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Evaluation of Topical Anesthetics by Laser-Induced Sensation: Comparison of EMLA 5% Cream and 40% Lidocaine in an Acid Mantle Ointment

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Background and Objective: **Current techniques for assessing local anesthetics (e.g., pin-prick test) cannot elicit a specific afferent activity without contamination from mechanosensitive receptors. This study was aimed to validate the use of non-scarring laser pulses as a reproducible method to assess effectiveness of topical anesthetics by comparing EMLA 5% cream and 40% lidocaine ointment.**
Study Design/Materials and Methods: **Thirty-two evaluations per compound were achieved in a total of eight healthy subjects. Non-scarring pulses from a 585 nm Pulsed-dye laser and a double-frequency Nd:YAG laser were investigated as pain inducers and the results were statistically analyzed by using a Student *t*-test.**
Results: **Discrimination of anesthesia was better assessed with the 1,064 nm Nd:YAG laser. Anesthesia obtained by EMLA 5% cream was significantly higher than for 40% lidocaine ointment ($P < 0.0001$). For EMLA cream, the number of evaluations with complete anesthesia was twice as much as for 40% lidocaine.**
Conclusions: **Non-scarring laser pulses are reliable and reproductive pain inducers for assessing topical anesthetics showing a low intra-individual variation. This technique demonstrated that EMLA 5% cream is significantly more effective than 40% lidocaine ointment. Lasers Surg. Med. 23:167–171, 1998.**

Key words: anesthetics; double-frequency Nd:YAG laser; EMLA; lidocaine; pulsed-dye laser; thermal threshold

INTRODUCTION

Local anesthetics are agents whose prime objective is to reduce the sensory input to the central nervous system by blocking nerve conduction on any type of nerve fiber in the nervous system when applied locally in appropriate concentrations [1]. The ideal local anesthetic should have minimal or no side effects, should exert its effect in the shortest time possible, and should not produce irreversible damage to nerve fibers while providing a lasting effect to complete any planned procedures. Furthermore, the delivery methods of local anesthesia should produce no distress or pain. It is known that the effects of topical anesthetics is faster in the mucosa than in the skin, and it seems that the duration is directly related to the time in contact with nervous fibers [1].

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Lidocaine and prilocaine hydrochloride are amide compounds that provide anesthesia by combining with a specific membranous receptor within or near the sodium channel. These agents physically block the channel that stops the impulse transmission by reducing the transient increase in the permeability of the membrane to sodium ions [1]. Forty percent (40%) lidocaine in an acid mantle ointment has been used empirically as a topical anesthetic for dermatologic procedures. Recently the two local anesthetic bases have been combined in an eutectic mixture that increases the droplet concentration by a factor of 4, compared with a lidocaine emulsion, enhancing significantly the dermal analgesic properties [2,3].

Different perceptible pain inducers for evaluating anesthetic efficacy have been carried out, including pin-prick test and thermal stimuli. Laser pulses as thermal pain stimulus are especially suitable and seem to offer some advantages over the above methods because a) laser stimuli are well controlled, measurable, and reproducible, b) they can be applied to different skin areas, and c) they can elicit a specific afferent activity without contamination from mechanosensitive receptors [4,5]. Laser-induced perceptible sensations consist of short, mechanical "snaps" from the laser pulse, accompanied by a pricking sharp sensation, and then a sensation of heat. These cutaneous sensations seem to be conducted by C- and Aδ-fibres in skin nerves [6–9]

The aims of this study therefore are to validate the use of non-scarring pulses of a 585 nm Pulsed Dye laser and double frequency Nd:YAG laser as a method to evaluate the effectiveness of topical anesthetics as well as to compare the relative efficacy of EMLA 5% cream with 40% lidocaine in an acid mantle ointment for reducing the pain sensation associated with laser pulses.

MATERIAL AND METHODS

Subjects

Eight healthy volunteers older than 18 years old were enrolled for this investigation after receiving and signing an informed consent. Subjects were tested once a week for 4 weeks. Thirty-two evaluations per compound were carried out. Internal control tests were made prior and after anesthetics' assessment in order to ascertain reproducibility.

Local Anesthetics Evaluated

Ninety grams of EMLA 5% cream (Astra USA, Inc., Westborough, MA) and of 40% lidocaine in an acid mantle ointment were prepared and placed in labeled syringes by a pharmacist blinded to the study. The mixture compounds remained blinded for all study participants (investigators and subject volunteers).

