Comparative Study of the Efficacy of Four Topical Anesthetics

Paul M. Friedman, MD, Joshua P. Fogelman, MD, Keyvan Nouri, MD, Vicki J. Levine, MD and Robin Ashinoff, MD

Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York

BACKGROUND. With the emergence of new laser and dermatologic procedures, the need for more effective topical anesthesia continues to grow. There are now several topical anesthetics that are being used prior to laser and surgical procedures.

OBJECTIVE. To compare the degree and duration of anesthesia produced by four commonly used topical anesthetics, we performed a prospective study investigating the efficacy of EMLA (eutectic mixture of local anesthetics), ELA-Max, 4% tetracaine gel, and betacaine-LA ointment (formerly eutectic-LA). Methods. Equal amounts of the above topical anesthetics plus a control (eucerin cream) were applied to 10 test sites under occlusion on the volar forearms of 12 adult volunteers. After a 60-minute application time, the degree of anesthesia was assessed immediately by a Q-switched Nd:YAG laser at 1064 nm. Pain testing was also performed 30 minutes after the 60-minute application period. Volunteer responses to pain stimuli were recorded using an ordinal scale of 0 (no pain) to 4 (maximal pain). The mean scores for the time intervals were obtained. Analysis of the data was performed using analysis of variance (ANOVA), Newman–Keuls test, Friedman rank order test, and paired t-tests.

RESULTS. ELA-Max, EMLA, and tetracaine were statistically superior to control after the 60-minute application period. Thirty minutes later, ELA-Max, EMLA, tetracaine, and betacaine-LA were all statistically superior to the control. Comparing individual anesthetics, ELA-Max and EMLA were the superior anesthetics at both time intervals. Although the mean pain scores for each anesthetic were lower 30 minutes after their removal, the differences did not reach statistical significance.

CONCLUSION. This is the first prospective study comparing the efficacy of several new topical anesthetic agents. Using the methodology of this study, in which the anesthetics were applied under occlusion, ELA-Max and EMLA were the superior anesthetics after a 60-minute application time and 30 minutes later. In addition, there was a clinical increase in efficacy suggested with all of the anesthetics 30 minutes after their removal.

WITH THE EMERGENCE of new laser and surgical techniques, the need for more effective topical anesthesia continues to increase. There are now several topical preparations of local anesthetics that are being used prior to dermatologic procedures. Topical anesthetics block impulse conduction by interfering with the function of sodium channels. By inhibiting sodium flux, the threshold for nerve excitation increases until the ability to generate an action potential is lost. Topical anesthetics are weak bases typically constructed of three important components: an aromatic ring, an intermediate-length ester or amide linkage, and a tertiary amine.

Different methods for evaluating and comparing anesthetic efficacy have included venipuncture,1–7 pin-prick testing,8 split-thickness skin graft donation,9–11 and laser pulses as pain stimuli. Laser pulses are advantageous as pain stimuli, offering reproducible, quantifiable stimuli with minimal intraindividual variation. Laser pulses also provide selective activation of nociceptors, without interference from mechanosensitive receptors.12,13

EMLA cream is a 5% eutectic mixture of two local anesthetics, lidocaine and prilocaine. It was released in the United States in 1993 and is composed of 25 mg/ml of lidocaine and 25 mg/ml of prilocaine in an oil-in-water emulsion cream. It is the most widely used topical agent, with proven efficacy from several clinical trials.1–13 EMLA has shown dermal analgesia after application under an occlusive dressing for 60 minutes, with inadequate analgesia after application for only 30 minutes (Table 1).14–16 Dermal analgesia has been shown to continue and even increase for 15–30 minutes after its removal.12,14

ELA-Max is a 4% lidocaine cream in a liposomal vehicle. The liposomal encapsulation uses lipid bilayers to deliver the anesthetic into the dermis. The recommended application time is 15–45 minutes with no occlusion required (Table 1).

Betacaine-LA ointment is a newly formulated topical anesthetic containing lidocaine, prilocaine, and a
vasoconstrictor. It is a proprietary anesthetic and the exact concentrations of its ingredients are a trade secret. The manufacturer reports concentrations of lidocaine and prilocaine to be four times that found in EMLA in a petrolatum vehicle. This compounded anesthetic also contains a vasoconstricting agent similar to epinephrine. Betacaine-LA is not approved by the U.S. Food and Drug Administration (FDA) and must be obtained through its manufacturer. The recommended application time is 30–45 minutes with no occlusion required (Table 1).

Tetracaine gel is a compounded, proprietary anesthetic containing 4% tetracaine in a lecithin gel base. It is a long-acting ester anesthetic with a recommended application time of 30 minutes under an occlusive dressing. Allergic contact reactions to the ester group of anesthetics are common, while amide anesthetics, including lidocaine and prilocaine, are rare sensitizers.\(^{17,18}\) Tetracaine gel is not approved by the FDA and must be obtained through its manufacturer (Table 1).

