The rates of nonsurgical cosmetic surgery procedures such as botulinum toxin injections, fillers, and laser treatments are increasing. Often, these nonsurgical procedures require either a topical or injectable anesthetic to ensure adequate analgesia during the procedure. Injectable forms of anesthetic, although efficacious, are uncomfortable for the patient. Preclinical studies have demonstrated that laser pretreatment at low energies enhances absorption of topical lidocaine. Preclinical studies have demonstrated that laser pretreatment at low energies enhances absorption of topical lidocaine. Injectable forms of anesthetic, although efficacious, are uncomfortable for the patient. Preclinical studies have demonstrated that laser pretreatment at low energies enhances absorption of topical lidocaine. Injectable forms of anesthetic, although efficacious, are uncomfortable for the patient. 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Abstract

**Background:** Injectable forms of anesthesia for nonsurgical facial rejuvenation, although efficacious, are uncomfortable for the patient. Preclinical studies have demonstrated that laser pretreatment at low energies enhances absorption of topical lidocaine.

**Objectives:** The authors assess the safety and efficacy of laser-assisted transdermal delivery of topical anesthetic.

**Method:** Ten patients were split into 2 groups (A and B). All patients received 15 g of BLT (20% benzocaine, 6% lidocaine, and 4% tetracaine triple anesthetic cream) for 20 minutes with no occlusion. Then the cream was removed and the first blood draw taken. Group A patients were pretreated with the full ablative laser and group B patients with a fractional ablative laser to the full face. A further 15 g BLT was applied for another 20 minutes. Group A patients then underwent full ablative laser treatment, and group B received fractionated ablative laser treatment. Blood draws were taken at 60, 90, 120, 180, and 240 minutes after the initial topical anesthetic application, and the serum was analyzed for lidocaine and monoethylglycinexylidide (MEGX) levels. Patients were asked to rate the pain felt at intervals during the procedure.

**Results:** No patient required supplemental nerve blocks. Pain scores were equivalent at the end of the first pass for both groups (P = .436). Group A patients had significantly lower pain scores at the start of the second laser treatment (P = .045), but pain scores became equivalent by the end (P = .325). Combined serum lidocaine and MEGX levels were significantly higher in group A patients up to 90 minutes (peak average of 0.61 µg/mL for group A and 0.533 µg/mL for group B; P = .0253), which corresponded to greater initial analgesic effect.

**Conclusions:** Data from this study demonstrate that topical anesthetic for facial rejuvenation can be enhanced with laser pretreatment while maintaining safe blood serum levels. Further studies should examine optimal application amount and time to allow safe multipass facial rejuvenation without the need for invasive nerve blocks.

**Level of Evidence:** 3

**Keywords**

cosmetic medicine, research, topical anesthetics, laser-assisted transdermal delivery, pain

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Preclinical studies by our group have demonstrated that laser pretreatment at low energies enhances absorption of topical lidocaine.5 Our previous study demonstrated that at very low energy settings, pretreatment with the laser caused increased systemic absorption of lidocaine in a porcine model. The serum levels of lidocaine and its metabolite, however, remained well below the levels that would be considered toxic. Physiologically, lidocaine is broken down into monoethylglycinexylidide (MEGX), an active metabolite that has a similar toxicity. Lidocaine typically has a half-life of approximately 2 hours in individuals with normal hepatic function. We have also seen significant interperson variability with regard to lidocaine metabolism in previous studies.6

We hypothesized that serum lidocaine levels would rise and the risk of lidocaine toxicity would increase in individuals who undergo treatments leading to the disruption of normal physiological barriers to dermal absorption, although this has not been proven. Lasers can be used to ablate the stratum corneum of the skin and therefore enhance absorption of topically applied drugs. To our knowledge, no documented studies have examined the serum concentrations of lidocaine and its metabolite MEGX in this context, so that was our aim: to look at the serum levels of lidocaine and MEGX after the application of topical lidocaine following pretreatment of the skin with an ablative laser.

**METHOD**

Ten patients were consented and screened in accordance with Title 45 Code of Federal Regulations, Part 46, Protection of Human Subjects (45 CFR part 46) for participation in this study, approved by the University of Texas Southwestern Medical Center Institutional Review Board (IRB). Prior to treatment, all patients had photographs taken. The inclusion/exclusion criteria are summarized in Table 1. Patients were randomly assigned to either group A or group B.

