Laser-Assisted Penetration of Topical Anesthetic in Adults

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Objective: To determine whether pretreatment of skin with erbium:YAG (Er:YAG) laser-assisted delivery facilitates the penetration of lidocaine cream to provide anesthesia suitable for needlesticks after just 5 minutes.

Design: Trial 1 was a double-blind randomized controlled trial, whereas trial 2 was a nonblinded randomized controlled trial.

Setting: The study was conducted in 2 facilities, an academic and a private clinical research unit.

Participants: A total of 320 healthy volunteers, aged 18 to 65 years and of any Fitzpatrick skin phototype.

Interventions: Trial 1 involved an Er:YAG laser pretreatment to disrupt the stratum corneum followed by an application of 4% lidocaine cream on one arm, and a laser pretreatment plus placebo on the other arm. Trial 2 involved an application of 4% lidocaine cream alone on one arm, and a laser pretreatment followed by an application of 4% lidocaine cream on the other arm.

Main Outcome Measure: Self-reported pain perception on a 100-mm visual analog scale after quick insertion and removal of a 25-gauge hypodermic needle on the treatment sites.

Results: Data from the 2 trials showed that there was a 62% pain reduction with laser pretreatment plus lidocaine compared with laser pretreatment plus placebo, and a 61% pain reduction with laser pretreatment plus lidocaine, compared with lidocaine alone. The decrease in pain in both trials was statistically significant (P<.001). Adverse events reported 48 hours after treatment were few and mild.

Conclusion: Treatment with the Er:YAG laser followed by lidocaine cream is a safe, effective, and efficient means of inducing skin anesthesia that significantly reduces the pain of hypodermic needle insertion.

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Health care delivery often necessitates the use of painful interventions such as needlesticks. In one study, at least 20% of 150 children experienced serious distress in the process of vaccination. Likewise, adults experience significant pain from standard hospital procedures such as intravenous catheter insertion. Regardless of the patient’s age, local anesthesia is desirable to reduce anxiety, improve compliance, and allow the intervention to be performed less stressfully. Lidocaine is one of the most commonly used local anesthetic agents. The barrier function provided by the skin’s stratum corneum, however, prevents adequate penetration of topically applied lidocaine. Hence, it must be administered via (1) subcutaneous injection; (2) iontophoresis-aided delivery; (3) topical application after repeated tape stripping of the skin; or (4) topical application, with or without occlusion, of a formulation with enhanced penetration. Subcutaneous injection is painful, mitigating the goal of minimizing pain. Iontophoresis, which is uncomfortable, can result in irritation, erythema, and electrical burns, and which is rarely effective in low voltage, may require chemical enhancers and specialized skill to use. Tape stripping prior to lidocaine application is inconvenient, time consuming, uncomfortable for the patient, and perhaps unreliable. Lidocaine formulations with enhanced penetration are helpful but not ideal because of the prolonged contact time (30-60 minutes) required.

The erbium:YAG (Er:YAG) laser has ablative properties similar to those of the carbon dioxide laser, and is used in superficial skin resurfacing. Because its wavelength (2940 nm) coincides with the absorption peak of water (3000 nm), it is avidly absorbed by the epidermis. A single
pulse of Er:YAG laser irradiation can remove an area of the stratum corneum, leading to enhanced uptake of topical agents such as lidocaine and epinephrine while leaving the rest of the epidermis intact.\textsuperscript{10}

Our goal was to determine the efficacy and safety of Er:YAG laser ablation of the stratum corneum of the skin, followed by an application of topical 4% lidocaine cream, in reducing the pain of a needlestick.

### METHODS

All procedures were approved by the institutional review boards of Case Western Reserve University, Cleveland, Ohio, and HealthONE Alliance, Denver, Colo.

Healthy individuals aged from 18 to 65 years, of all skin phototypes, were enrolled after written informed consent was obtained. Individuals with known hypersensitivity to anesthetic agents or who had taken a pain medication in the last 12 hours were excluded. In each institution, 2 independent trials were conducted.

Trial 1 was a randomized, double-blind, 2-treatment crossover design in which each subject received laser pretreatment followed by an application of lidocaine cream on one arm and laser pretreatment followed by placebo cream on the other arm.

Trial 2 was a randomized, nonblinded, 2-treatment crossover design, in which each subject received laser pretreatment followed by an application of lidocaine cream on one arm and an application of lidocaine cream alone on the other arm. Randomization was achieved by using precoded kits that determined the treatment sequence.

