Assessment of the Efficacy of Topical Anesthetics Using the Tactile Spatial Resolution Method

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SUMMARY
The aim of this study was to compare the purported advantages of 4% tetracaine gel (Ametop gel) and 4% liposomal lidocaine gel (LMX4 gel) with EMLA cream (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine) using an objective and repeatable method. Ametop gel and LMX4 gel were administered under occlusion for 30 min and compared to EMLA cream applied for 30 and 60 min on the intact upper lip skin of 15 volunteers each. The efficacy of the anesthetics was assessed by the spatial resolution method. Measurements were conducted just after removal of the products from the skin, then 20, 40 and 60 min later. Each of the formulations, except for EMLA cream applied for 30 min, decreased tactile spatial discrimination thresholds significantly just after removal from the skin when compared to the output levels (p<0.05). Ametop gel kept significantly good skin anesthesia also 20, 40 and 60 min later (p<0.05). The efficacy of LMX4 gel and EMLA cream decreased to the initial levels after 40-min application. Ametop gel anesthetized the skin in a highly homogeneous manner providing similar effect in most subjects, which was not the case in the EMLA and LMX4 groups. In conclusion, LMX4 gel and Ametop gel appeared to be faster acting than EMLA cream. Our results showed the 30-min application of LMX4 and Ametop gel under occlusion to be equivalent to 60-min administration of EMLA cream. Ametop gel, in contrast to the rest, provides very good anesthesia for up to 60 min. The application of EMLA cream under occlusion over only 30 min cannot guarantee appropriate effects.

KEY WORDS: tetracaine, liposomal lidocaine, EMLA, spatial resolution method, topical anesthesia

INTRODUCTION
The majority of minor dermosurgical and aesthetic medicine procedures are connected with pain and significant patient discomfort. Consequently, the associated stress and anxiety for some patients represent essential clinical concerns and even reasons to reject the treatment. Lately, with the emergence of
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As location is one of the factors influencing the action of topical anesthetics, our study on facial skin represents a new and interesting approach.

PATIENTS AND METHODS

Subjects

Forty adult volunteers were enrolled in this prospective, randomized clinical study (25 women and 15 men). The age of the subjects ranged from 23 to 60 (mean 36) years. All volunteers were in good health and no one breached any of the exclusion criteria, for example, known allergies or sensitivities to lidocaine, tetracaine, prilocaine, or other local anesthetic and known sensitivity to any component of the topical formulations (e.g., sulfites and adhesives). Skin on the examined site was not damaged, denuded, or broken. None of the women was pregnant or breast feeding. Concomitant use of any other medication, especially analgesic drugs (NSAID, opioids or acetaminophen), during the previous 48 h was excluded.

Anesthesia induction

Isopropyl alcohol swabs were used for skin disinfection and allowed to dry. An identical amount of each topical analgesic was used to cover the upper lip skin with an area of 1 cm x 1 cm indicated with eye pencil. LMX4 gel (4% liposomal lidocaine, Ferndale Laboratories, USA) and Ametop gel (4% tetracaine, Smith&Nephew, UK) were administered for 30 min in 15 volunteers each. EMLA cream (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, AstraZeneca, Sweden) was applied either for 30 min (EMLA5) or 60 min (EMLA6) in 15 volunteers each. The application of subsequent analgesic in the same patient was preceded by one week off. The occlusive dressing (Stella Pack SA, Poland) was placed over the study drugs. The sample selection was independent of sex and age. There was no difference in Fitzpatrick skin phenotype between the compared subgroups.

Spatial resolution measurements

Immediately upon drug removal from the skin, cutaneous spatial resolution measurements were introduced with JVP domes (Stoelting Co., Wood Dale, USA) according to standard practice (5). The method invented by Johnson, Van Boven and Phillips was employed to enable objective assessment of touch sensation on the lip, tongue and finger. The kit consists of 8 acrylic probes with equidistant bar and groove widths nominally equal to 0.35, 0.5, 0.75, 1.00, 1.25, 1.5, 2.00 and 3.00 mm. Each probe has a columnar handle and a dome shaped head. The head has an alternating ridge/slot pattern with different widths for each probe.