At time 0, all patients had 15 g of BLT (20% benzocaine, 6% lidocaine, and 4% tetracaine) triple anesthetic cream applied to their face for 20 minutes with no occlusion. The topical anesthetic was then removed and the first blood draw made.

**First, Superficial Laser Treatment**

Patients in group A underwent a superficial pretreatment to the face with the full ablative Er:YAG laser (Sciton PROFILE 2940 nm; Sciton, Palo Alto, California). Laser settings were 15 microns (2.8 J/cm²). Patients in group B had a superficial pretreatment with the fractionated CO2 laser (UltraPulse; Lumenis, San Jose, CA) (15 mJ [1.1 J/cm²], 300 MHz [4.5 W], density 2, column spot size 1.3 mm). Immediately after these treatments, a further 15 g of BLT was reapplied to the faces of patients in both groups and left without occlusion for another 20 minutes.

**Second, Deeper Laser Treatment**

After removal of the second application of topical anesthetic, the second laser treatment commenced. For group A patients, the Er:YAG laser setting for the deeper treatment was 100 microns (25 J/cm²) on the full ablative setting. For group B patients, the fractionated CO2 laser (UltraPulse; Lumenis) setting for the deeper treatment was 50 mJ (3.8 J/cm²), 300 MHz (15 W), density 3, and column spot size 1.3 mm.

At the patient’s request, analgesia could be supplemented with 1% lidocaine (plain) in the form of nerve blocks. We planned that these requests would be recorded and those patients would still have their blood taken. The total amount of lidocaine administered by any route was capped at 2 mg/kg.

**Blood Draws**

Blood serum samples (approximately 1 tablespoon, or 7 mL) were taken at 20 (immediately after the topical anesthetic was removed), 60, 90, 120, 180, and 240 minutes after application. These samples were taken via

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**Table 1. Inclusion/Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion</th>
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<tr>
<td>All races, sexes, and ethnicities</td>
<td>Pregnancy</td>
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<tr>
<td>Age between 18 and 89 years</td>
<td>Allergy to topical anesthetics</td>
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<tr>
<td>Seeking consultation for laser correction of fine lines, melasma, and/or acne scarring</td>
<td>History of heart arrhythmia, liver dysfunction, congestive heart failure, hypertension, chronic renal insufficiency, chronic renal failure, anxiety disorder, psychosis, or seizure</td>
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<tr>
<td>Wish to undergo full facial rejuvenation</td>
<td>Had microdermabrasion, severe sunburn, chemical peel, laser treatment, or other severe abrasions to the face/neck in the past 45 days</td>
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<td>Severe acne or subjects being treated with Accutane</td>
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<td>Had any disease causing abrasion or sloughing of skin of treatment area in the past 45 days</td>
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an intravenous line left in place for the course of the procedure.

**Patient Pain Score Questionnaire**

Patients were required to complete a short questionnaire rating their pain experience prior to discharge.

**Blood Sample Procurement and Analysis**

Again, whole-blood samples (approximately 7 mL) were collected in serum separator tubes (BD Vacutainer; BD, Franklin Lakes, New Jersey). The blood samples were centrifuged (3000 rpm for 10 minutes at 4°C), and the serum was aliquoted into Eppendorf tubes in duplicate and stored at −80°C until analyzed. The samples were sent to the Department of Clinical Chemistry at George-August University (Goettingen, Germany), where lidocaine and MEGX in plasma were analyzed using a previously described technique.

**Statistical Analysis**

The serum concentration-time courses of lidocaine and MEGX were characterized using Microsoft Excel (Microsoft Corp, Redmond, Washington). A repeated-measures analysis of variance (ANOVA) test for nonparametric data was used to analyze differences between the groups. Associations with $P < .05$ were considered statistically significant.

**RESULTS**

All 10 patients completed the study with no adverse events related to the topical anesthetic. No patient requested supplementary analgesia during the procedures.

**Pain Scores (Table 2)**

**Group A**

For group A patients, the average pain score for the first pass was 2.8 out of 10 (range, 1-6). For the second pass, the average pain score at the beginning was 1.4 (range, 0-4); it rose to 3.0 during the treatment (range, 1-4) and, by the end of the treatment, reached a peak of 4.6 (range, 2-7). All patients stated that they would undergo repeat treatments with this method of analgesia again.

**Group B**

For group B patients, the average pain score for the first pass was 3.0 out of 10 (range, 2-4). For the second pass, the average pain score at the beginning was 3.4 (range, 3-4); it rose to 3.6 during treatment (range, 2-6) and, by the end of the treatment, reached a peak of 4.0 (range, 2-6). All patients stated that they would undergo repeat treatments with this method of analgesia again.