Laser Stimulation

A 585 nm flashlamp-pumped PDL (LPDL-1, Candela Laser Corp., Natick, MA) was used. The stimulation duration was 300 ns covering a spot size of 5 mm diameter. Energy density used was 5.5 J/cm^2.

A Nd:YAG laser (1064 nm, Continuum MEDLITE, Santa Clara, CA) emitting energy at 1,064 nm was used. The stimulus duration was of 6 to 10 ns and the beam diameter 3 mm. Energy density used was 5.2 J/cm^2 in the three first test weeks; finally, all test sites studied in the last week received energy density pulses of 6.5 J/cm^2.

Energy levels used were selected according to our experience with these two laser systems and were enough to provoke perceptible sensation but insufficient to induce scarring or pigmentary changes. Stimuli were applied to the ventral forearm within a target area, always measured at 10 cm from the wrist.

Protocol Design

Forty percent lidocaine in an acid mantle ointment was prepared three days in advance. The latter and EMLA 5% cream were placed in similar containers and kept at room temperature (25°C). Containers were labeled in a double-blind manner with the code known only to the pharmacist. The applied quantity of each compound was approximately 1.3 gm (1 ml). They were applied on test sites on the ventral forearm, 10 cm from the wrist, using coded labeled syringes. After application, the area was covered with a small impermeable plastic (Tegaderm, 3M Health Care, St. Paul, MN) for an average time of 90 minutes. Cross-over testing of the arms was done on all subjects.

Evaluation Criteria

During skin test exposure to laser pulses all subjects were asked to close their eyes so they would not expect sensation in a particular area. The maximum pain sensation was obtained by testing the untreated skin with both lasers. It was considered individually as 100% sensation and

used as internal control. By using this internal control sensation, each subject was then tested by both laser procedures in order to evaluate anesthesia degree of each compound and the perception felt was assessed as a certain percentage and scored as follows: 0, no sensation; 1+, 1 to 25%; 2+, 26 to 50%; 3+, 51 to 75%; and 4+, 76 to 100%. The lowest stimulus intensity was below sensory threshold and the highest intensity was well above pain threshold.

Statistical Treatment

The reduction of perceptible pain sensation referred to us by all the volunteers as a response to treatment with each topical anesthetic was expressed as an absolute number and as mean ± standard deviation from the mean in case of group population tested. The results were analyzed statistically by using unpaired or paired Student's *t*-test.

RESULTS

All subjects developed mild, transient signs of local irritant skin reactions to the impermeable occlusions as well as slight blanching of the skin. These cutaneous reactions lasted less than 2 hours after removal of the occlusive dressing.

Skin Sensation to Specific Pulse-Doses of Nd:YAG And PDL

Control skin sites exposed to a 5.5 J/cm^2 pulse from the 585 nm PDL showed none or very slight sensation graded 0 to 1+ respectively, according to our evaluation criteria. However, sensation after exposure of control skin sites to a 5.2 J/cm^2 pulse from Nd:YAG were referred by all tested volunteers as moderate to severe sensation, graded 2+ and 3+, respectively. Individual sensations from skin test sites during the four consecutive weeks were reproducible (see Table 1).

Anesthetic Response to EMLA 5% Cream and 40% Lidocaine Ointment

Since perceptible sensations from internal controls were very low with the PDL at the selected non-scarring dose, we decided to investigate the degree of anesthesia induced by these two mixture agents using the selected non-scarring dose of the Nd:YAG laser.

In general, anesthesia degree obtained by topical application of EMLA 5% cream was significantly greater than that obtained by topical application of 40% lidocaine ointment ($P<0.0001$). As shown in Figure 1, the tests carried out during weeks 1 and 4 evidenced a significant greater degree of anesthesia with EMLA cream than with 40% lidocaine ointment ($P=0.0069$ and $P=0.039$, respectively); however increases considered non-significant were found in the second and third tests. Lack of anesthesia was found in two of the test sites treated with EMLA 5% cream and in eight of those treated with 40% lidocaine ointment. Sensation in all these skin sites was described as severe or equivalent to individual internal control tests.

