Efficacy of Topical 1% Lidocaine in the Symptomatic Treatment of Pain Associated With Oral Mucosal Trauma or Minor Oral Aphthous Ulcer: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Single-Dose Study

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Aims: *To determine the efficacy in pain reduction of a topical 1% lidocaine compared to a placebo cream in patients with oral mucosal lesions due to trauma or minor oral aphthous ulcer.* ***Methods:*** *The design was a double-blind, randomized, placebo-controlled, six-center trial on 59 patients. Pain intensity and relief were measured using a 100-mm visual analog scale (VAS). One-tailed Student* t *test and ANOVA analyses were used for statistical analyses.* ***Results:*** *Independent of the pain origin (oral mucosal trauma or minor oral aphthous ulcer), the application of the 1% lidocaine cream led to a mean reduction in VAS pain intensity of 29.4 mm ± 17.0, which was significantly greater than the decrease obtained with the placebo cream. Analysis showed a statistically significant efficacy of the 1% lidocaine cream (P = .0003). Its efficacy was not related to the type of lesion, and no adverse drug reaction, either local or systemic, was reported by any of the patients.* ***Conclusion:*** *A significant reduction in pain intensity occurred after application of 1% lidocaine cream and was significantly greater than that with the placebo cream. Taking into account the study's limitations, this product seems safe to use.*
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Key words: acute pain, aphthous, lidocaine, mucosal trauma, topical

Most injuries to the oral mucosa are painful and are a common reason for patients to choose self-treatment or to seek professional dental help.[1] The nosological origins of such wounds are multiple, including mechanical injury, infection, inflammation, or tumor-associated.[2] Very often, the lesions are caused by mechanical trauma, eg, as a result of a fractured tooth, poor-fitting dentures, a bite (mainly at the cheek level), or a burn due to ingestion of food that is too hot.[3] The clinical examination usually shows a slightly erythematous lesion with regular borders. There is little or no induration. Generally, removing the causative agent leads to lesion healing within 8 to 15 days.

Oral aphthous ulceration is another frequent cause of oral mucosal pain.[1] Different types of oral aphthous ulcers exist: minor, major, or herpetiform. The most common is the minor aphthous ulcer, which affects 80% of patients presenting with aphthous ulcers. The lesion is round or oval, usually < 5 mm in diameter, with a gray-white pseudomembrane and an erythematous halo.

Whether caused by mucosal trauma or common aphthous ulceration, these benign lesions are a source of acute pain that can disturb daily activities (causing dysphagia, speaking impairment, etc).

A multitude of products are available for the treatment of oral soreness.[1,4,5] Over-the-counter products indicated for oral ulcers include different formulations and different active compounds.[5] Among these products are those covering the lesion and providing a barrier, some mouthwashes (including those containing benzydamine), and medicines containing local anesthesics. These products typically contain either benzocaine in varying percentages (6.4% to 20%) or lidocaine (2% to 5%). One characteristic of all these products is that data from clinical trials are limited.[5,6,7] The primary objective of this randomized clinical trial was to determine the efficacy in pain reduction of a topical 1% lidocaine compared to a placebo cream in patients with oral mucosal lesions due to trauma or minor oral aphthous ulcer. The secondary objective was to assess the general tolerance of this cream.

Materials and Methods

Study Design

This study was a randomized, double-blind, placebo-controlled, single-dose, parallel-group study. It was conducted in six dental practices in France. The study received ethics committee approval by Comité de Proctection des Personnes (Ile de France I, Paris) and by the French Medicine Agency (Afssaps) (Eudract N°: 2009-011901-18, N° AFSSAPS: A90542-68.). The study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice, and written informed consent was obtained from each subject.

Patients and Treatment

The participants were healthy male or female outpatients admitted for acute oral mucosal or gingival pain caused by a trauma or an aphthous ulcer. Differential diagnosis between these two lesions was based on patient anamnesis and medical records, more specifically concerning the presence of known traumatic agents (eg, bite, poorly fitting prosthesis). To be included in the study, the patient had to be 18 to 90 years old and have moderate to severe pain (≥ 40 mm on a visual analog scale [VAS] ranging from 0 to 100 with 0 = no pain and 100 = worst pain imaginable). Patients who fulfilled these inclusion criteria were randomly allocated to one of the two treatment groups (1% lidocaine cream or placebo cream) in a 1:1 ratio.

Exclusion criteria were: history of significant disease that rendered the patient unsuitable for inclusion; history of lidocaine allergy; use of concomitant medication that may have confounded assessment of pain relief (eg, psychotropic drugs, antidepressants, or sedative-hypnotics); presence of cancerous or neuropathic pains with an infectious pathology; and ingestion of any analgesic or anti-inflammatory drugs 6 hours before the examination.