**Comparing Pain Scores Between Groups A and B (Table 2)**

All patients in both groups complained of the most discomfort either around the lips or in the preauricular region. For the first pass, pain scores were equivocal between the 2 groups ($P = .436$). At the start of the second pass, pain scores were significantly higher in group B than in group A ($P = .045$). However, there was no statistical difference in pain scores between the groups during the middle of the second pass ($P = .213$) and treatment end ($P = .323$).

**Blood Serum Lidocaine and MEGX Levels**

For all patients in all groups, the serum levels of lidocaine and MEGX did not reach toxic levels (serum concentrations of greater than 5 µg/mL).

**Group A (Figure 1)**

For group A patients, the maximum combined serum level of lidocaine and MEGX in an individual patient was 0.935 µg/mL, and this occurred at 90 minutes. For all patients in this group, peak serum levels occurred between 60 and 90 minutes and started to decline thereafter. The average peak reading was 0.61 µg/mL, which occurred at 90 minutes.
There was significant interindividual variation among the patients within the group (P < .0001).

Group B (Figure 2)

For group B patients, the maximum combined serum level of lidocaine and MEGX in an individual patient was 0.533 µg/mL, and this occurred at 90 minutes. For all patients in this group, peak serum levels occurred between 90 and 120 minutes and started to decline thereafter. The average peak reading was 0.315 µg/mL, which occurred at 120 minutes. There was significant interindividual variation among the patients within the group (P < .0001).

Comparing Groups A and B

Over the entire time course, group A patients had higher average serum levels of lidocaine and MEGX, and this was statistically significant (P = .0253). On average, the serum levels of combined lidocaine and MEGX rose and fell more quickly in group A than in group B.

Correlating Pain Scores With Combined Serum Levels of Lidocaine/MEGX

For group A patients, there was a rapid increase in serum levels of lidocaine/MEGX by 60 to 90 minutes. These patients had the lowest pain scores at the start of the second pass. This correlates with rapid absorption of lidocaine and its metabolism—hence the increase in pain scores by the end of the second pass. In contrast, group B patients experienced a slow increase in serum lidocaine/MEGX levels with lower serum levels overall but also had a fairly consistent pain score throughout both first- and second-pass laser treatments compared with group A. This correlates with slower absorption (and, therefore, slower metabolism) of lidocaine.

Adverse Events

No patient developed any complications with regard to the topical anesthetic. One patient in group B (the fractionated laser group) developed posttreatment hyperpigmentation, despite being prescribed pretreatment hydroquinones to reduce her risk. Posttreatment, she was given a 1-month course of hydroquinone cream, and the hyperpigmentation resolved completely.

DISCUSSION

Topical anesthetics are used to perform countless procedures across a number of medical disciplines. Non-surgical cosmetic/rejuvenation procedures, such as laser resurfacing of the face, are becoming increasingly popular. For laser resurfacing, topical anesthetic is often used, either with conscious sedation or with nerve blocks. This is the first study, to our knowledge, that examines the use of lidocaine-containing topical anesthetic only for laser resurfacing and assesses the possibility of enhancing its efficacy with the elimination of the superficial epidermis while correlating this with the serum levels of lidocaine. Previous studies from our group have demonstrated the histopathological injury that fractionated devices can cause in human skin.7-12

The aim of this study was to investigate whether the principles of laser-assisted transdermal drug delivery could be used to provide complete anesthesia for facial rejuvenation without the need for supplementary nerve blocks. Several articles in the literature describe the use of laser assistance to enhance topical anesthetics—2,13,14—for example, for venipuncture and intramuscular injections.4 However, there is little literature that examines the role of laser-assisted anesthesia for facial rejuvenation and/or correlates this with serum levels of the drug. Previous work performed by our group demonstrated that the depth of fractional ablation used influences the absorption of lidocaine and subsequent metabolite levels. Animal pre-clinical studies performed in our laboratories investigated the role of the fractionated laser (Er:YAG) to assist transdermal delivery of drugs, using lidocaine as the study drug.5 This study found that as the depth of laser treatment increased, so too did the serum levels of lidocaine. In addition, we have also investigated the safety of topical anesthetics applied to the face.6 All of our prior clinical studies regarding lidocaine-containing topical anesthetics demonstrated considerable interindividual variability in the way lidocaine is metabolized.