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During measurement, the ridged head is pressed against the skin, and the subject reports the alignment of the ridges, longitudinal or transverse. Subjects were comfortably seated in a noise-reduced room at an ambient temperature of 24 °C. All the measurements were made by the same investigator and special care was taken to press the probe with identical force.

Two series of measurements were recorded with a maximum of 10 applications of each probe starting with the largest groove diameter. The aim of the measurement is to find two boundary probes: one which is recognized by the subject properly in more than 75% of attempts and a second probe which is recognized in less than 75% of attempts. The number of correct answers obtained with those two probes was fed into an equation that interpolates and yields a sensitivity number determined as a spatial discrimination threshold (SDT). SDTs were plotted in a range from 0.35 to 4.0, wherein higher (near 4.0) values reflected better topical anesthesia and contrary values close to 0.35 indicated very good skin sensation (poor anesthesia). Measurements were made 4 times, i.e. just after product removal from the skin, then 20, 40 and 60 min later.

**Analysis of side effects**

Safety and tolerability were evaluated based on the frequency of adverse effects and on the evaluation of skin reactions after removal of each study analgesic. A written informed consent was obtained from each person.

**Statistical analysis**

Statistical analysis of the results was conducted using Statistica software (Statsoft, Krakow, Poland). The ANOVA rank Kruskal-Wallis test was employed. Results were expressed as means ±SD. P values under 0.05 were considered statistically significant.

**RESULTS**

The mean spatial discrimination thresholds (SDT) in each group were similar before analgesic application. The mean values of SDT were as follows: 0.825±0.382 for Ametop gel, 1.03±0.248 for LMX4 gel, 0.971±0.349 for EMLA cream, and 0.879±0.279 for EMLA cream (Fig. 1).

Each of the formulations applied under the occlusion decreased tactile spatial discrimination significantly when measured just after removal from the skin compared to the output levels (P<0.05). When removed from the skin, Ametop gel showed the strongest anesthetic effect with a mean SDT of 3.169±0.537, followed by LMX4 gel (2.881±1.217), EMLA cream applied for 60 min (2.673±1.025) and EMLA cream applied for 30 min (1.877±0.794). The anesthetic properties of Ametop gel differed statistically significantly (P<0.05) from EMLA cream, which showed the poorest result.

Twenty minutes after removal, the efficacy of LMX4 gel and EMLA cream decreased significantly to 1.62±0.691 and 1.367±0.115, respectively (P<0.05). At that time, Ametop gel still showed the best anesthetic force (3.011±0.837), significantly better than LMX4 gel and EMLA cream, and at the border of significance compared to EMLA cream (2.02±0.764; P=0.06).

The degree of anesthesia assessed 40 min after Ametop gel removal from the skin slightly increased (3.188±0.546) and was statistically better than LMX4 gel (1.339±0.558), EMLA (1.391±0.685) and EMLA cream (0.984±0.327) (P<0.05). The efficacy of LMX4 gel and EMLA cream after 40 min decreased and did not differ from the initial measurements.

Sixty minutes after removal from skin, the mean spatial discrimination thresholds reached output levels, i.e. 0.96±0.297 for LMX4 gel, 1.13±0.365 for EMLA cream, and 0.91±0.286 for EMLA cream. All of them were statistically lower than SDT for Ametop gel, which was reduced slightly to 2.03±0.778 (P<0.05). At that time point, 4% tetracaine still provided good anesthesia, superior to the initial measurements (P<0.05).

After 30 min of occlusion, Ametop gel anesthetized the skin in a very homogeneous manner providing a similar effect in most of the subjects, a result that was not seen in the EMLA and LMX4 groups. Additionally, 4% tetracaine was also shown to be superior to output measurements at each time point, i.e. just after, and 20, 40 and 60 min after gel removal (P<0.05).