Laser treatment was delivered over the deltoid area as a single, painless pulse using a lightweight, portable Er:YAG unit (LAD-01; Norwood Abbey, Victoria, Australia), with a fluence of 250 mJ/pulse, a pulse width of 300 microseconds, and a spot diameter of 3.0 mm. About 0.5 g of over-the-counter 4% lidocaine cream (ELA-Max; Ferndale Laboratories, Mich) or placebo (Vaseline Intensive Care Lotion Advanced Healing formula; Chesebrough-Pond’s, Greenwich, Conn) was applied on the test site using a cotton-tipped applicator, and wiped off after 5 minutes with sterile gauze. The placebo and anesthetic cream were identical in appearance and dispensed in precoded kits.

The degree of anesthesia was assessed using the subjects’ self-reported pain perception after the single, quick insertion and withdrawal of a ½ inch (1.6 cm), 25-gauge needle. This level of needle insertion reaches the deep dermis and subcutaneous fat. Pain was quantified by each subject using a 100-mm visual analog scale (VAS).\textsuperscript{11}

Each subject was contacted by telephone 48 hours after treatment to determine the presence of side effects such as pain, erythema, and edema on the treated sites.

Data were scanned into a spreadsheet (Excel; Microsoft Corp, Redmond, Wash). Two-way analysis of variance and t tests were performed.

### RESULTS

A total of 320 subjects (160 per trial) completed the study. The mean age was 36 years (range, 18-65 years), the male-female ratio was 1:1.4, and racial distribution was reported as follows: whites, 73.1%; African Americans, 11.6%; Hispanics, 9.7%; Asians, 4.4%; other, 1.2%. Analysis of variance showed that pain scores on the VAS for all treatment regimens were independent of age (P=.27), sex (P=.95), and race (P=.17).

For each trial, t tests were performed to determine if the treatment sequence influenced the VAS scores. No significant carryover effect was observed in trial 1 (P=.99). A possible carryover effect was suggested in trial 2 (P=.06), although not significant at the P=.05 level. In this trial, there was a tendency to record lower VAS scores when laser plus lidocaine was received on the second arm, which may be due to the lack of blinding in trial 2, as this effect was not observed in trial 1.

Within-subject difference in VAS scores was analyzed using t tests, and the percentage of pain reduction was calculated as [(VAScontrol − VASactive)/VAScontrol] × 100%. For trial 1, the mean VAS for laser pretreatment plus placebo was 21.5 mm, whereas the mean VAS for laser plus treatment with 4% lidocaine cream was 8.1 mm (Figure), resulting in a difference of 13.3 mm in VAS scores (95% confidence interval [CI], 9.9-16.7; P<.001). This indicates that lidocaine cream after laser pretreatment effectively induces anesthesia, as shown by a 62% reduction in pain compared with placebo. For trial 2, the mean VAS for lidocaine treatment alone was 15.1 mm, whereas the mean VAS for lidocaine plus lidocaine cream was 6.0 mm (Figure), resulting in a difference of 9.2 mm in VAS scores (95% CI, 6.5-11.8; P<.001). This indicates that pretreatment with the Er:YAG followed by lidocaine cream produces more effective dermal anesthesia, as evidenced by a 61% pain reduction, compared with lidocaine application alone. Analysis of variance tests showed that treatment effects were consistent between centers (P=.88 for trial 1 and P=.93 for trial 2).

Only 10 of the 320 subjects reported mild pain or erythema 48 hours after treatment. No association was observed between the use of an Er:YAG laser and self-reported adverse events (Fisher exact test, P>.99).

### COMMENT

Components of the stratum corneum form a permeability barrier against external agents.\textsuperscript{12} Barrier perturbation results in ultrastructural change\textsuperscript{13} and an influx of substances from the surface into the deeper layers of the skin. Such disruption in barrier integrity is helpful in certain therapies, eg, transdermal drug delivery.
This study demonstrated that a single, painless pulse of an Er:YAG laser hastens the absorption of a lidocaine cream with enhanced penetration, consequently inducing anesthesia in just 5 minutes—a tremendous improvement from the 60 minutes required to achieve a pain reduction of 50% to 60% if the same cream were applied under occlusion over an intact stratum corneum. Using this laser will thus result in the more efficient delivery of interventions that warrant cutaneous anesthesia, and will benefit various medical and surgical fields. Although the anesthetic effect achieved may not be adequate for more invasive procedures such as full-face laser resurfacing, it is clearly sufficient for minimizing the pain of hypodermic needle insertions, as was also shown in a pilot study conducted among 80 healthy volunteers. Because the laser causes perturbation of the epidermal barrier noninvasively and facilitates substance delivery, its potential applications are many. Future studies should investigate its use in atopic and contact dermatitis research and in cancer immunotherapy.

In summary, laser ablation of the stratum corneum with an Er:YAG in preparation for topical anesthetic application appears to be a safe and effective means to reduce pain from needlesticks.

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