Yun et al15 compared laser-assisted topical anesthetic and topical anesthetic alone for facial rejuvenation. Half of each subject’s face was pretreated with the laser, and then the whole face was covered with EMLA (Eutectic Mixture of Local Anesthetic containing 2.5% lidocaine and 2.5% prilocaine) cream (AstraZeneca, London, United Kingdom) for 60 minutes. Patients then underwent passes of treatment with the ablative Er:YAG laser. The investigators
found that supplemental nerve blocks were required during both the first and the second passes of treatment. However, they concluded that laser pretreatment reduced the need for supplemental nerve blocks. In our study, no patient requested supplemental analgesia.

Kilmer et al. used a supplemental protocol in which patients had topical EMLA applied to their faces (30 g for 90 minutes with occlusion) prior to oral analgesia, sedatives, and intramuscular analgesia being given. Then another 30 g of EMLA was applied 45 to 60 minutes before the actual laser treatment. Of the 200 patients treated with this protocol, 5% required supplemental nerve blocks. Most patients had 2 to 3 laser passes on the face and 1 laser pass to the neck. No evidence of lidocaine toxicity was recorded in any patients in that series, but serum levels were not measured.

Carruthers et al. investigated the serum levels of lidocaine applied to the face, neck, and chest after intense pulsed light treatment. Their study drug contained 15% lidocaine and 5% prilocaine (less than 10 g in all cases). They found low levels of serum lidocaine and no evidence of lidocaine toxicity in any of their patients. Intense pulsed light is a broad-spectrum-focused treatment and does not disrupt the stratum corneum in the way that a monochromatic laser does. Its action for increasing transdermal drug delivery is most likely through warming of the skin, as opposed to perforation of the stratum corneum.

The highest serum level seen in this study for any one patient was 0.935 µg/mL. To put this into context, the lower therapeutic limit for intravenous lidocaine treatment of cardiac arrhythmias is 1.0 µg/mL. The toxic levels for lidocaine are 5.0 µg/mL, and so the levels seen in this study are way below this threshold, and no patient had any adverse events.

Efficacy of Topical Lidocaine Enhanced by Laser Treatments

Few studies have investigated the use of topical anesthetic only as a method of analgesia for laser treatments, and even fewer have included serum levels of lidocaine/MEGX to assess systemic toxicity. Alster et al. compared the analgesic effect of EMLA with the S-Caine peel (which is no longer manufactured) when a 4 × 4-cm area on the cheek was treated with the CO2 fractional laser. They used assessors to rate the patient’s discomfort rather than asking the patient directly and found that 85% of patients had moderate pain (pain score average 5.25) on the EMLA side. In our study, we treated the whole face and asked the patient to rate the experience.

Marra et al. described the case of a woman with a body mass index of 17 who developed systemic toxicity following fractional laser treatment to the face. In this instance, 30% lidocaine was applied topically to the face and neck and left for 60 minutes before treatment began. The patient then underwent multiple-pass treatments (8 on the face) and developed symptoms of toxicity, with a serum level of 1.5 µg/mL 60 minutes after the onset of symptoms. There have also been reports of lidocaine toxicity from application of topical lidocaine applied copiously to the lower limbs and wrapped in occlusive dressings prior to laser hair-removal treatments.

Several lessons are to be learned with cases such as these. Our study has demonstrated that peak serum levels of lidocaine and its metabolite occur between 60 and 90 minutes after treatment, depending on the laser used. In addition, greater absorption is expected when 30% of the topically applied substance is lidocaine. Also, in the previous publication, the drug was left on for 60 minutes before treatment. The half-life of lidocaine is 90 to 120 minutes and, therefore, it is not surprising that the patient developed toxic symptoms, especially with laser treatments. (Depending on the laser, we know that treatment could perforate or obliterate the stratum corneum in its entirety. This would then lead to absorption of any remaining lidocaine in the skin into the bloodstream.)
Increasing temperature also facilitates drug diffusion, and the laser treatment generates heat within the skin, as does the occlusive dressing. The cumulative effect, therefore, of stratum corneum disruption and tissue heating caused by the laser would lead to increasing absorption of the topical lidocaine.