**Site effects**

In the study group, all of the analgesics were well tolerated, with only mild treatment-related adverse events. Skin blanching was noted in three of 15 subjects treated with EMLA cream under 60-min occlusion, and two of them suffered additionally from skin burning. Skin erythema appeared in two of 15 subjects anesthetized with Ametop gel. No adverse skin reaction was recorded after LMX4 gel treatment. In all cases, side effects were transient and resolved spontaneously before the end of the protocol.

**DISCUSSION**

Using the objective and repeatable measurement method, this study demonstrated the superiority of Ametop gel over EMLA cream and LMX4 gel in cutane-
ous anesthesia. In contrast to our data, in earlier studies topical analgesics were compared only by visual analog scale or verbal rating scale. The lack of painful stimuli could be considered as a disadvantage. Preferably, tactile sensation is conveyed mainly by Aβ class of nerve fibers, which are affected by local anesthetics in a slightly higher concentration as compared to Aδ and C fibers conducting pain stimuli. However, the proposed method enables repetition of measurements in various periods with many measurements in a single series. Moreover, results are more reliable given that examination was performed on facial and not limb skin, as had been the case in previous studies.

Our results are in accordance with data published by Lander et al. (6), which significantly favor tetracaine over EMLA with regard to the efficiency in reducing pain on venous cannulation in children. Olday et al. (7) compared a 60-min application of topical 4% tetracaine gel with infiltrated local anesthetic during radial artery puncture and found comparable efficacy between these forms of anesthesia. Other reports based on visual analog scale score did not show statistically significant differences between EMLA and tetracaine in reducing pain and distress on intravenous cannulation (8-10).

Indisputably, tetracaine has a much faster onset of action, which is advantageous in many clinical situations. The depth and thus the efficacy of analgesia is dependent on the duration of analgesic application on the skin. Maximum depth achieved by EMLA cream is 4.5 mm after 90 min, 3.0 mm after 60 min and 5 mm at the end of 2 h application (11). Therefore, the optimal occlusion time for EMLA ranges from 60 to 120 min and for both 4% tetracaine and 4% liposomal lidocaine from 15 to 60 min only. The manufacturer discourages the application of Ametop gel for more than 1 h.

In this study, we proved that 30-min application of both Ametop and LMX4 gel appeared to be sufficient for adequate anesthesia. The analgesic effect after 30-min EMLA cream occlusion will probably be unsatisfactory or at least not long enough.

Our results revealed that Ametop gel, in contrast to LMX4 and EMLA cream, provided a very similar degree of anesthesia in each subject. We also noted an increased anesthetic benefit 30 min after removal of Ametop gel from the skin, probably resulting from a reservoir of anesthetic that is located and stored in the stratum corneum (12).
The very low permeability of intact skin is the main rate limiting factor of drug efficacy. Thus, attempts are made to improve the penetration of creams. EMLA cream is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine in oil and water emulsion with a melting point (17 °C), which is lower than either for lidocaine (66-69 °C) or prilocaine (36-38 °C) and hence exists as a liquid at body temperature enhancing its absorption. EMLA pH of 9.6 is also higher than that of other analgesics, which is in accordance with Setnik, who found that increasing the pH increased the potency of the topical anesthetic agent (13). Also, a combination of two drugs in a single agent contributes to its increased efficacy (14). Despite these potential superiorities, the EMLA cream action seems to be unsatisfactory.

