the utmost safety and compliance for both the patient and dentist and thereby displaying a meaningful advance in the dental care practice. Formulation and design optimization, long-term stability evaluation and manufacture upscaling are still required for a full validation of this patch as a topical anesthetic product, which will be the focus of further investigations.

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