**Effect of the Laser Device**

In this study, a fractionated CO₂ laser device was used. Previous studies by our group and by many others in preclinical animal models have used the fractionated Er:YAG laser to facilitate transdermal drug delivery. Farkas et al demonstrated that the fractionated CO₂ device causes more thermal injury than the fractionated Er:YAG. It may well be that the amount of drug absorption would be affected by the differences in thermal injury between the devices. We have already alluded to this, with the ablative Er:YAG device facilitating greater drug absorption than the fractionated CO₂ device. Therefore, one could extrapolate that the fractionated Er:YAG device would cause less drug absorption than the fractionated CO₂ device, because less thermal injury occurs initially. It may well be that if the topical drug were applied after a delay, the channels generated would become sealed off with exudate/blood and general tissue edema, thus preventing any further drug absorption. This would be more marked with the fractionated CO₂ laser because it generates more thermal injury than the fractionated Er:YAG laser. Therefore, *timing* of drug application may be important in the amount of drug absorption.

In addition, the treatment density of the fractionated device could be examined. In preclinical studies on a porcine model conducted by our group, reducing the treatment density of the fractionated Er:YAG laser led to less lidocaine being absorbed into the animal’s bloodstream (data not published). A further study would have to be conducted to test this hypothesis.

**Limitations and Future Directions**

In this study, only serum levels of lidocaine and its metabolite MEGX were measured. However, BLT contains 20% benzocaine as well as 4% tetracaine. Both of these drugs also have potential toxicity. The toxicity profile of lidocaine is fairly well investigated because of the work done in its role as an intravenous treatment for cardiac arrhythmias, but the literature examining the safety profile of the other 2 drugs is extremely limited. It would have been interesting to measure the serum levels of these drugs to note if they rose in a similar fashion to lidocaine.

Despite all patients stating that they would undergo future laser treatment with this method of anesthesia again, it is unclear whether they would have tolerated more than 1 pass at the deeper fluence. The amount of topical anesthetic applied was based on our previous study, in which 30 g of BLT was applied to the face with occlusion for 1 hour. While there were no controls, this present study demonstrated, on average, a 3-fold rise in serum levels with full ablative treatments compared with no laser at all (Figure 3) and compared with historic results from our previous studies.

These results suggest several areas for further investigation. First, in this study, a time of 20 minutes was arbitrarily chosen as sufficient to achieve anesthesia. The effect of a shortened period on serum levels of lidocaine/MEGX and pain scores is worthy of study. Second, investigators could compare the amount of BLT applied with serum levels and patient pain scores. The potential benefit of this would be that a lower dose of BLT (and, therefore, serum lidocaine/MEGX levels) could possibly be used with similar anesthetic effect. Third, if the dose of BLT is reduced, could it be reapplied at this lower dose (eg, 5 g between each laser pass), thus facilitating multipass laser treatments? An accumulative effect on a rise in serum lidocaine/MEGX levels would be expected, and this study would allow titration of serum levels against multipass laser treatments. Fourth, our previous study demonstrated that preparation of the drug has an effect on serum levels of lidocaine/MEGX when applied to the face with occlusion. Much of the literature surrounding laser-assisted topical analgesia uses EMLA as the study drug, probably because it is one of few Food and Drug Administration–approved topical anesthetics. A study looking at the effect on differing drug absorption when used in combination with laser treatment would be useful, since a number of different topical lidocaine preparations are available over the counter as well as by prescription. It may well be that a certain specific preparation demonstrates better efficacy and safety than the others when used for laser treatments. Certainly, in our previous studies, LET (lidocaine, epinephrine, and tetracaine) topical anesthetic had a low systemic absorption compared with its counterparts. This formulation may persist for longer at the dermal level because it includes epinephrine and therefore would have a longer analgesic effect. This would need further investigation.

Last, the influence of surface area treated in relationship to the laser treatment and the amount of drug applied has not been fully examined. In this study, the whole face...
was treated. However, laser treatments for specific cosmetic units (e.g., the periorbital region for wrinkles) would require a lesser amount of topical anesthetic applied to a smaller area, and thus the amount of drug absorbed would be expected to be much less. This would render this method of analgesia less of a toxicity risk.

**CONCLUSIONS**

This study is the first step in understanding the relationship between lidocaine-containing topical anesthetics and their interaction with laser treatments. It has demonstrated that there are differences in the amount of drug absorption depending on the type of laser used; ablative lasers significantly increase the amount of topical lidocaine absorption compared with fractionated lasers. Our data also highlight the fact that a patient’s ability to metabolize lidocaine is highly individual. It is therefore unsurprising that there are instances of toxicity and even death with seemingly innocuous topical applications of the drug. Topical anesthetics, however, can be a good form of anesthesia for laser treatments, relieving the need for nerve blocks, conscious sedation, or general anesthetics. Therefore, further work must be done to define the safety parameters for this method of analgesia.

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**Disclosures**

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