Esters, but not amides, are metabolized to highly antigenic p-aminobenzoic acid (PABA), which is the most likely cause of allergic reactions to ester anesthetics. Hence, amides are safer and preferred to esters (15). Contact hypersensitivity to topically applied analgesics was, however, observed before (16,17). Topical allergic reaction is usually mild, limited to development of dermatitis or contact urticaria. Transient local skin reactions, usually after prolonged application of topical anesthetic, include erythema, blanching and edema, as recorded in our study. Special care must be taken when applying EMLA cream close to the orbit. Contamination of eye can cause irritation, pain, tearing and even damage to the cornea (18). The most important adverse effect of EMLA cream is methemoglobinemia (MetHb), which has mostly been seen in infants (19). Thus, EMLA cream should not be used with other drugs accelerating the formation of methemoglobin (20).

The local side effects described above also result from the vasoconstrictive and vasodilative properties of local analgesics. Topical tetracaine in various forms has a known intrinsic vasodilatory influence that produces erythema (21). In contrast, EMLA cream shows biphasic vasoactive response. Initially, it causes vasoconstriction with skin blanching, but with a longer application time of up to 180 min EMLA cream may also result in vasodilatation (22). LMX4 gel was proved in our group to have no visible influence on skin vessels. Due to their vasoactive properties, local analgesics may influence laser energy absorption. Thus, the effects might be either problematic (in case of EMLA cream) or beneficial (in case of Ametop or LMX4 gel) during such procedures as vascular-specific laser treatment. In a double-blind randomized controlled trial conducted by McCafferty et al. (23), amethocaine preparation was significantly better than EMLA in reducing pain during pulse dye laser treatment of port-wine stains.

Lidocaine itself has low skin permeability, so liposomes as drug carriers were introduced to protect the anesthetic from metabolic degradation, to provide sustained release, and to exert better overall anesthetic effect (24). According to the literature, the advantages of liposomal formulations over older analgesics are not so clear. In children, comparable efficacy between liposomal lidocaine 4% gel and EMLA cream has been described (25). EMLA cream administered for 60 min gave equivalent analgesia to 4% liposomal lidocaine applied for only 30 min. Our results do not unequivocally favor LMX4 gel; however, liposome-encapsulated lidocaine is preferable to EMLA cream because of the shorter application time required and the fact that there is no need to use occlusive dressing. The data presented do not coincide fully with the randomized, double-blind comparison reported by Carter et al. (26), where both LMX4 gel and EMLA cream provided comparable and sufficient levels of anesthesia after a short (30-min) application under occlusion prior to electrodesiccation of superficial skin lesions. It has also been proved that LMX4 gel can be used safely before superficial and medium-depth peels, even on larger areas. The clinical and histopathologic results of the 35% TCA and 70% glycolic acid peel were not affected by the combination of medium-depth peel with topical anesthesia (2,27). Carruthers et al. (28) revealed that LMX4 gel effectively anesthetized skin before botulinum toxin type A injections. LMX4 gel is not associated with Met H band in comparison to other formulations it has a higher safety profile.

None of these drugs is recommended for use in pregnant women or breast-feeding mothers. According to the manufacturer’s information, in the absence of more secure methods of anesthesia, lidocaine can be used in pregnant women. This medication is not expected to be harmful to an unborn baby. Although lidocaine is excreted in breast milk, after application of typical doses there is no harm to the health of a breast-fed child (29). There is no specific information as to the safety of tetracaine in pregnancy. It is not known whether tetracaine is excreted in breast milk.

CONCLUSIONS

In conclusion, it can be stated that topical analgesics are safe formulations when properly used. LMX4 and Ametop gels appeared to be faster acting than EMLA cream. Our results showed the 30-min application of LMX4 and Ametop gels under occlusion to be equivalent to 60-min administration of EMLA cream measured just after removal. The degree of anesthesia obtained after LMX4 gel and EMLA cream decreased quickly compared to Ametop gel, which pro-
vided a significantly greater effect up to 60 min with a maximum after 40 min. At the same time, tetracaine in contrast to LMX4 gel and EMLA cream ensures very homogeneous results. Our outcomes also confirmed that 30-min application of EMLA cream, even under occlusion, could not guarantee adequate effects. Additional research with shorter administration times is expected to bring new, useful data.

Acknowledgments

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