TABLE 1. Comparison Between EMLA Cream (A) and Lidocaine Ointment (B): Assessment Using a 1,064 nm Nd:YAG laser

	Week 1		Week 2		Week 3		Week 4	
Subject	A	B	A	B	A	B	A	B
1	2+	4+	0	0	0	0	0	0
2	4+	4+	0	1+	0	0	0	1+
3	0	1+	0	0	0	0	0	0
4	0	4+	0	0	0	0	0	0
5	0	3+	0	0	0	1+	0	1+
6	2+	2+	0	1+	0	1+	1+	1+
7	2+	4+	3+	3+	2+	4+	1+	4+
8	0	1+	0	4+	4+	4+	0	1+

On the other hand, complete anesthesia and absence of perceptible sensation were found in 23 (71.9 %) skin sites treated with topical application of the EMLA 5% cream and only in eleven (34.4 %) treated with the 40% lidocaine ointment.

The greatest anesthetic induction was reported in the second week of our investigation not only with EMLA 5% cream, but also with the 40% lidocaine ointment (Fig. 1).

DISCUSSION

Many attempts have been made to obtain a suitable topical anesthetic to minimize or eliminate the pain stimulus produced by a number of painful procedures, especially in children or adults with low pain threshold.

The main problem with topical anesthetics has been poor penetration through the epidermis. Of the topical anaesthetic agents, emulsified lidocaine has only 20% of the active compound per droplet; manufacturers of EMLA cream, however, claim that when lidocaine and prilocaine crystals are mixed, they form an eutectic mixture that produces an anesthetic emulsion with approximately 80% active compound [2,10]. Several studies have

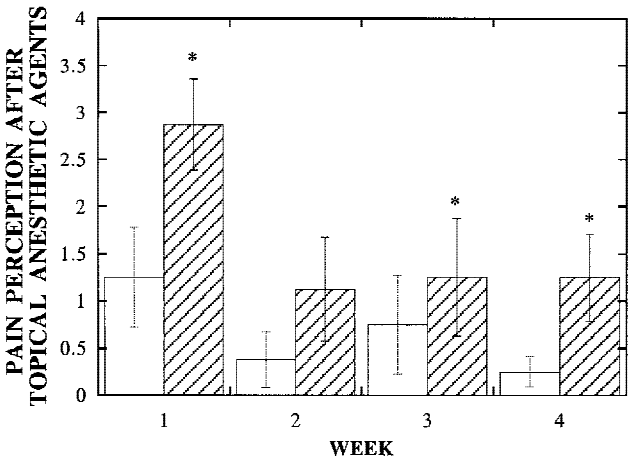

Fig. l. Pain perception values after topical application of EMLA cream (white column) and Lidocaine ointment (shaded column). Assessment using a 1064 nm Nd:YAG laser. *P <0.05 versus lidocaine ointment-treated skin.

shown that EMLA 5% cream can reduce pain associated with different therapeutic [11–14] or diagnostic procedures [3,15,16] after being under occlusion for only 5 minutes. A careful analysis of these studies, however, shows that the reduced perception of the sensation was not experienced uniformly by all the subjects. Furthermore, in a well-designed study, Arendt-Nielsen and Bjerring [17] showed that they were able to block pain sensation if EMLA cream was topically applied for 80 minutes and all sensations if applied for 100 minutes. These effects lasted up to two hours after application [18]. We thus decided to place both topical anesthetic compounds under occlusion for 90 minutes to ensure complete anesthetic effect.

We observed local irritant reaction as well as slight blanching on all skin sites lasting less than 2 hours after removal of the bandage. The blanching reaction seems to be due to superficial cutaneous vasoconstriction [2] caused by moisture under the occlusive dressing [18,19].

In our study, topical application of both anesthetic mixtures were effective in reducing the perceptible sensation induced by non-scarring doses of Nd:YAG laser pulses. The acid mantle ointment possibly allowed penetration through the skin due to its hydrophilic characteristics and to the increased hydration of the stratum corneum, but it does not cause complete anesthesia as often as the EMLA 5% cream. EMLA 5% cream was, therefore, significantly more effective than 40% lidocaine in an acid mantle ointment and induced complete anesthesia in twenty three out of the 32 tested skin sites (71.9 %), while 40% lidocaine in an acid mantle ointment induced complete anesthesia in 11 (34.4 %) areas.

The difference in the anesthetic effect between the two tested products may be due to the additive or synergistic effect of the two anesthetic ingredients in EMLA 5% cream, the enhanced penetration by the vehicle, and/or to the higher degree of homogeneity of EMLA 5% cream.

The quantification clinical technique used in this study gives us a reliable and reproducible measurement of perceptible pain thresholds as a function of thermal and nociceptive pathways with a low intra-individual variation.

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