Sample Size Determination

It was determined that with a baseline mean pain value of 60 mm on a VAS, and a mean pain reduction of 20 mm corresponding to a posttreatment VAS mean value of 40 mm with a SD of 25, an alpha error of 0.05, and a beta error of 0.1, 30 patients were necessary in each group. This calculation was carried out using nQuery Advisor software version 6.0 (Statistical Solutions). The number of patients was not increased to make up for any subjects lost to the study.

Clinical Procedure

The double-blind design was as follows: every tube of cream was identical in appearance and numbered from 1 to 60. Patients, investigators, and sponsor staff were blinded to treatment assignment throughout the study. Randomization was insured according to a computer-generated randomization schedule. The dental surgeon applied in random order 0.2 g of either an active or placebo cream on the mucosal lesion, rubbing for a full minute. The active cream contained 1% of lidocaine chlorhydrate (10 mg for 1 g of cream). The placebo cream had an identical composition to that of 1% lidocaine except for the addition of 10 mg of water in place of lidocaine chlorhydrate. The ingredients contained in the cream were essentially preservative (benzalkonium chloride), flavoring (thymol, aromatic oils), or emollient (liquid paraffin) that have no anesthetic or analgesic properties. The amount of cream was measured by means of a digital spoon scale (Sunartis). In addition, as the lidocaine chlorhydrate does not readily enter the systemic circulation when locally applied, other medications were allowed; the patients could follow their usual treatment regimes without modification.

Pain intensity was evaluated (by the same dentist who applied the cream) by means of a 100-mm VAS, both at baseline, ie, before application (T0) and at 3 minutes after cream application (T3). The VAS anchor points were: 0 = no pain and 100 = worst imaginable pain. Product efficacy was estimated by calculating the difference in VAS between the value at T0 and T3. The whole drug assessment was carried out during a single consultation.

Table 1 Sample Characteristics

	Treatment group, n (%)			
	1% Lidocaine (n = 29)	Placebo (n = 30)	Total (n = 59)	*P*
Mean age, y (SD)	47.4 (17.3)	59.8 (19.5)	53.7 (19.3)	.0125
Gender				.8235
Male	7 (24.1)	8 (26.7)	15 (25.4)	
Female	22 (75.9)	22 (73.3)	44 (74.6)	
Nature of pain				.0117
Aphthous ulcer	11 (37.9)	3 (10%)	14 (23.7)	
Traumatic wound	18 (62.1)	27 (90.0)	45 (76.3)	

Safety Assessments

Every adverse event was actively investigated following the patient's spontaneous declaration at T3. All adverse events were reported in the observation book, including the nature of the event, the date of occurrence, the duration, the end date, the gravity, the therapeutic consequences and evolution, and the relationship with the studied treatment (according to the investigator's opinion). Patients were also asked to report potential side effects occurring after T3. The investigator evaluated whether the side effect was relevant or not.

Statistical Analyses

For each group, the quantitative variables are presented as number of patients, mean, SD, and extreme values (minimum and maximum). The chi-square (χ^2) test was used to compare patient characteristics such as sex and pain origin. A Shapiro-Wilk statistical test was used to assess the normal distribution of the variable (pain intensity) before conducting subsequent statistical tests. To compare the two groups of patients at T0 and then at T3, a one-tailed Student *t* test was done. In order to evaluate the pain reduction within the two groups, a paired Student *t* test was carried out. A repeated measures ANOVA test that included two factors (time and group) and the first-order interaction term was also conducted. To evaluate the influence of pain origin, another repeated measures ANOVA was conducted with three factors (time, group, and pain origin) and the first and second interaction terms. To evaluate the product tolerance, the frequency and nature of the side effects were compared between the two groups by a χ^2 test. Except for the one-tailed Student *t* test, all the tests were two-sided. The level of significance was fixed at $P < .05$. Statistical analyses were performed with Statistical Analysis System software (SAS Institute).

Results

Baseline Patient Characteristics

Between September and November 2009, a total of 59 patients (overall mean age 53.7 years, ranging from 18 to 90 years) was randomized to receive either the active or placebo cream. All 59 patients (100%) completed the study.

The age, sex, and pain characteristics are shown in Table 1. Note, there was a large age range in both groups, as the extreme values show, and a significant difference in mean age ($P < .05$). There was no significant sex difference. However, there were more patients with aphthous ulcers in the 1% lidocaine group than in the placebo group (37.9% versus 10.0%); conversely, there were more traumatic wounds in the placebo group than in the 1% lidocaine group (90.0% versus 62.1%) ($P < .05$).