There have been no published clinical trials to date regarding the safety or efficacy of these newer topical anesthetics, which were released in 1997–1998. The aim of this study was to compare the efficacy of these four commonly used topical anesthetics by selective stimulation of cutaneous nociceptors with laser pulses.

### Materials and Methods

#### Subjects

Twelve healthy, adult volunteers (5 women, 7 men) with a mean age of 35 years, participated in this study. Subjects with a history of allergy to amide or ester anesthetics, cardiac or respiratory disease, seizure disorders, or neuropathy were excluded. Exclusion criteria also included pregnancy and age less than 18 years. Nine of the 12 volunteers returned for two additional sessions at 2-week intervals, improving the precision of the data points. Informed consent was obtained.

#### Topical Anesthetics Evaluated

The volar forearms of the volunteers were cleansed with isopropyl alcohol swabs and allowed to dry. Equal amounts (0.3 ml) of betacaine-LA ointment, ELA-Max cream, EMLA cream, 4% tetracaine gel, and placebo (eucerin cream) were applied to 10 test sites under an impermeable plastic occlusion dressing. The volunteers were blinded to individual test areas.

The anesthetics were placed on the volar forearms in reverse order so that the anesthetics that were placed distally on one forearm, where there are increased nerve fibers and pain receptors, were placed proximally on the other forearm (Figure 1). The results were then averaged so that a mean overall pain score was obtained. All of the anesthetics were occluded, including betacaine-LA and ELA-Max, to allow for controlled, uniform application and comparison without adding an additional variable.

#### Laser Stimulation

Following a 60-minute application period, the occlusive dressings and anesthetics were removed. The degree of anesthesia was immediately assessed using two pulses of a Q-switched Nd:YAG laser emitting energy at 1064 nm. The stimulus duration was 10 nsec and the beam diameter 3 mm. Fluence was standardized at 5 J/cm\(^2\). At these settings, the Nd:YAG laser has been shown to produce a perceptible pain sensation for assessing topical anesthetics without the risk of inducing pigmenary or scarring changes.\(^{13}\) Pain testing was also performed 30 minutes after the 60-minute application period. Subjective responses to laser-induced pain stimuli were recorded using an ordinal scale of 0 (no pain) to 4 (maximal pain). Maximal pain for each subject was determined by testing untreated volar arm skin with a laser stimulus, which was used as an internal control.

#### Statistical Analysis

The results were analyzed statistically with repeated measures analysis of variance (ANOVA), allowing evaluation of each anesthetic compared with placebo after the 60-minute application period and 30 minutes after removal. Newman–Keuls tests were performed to compare individually each of the anesthetics against placebo, and then used to determine differences in efficacy between each individual anesthetic by parametric analysis. Friedman rank order tests were utilized to confirm any significant differences between anesthetics with nonparametric evaluation.\(^{19,20}\) Paired t-tests were used to compare each of the anesthetics at both time intervals.

### Table 1. Topical Anesthetics

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Ingredients</th>
<th>Vehicle</th>
<th>Recommended application time (minutes)</th>
<th>Occlusion required</th>
<th>FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betacaine-LA</td>
<td>Lidocaine:prilocaine*</td>
<td>Vaseline ointment</td>
<td>30–45</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ELA-Max</td>
<td>4% lidocaine</td>
<td>Liposomal</td>
<td>15–45</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>EMLA cream</td>
<td>2.5% lidocaine:2.5% prilocaine</td>
<td>Oil-in-water</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tetracaine gel</td>
<td>4% tetracaine gel*</td>
<td>Lecithin gel</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Compounded, proprietary anesthetic.
Results

Individual comparisons with ANOVA for the 60-minute data showed that ELA-Max ($P = .001$), EMLA ($P = .004$), and tetracaine ($P = .007$) were statistically better than the control, while betacaine-LA demonstrated borderline superiority ($P = .07$) (Figure 2). When the Newman–Keuls test was performed to control for multiple comparisons of the 60-minute data, each anesthetic group gave a significantly lower score than the control group. Individual anesthetics compared at 60 minutes using the Newman–Keuls procedure demonstrated that ELA-Max was significantly better than betacaine-LA ($P < .01$) or tetracaine ($P < .05$), and EMLA was significantly better than betacaine-LA ($P < .05$). There were no other statistically significant differences among the anesthetics at 60 minutes.

Individual comparisons with ANOVA for the data obtained 30 minutes after the removal of the anesthetics demonstrated that all topical agents were significantly better than the control ($P < .021$) (Figure 3). When the Newman–Keuls test was performed to control for multiple comparisons of the data obtained at this time interval, each anesthetic gave a significantly lower score than the control. Comparing individual anesthetics with the Newman–Keuls test, ELA-Max and EMLA were both significantly better than tetracaine and betacaine-LA ($P < .01$) (Figure 4).

The Friedman rank order test also demonstrated an overall statistical difference among the four anesthetics at 60 minutes ($P = .008$) and 30 minutes later ($P = .028$). These results are similar to the parametric results obtained with the repeated measures ANOVA, which suggests that the parametric ANOVA assumptions of normality and of common variances and covariances were appropriate.

Individual comparisons of the efficacy of each of the anesthetics at both time intervals were performed using paired $t$-tests. Although the mean pain scores for each anesthetic were lower 30 minutes after their removal, the differences did not reach statistical significance.

An occasional side effect from the topical anesthetics included blanching or erythema at the site of application, which resolved within 2 hours. A temporary, local irritant skin reaction to the occlusive dressing also occurred in some of the volunteers.

Discussion

Topical anesthetics are commonly used by dermatologists to decrease the pain associated with laser pulses or surgical procedures. EMLA is the most commonly used agent prior to dermatologic procedures, however, there has been a recent release of newer topical anesthetics claiming increased efficacy and faster onset of action. This is the first published clinical trial re-
Regarding the efficacy of betacaine-LA, ELA-Max, or tetracaine gel.

Using the methodology of our study, in which all of the anesthetics were occluded, ELA-Max and EMLA were the superior anesthetics at both time intervals. Although the data favored ELA-Max over EMLA, the difference was not statistically significant. ELA-Max contains lidocaine in a liposomal delivery system, which uses multilamellar vesicles containing several lipid bilayers dispersed in an aqueous medium. Liposomes facilitate the penetration of anesthetic into the skin, carrying the encapsulated drug into the dermis and providing sustained release. Liposomes as drug carriers also protect the anesthetic from metabolic degradation, allowing prolonged duration of action. Prior studies have also shown the benefit of liposomal encapsulation in the delivery of topical anesthetics. As assessed by the pinprick method, liposomally encapsulated tetracaine (0.5%) has been shown to be more effective than tetracaine in an inert base in producing significant skin anesthesia. Bucalo et al. found that after an application time of 30 minutes, liposomal lidocaine preparations evidenced longer duration of anesthesia than lidocaine preparations in nonliposomal vehicles.

There was a suggested clinical increase in efficacy noted with all of the anesthetics 30 minutes after their removal, as demonstrated by decreased mean pain scores. This difference did not reach statistical significance, likely due to the small sample size. The analgesic effect of EMLA cream has previously been shown to increase 15–30 minutes after its removal, likely resulting from a reservoir of anesthetic that is located and stored in the stratum corneum. After the anesthetics are removed, the diffusion from the stratum corneum to the dermally located sensory nerves continues, providing ongoing analgesia. Our results support the suggestions of Arendt-Nielsen and Bjerring, who recommend application of EMLA cream under occlusion 1 hour prior to laser treatment, followed by removal on the way to the hospital, increasing the ability to diminish pain during treatment.

A cost comparison of the two superior anesthetics in this study revealed that ELA-Max is substantially less expensive than EMLA (Figure 5). A 30 g tube of EMLA at the New York University Medical Center outpatient pharmacy cost $53.25, while the same amount of ELA-Max was obtained for $26.03 through the distributor for the manufacturer. All of the topical anesthetics used in this study except for EMLA can be obtained by a physician at the manufacturer’s cost.

The weaknesses of the study included a small sample size, a lack of randomization of placement of anesthetics, and the subjective reporting of pain sensations. An additional potential weakness is the assumption that the statistically significant differences in mean pain scores are clinically relevant. Additional parameters such as shorter application times and occlusion versus nonocclusion should be evaluated in future studies.

There are now several topical preparations of local anesthetics that are being used prior to various dermatologic procedures. We report the first prospective study comparing the efficacy of several new topical anesthetic agents and demonstrate their efficacy by comparison with a control. Our study indicates that liposomal encapsulation provides increased efficacy in the delivery of anesthetic into the dermis. In addition, our results suggest that a reservoir of anesthetic is located and stored in the upper skin layers during application, providing additional anesthetic benefit 30 minutes after removal.

Acknowledgment We wish to thank Dr. Roy E. Shore, Division of Epidemiology and Biostatistics, New York Univer-

![Figure 4. ELA-Max and EMLA were superior to tetracaine and betacaine-LA 30 minutes after the 60-minute application period.](image)

![Figure 5. Cost comparison.](image)

*Can be obtained at manufacturer’s cost.
**NYU pharmacy cost.
sity School of Medicine, for his assistance with the statistical analysis.

References