Pain Intensity

The variable (pain intensity) distribution was normal for each group (placebo at T0 and T3 and lidocaine at T0 and T3). At baseline, the pain intensity did not differ significantly between the two groups (see Table 2, Fig 1). The mean pain intensity of the two groups at T0 was 56.3 mm. Analysis showed a statistically significant efficacy of the 1% lidocaine cream. At T3, ie, 3 minutes after drug application, the pain intensity was statistically lower in the 1% lidocaine group ($P = .0001$) compared to the placebo group (Table 2, Fig 1). This was nearly a twofold

Table 2	Rating of Pain Intensity on a 100-mm VAS at Baseline and 3 Minutes After Application of a 1% Lidocaine Cream or a Placebo Cream (Values Reflect Mean + SD and Range)		
	Treatment group		
	1% Lidocaine	Placebo	*P**
T0	55.3 ± 8.4 (40–75)	57.2 ± 10.6 (42–84)	.22
T3	25.9 ± 17.6 (1.0–56.0)	42.5 ± 15.5 (10.0–70.0)	.0001

*One-tailed Student *t* test to compare the difference between groups at T0 and T3.

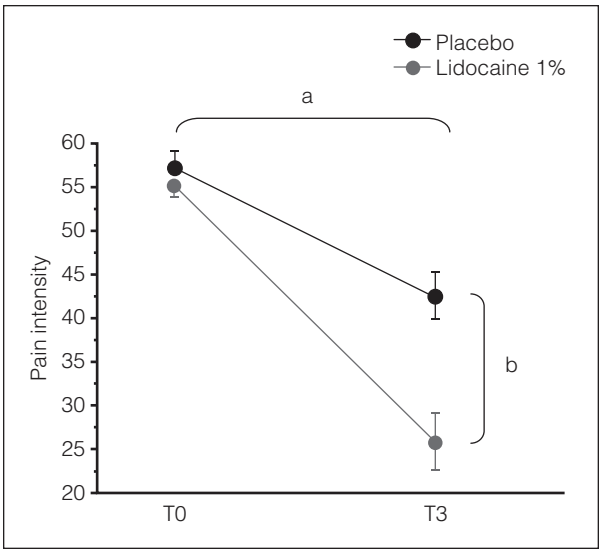

Fig 1 Graphic representation of the pain reduction as measured on a VAS (0–100). (a) $P = .0001$ between T0 and T3; (b) $P = .0001$ between placebo and lidocaine treated group at T3.

Table 3	Pain Improvement Between Treatment Groups			
	Time			
	T0	T3	Difference between T0 and T3	Student *t* test
Placebo	57.2 ± 10.6 (CI: 53.4–61.0)	42.5 ± 15.5 (CI: 37.0–48.0)	14.7 ± 18.5 (CI: 8.1–21.3)	T0 versus T3 ($P = .0001$)
1% Lidocaine	55.3 ± 8.4 (CI: 52.2–58.4)	25.9 ± 17.6 (CI: 22.5–35.3)	29.5 ± 17.0 (CI: 25.1–33.8)	T0 versus T3 ($P < .0001$)

Values reflect mean ± SD; CI = 95% confidence interval.

pain reduction in the lidocaine-treated group and this was confirmed by one-tailed Student *t* test ($P = .0001$) and ANOVA analyses ($P = .0023$) (Table 3, Fig 1).

Because the origin of the pain was not evenly distributed between the two groups, the analysis of the pain reduction was successively carried out with and without the pain origin included. These ANOVA analyses did not reveal a significant difference in pain reduction according to the pain origin (aphthous versus traumatic lesion, $P = 0.299$). No side effect, either local or systemic, was reported during or after the study.

Discussion

Lidocaine is a well-known, safe, and efficacious drug for local anesthesia. The drug has been used for many years, with the first patents granted in 1948. The pharmacology of lidocaine was established in the 1970s and the drug is regarded as a well-investigated substance.[8,9] Today, it is used topically for surface anesthesia of the skin or mucosa as well as for local anesthesia by means of nerve block (infiltration anesthesia).[7] To the best of the authors' knowledge, this is the first clinical trial carried out to assess the efficacy of a cream containing 1% lidocaine chlorhydrate in symptomatic treatment of oral mucosal trauma and minor oral aphthous pain. It is important to assess the efficacy and tolerance of such a preparation, as it is a widely available over-the-counter medication.[10] This is even more important as patients tend to self-medicate or ask advice from their pharmacist for the treatment of painful aphthous or traumatic mucosal lesions. Many drugs are marketed in Europe or the United States to treat such lesions. Several of these drugs aim to relieve the pain and mainly contain local anesthetics (eg, benzocaine, lidocaine), or barriers (carmelose). Other drugs contain an antiseptic agent (chlorhexidine), antiviral agents (acivlovir), or glucocorticoids.

This phase III, randomized, double-blind, placebo-controlled clinical trial had sought to evaluate the analgesic efficacy of a topical cream containing 1% lidocaine chlorhydrate on acute pain caused by traumatic mucosal wounds or aphthous ulcers. Pain improvement was self-assessed by means of a VAS, which is a very accurate and validated method to subjectively quantify pain intensity by the patient.[10–12] The inclusion criteria aimed to choose a patient sample that reflected the type of patients normally using the product, and addressed the treatment of frequent painful oral lesions whose morbidity does not normally require an intervention by a health professional. Moreover, these mucosal lesions—small mouth wounds or aphthous ulcers numbering fewer than four per year—are considered by the French Health Minister as indications for self-management by over-the-counter medications.

Application of 0.2 g of the 1% lidocaine cream produced a significant reduction in pain intensity within 3 minutes after application. The pain reduction obtained with the lidocaine cream was approximately twice as large as that reported after the application of the placebo cream. Pain intensity was reduced by approximately 30 mm on the VAS with the lidocaine cream, an amount that is clinically relevant. Indeed, it is generally agreed that a variation of ≥ 13 mm on a VAS represents the smallest measurable change in acute pain severity that is clinically important.[13,14] Although less important, the present results also revealed a significant reduction in pain intensity in the placebo group. This is due first and foremost to the placebo effect itself, which is well known and demonstrated in clinical studies as a psychobiological phenomenon attributable to the overall therapeutic context (for review see Finniss et al[15]). In addition to this placebo effect, it is also possible that different ingredients in the cream can act through a nonpharmacologic mechanism by forming a physical barrier, eg, through emollients.

This study has several limitations. The first is the total number of patients included. Sixty patients were planned, but only 59 were recruited because of regulatory issues concerning the duration of the study imposed by the French Medicine Agency. However, this reduction in the number of patients did not have any impact on the statistical analysis of this study. Secondly, the study did not assess the pain intensity after 3 minutes, which would have been interesting and will be a subject for future studies. The main question the authors wanted to address was whether the application of this cream is able to quickly (within 3 minutes) relieve the pain of benign lesions of the oral mucosa. The two groups also did not contain equal numbers of aphthous and traumatic lesions, as traumatic lesions were more represented in both groups. In particular, just three patients had an aphthous ulcer in the placebo group. However, both lesions were equally painful at baseline and, although their etiologies are different, they do share a common pathophysiological mechanism (acute inflammatory processes) that may explain why pain reduction was independent of the lesion etiology. Thus, it seems reasonable from both a biological and clinical point of view to conclude that topical application of 1% lidocaine cream over an aphthous ulcer leads to the same pain reduction reported for its use to treat a mechanically caused lesion. Although significant from a statistical point of view, the demographic differences between the two groups are not expected to influence the nature of the results obtained for the two groups; indeed, pain perception is not likely to vary between 50- or 60-year-old patients.[16,17] Although the two groups were not age-matched, an important dispersion of the age distribution in both groups was observed, as the extremes values show.

The present data also indicate that the lesion etiology (aphtous or trauma) did not influence pain intensity. But the pain intensity caused by these lesions can be disabling. Indeed, whether caused by aphthous ulcers or traumatic wounds, the pain intensity can be quite high as reflected by the overall mean pain intensity of 56.3 mm in the patient sample, with a maximum of 84 mm on a 100-mm VAS.

Data analysis concerning the product's safety confirmed the innocuousness of the lidocaine cream. Neither local nor systemic side effects were observed by the clinicians or reported by the patients during the study itself or in the days that followed. These data are consistent with previous reports of the safety of this drug, based on a small number of drug-monitoring cases in international publications.[18,19]

In conclusion, the data obtained in this clinical trial showed that topical application of a 1% lidocaine cream for 1 minute to either a traumatic wound or an aphthous ulcer produced a significant reduction in pain intensity 3 minutes after application, that the pain reduction was statistically significantly larger with the lidocaine cream than with a placebo cream, and that the amount of pain relief was independent of the lesion's etiology. The pain decreased by approximately 50%, on average, for both lesion types. The lidocaine cream did not elicit negative side effects. Thus, this clinical trial showed a benefit/risk ratio positive for the application of a 1% lidocaine cream in the symptomatic treatment of acute pain resulting from traumatic or aphthous lesions of the oral mucosa.

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