No Difference Between Doses in Skin Anesthesia After Lidocaine Delivered via Iontophoresis

Neal R. Glaviano, Noelle M. Selkow, Ethan Saliba, Jay Hertel, and Susan Saliba

**Context:** Iontophoresis is a method of administering medications transcutaneously using galvanic current. Dose is the product of current amplitude and treatment duration. It is assumed that higher doses of iontophoresis are more effective in delivering medication, yet research supporting this claim is insufficient. **Objective:** To compare high-dose lidocaine iontophoresis (80 mA-min), standard-dose lidocaine iontophoresis (40 mA-min), and 2 sham treatments indirectly by measuring skin anesthesia. **Design:** Double-blind crossover study. **Setting:** Research laboratory. **Participants:** 15 healthy volunteers (10 women, 5 men: age 24.06 ± 2 y, height 169.7 ± 8.3 cm, weight 72.5 ± 14.2 kg). **Intervention:** Four treatments were counterbalanced and applied on the anterior forearm: 2 true interventions (40 and 80 mA-min) and 2 sham interventions separated by at least 24 h. The true-intervention doses were applied at a current of 2 mA with 2.5 ml 2% lidocaine HCL for 20 and 40 min. The sham treatments were 2.5 ml of lidocaine without galvanic current (intensity = 0 mA, 40 min) and 2.5 ml of saline solution (galvanic current of 2 mA for 40 min). **Main Outcome Measures:** Semmes-Weinstein monofilament scores were taken preintervention and postintervention (at 0, 20, 40, and 60 min) to measure skin anesthesia. **Results:** A significant interaction between treatment and time \( (F = 4.137, P < .01) \) was identified. The 40-mA-min dose produced greater anesthesia than the lidocaine and saline shams at all times. The 80-mA-min dose produced greater anesthesia than saline sham at all times. There was a significant difference noted, with 40 mA-min over 80 mA-min, at the 20-min posttest, but there were no other significant differences between the 40- and 80-mA-min doses at 0, 40, or 60 min posttreatment or between the 2 sham treatments at any time. **Conclusions:** The 40-mA-min treatment was just as effective as the 80-mA-min treatment, suggesting that shorter treatments may be more time efficient for clinicians and patients.

**Keywords:** noninvasive, Semmes-Weinstein monofilaments, transcutaneous

Iontophoresis is a noninvasive method of delivering medication transcutaneously through the sweat glands and pores of the skin. It is commonly used in medicine and rehabilitation to treat pain and inflammation of musculoskeletal...
injuries. The medicinal ions are transported through the skin by an electrical charge for a local effect. A common medication used to treat pain is lidocaine. Lidocaine functions by blocking the fast-gated sodium channels in a cell that inhibit the presynaptic neurons from depolarizing. If those neurons cannot depolarize, an action potential will not be produced, thus eliminating the perception of pain from being transmitted via the sensory neurons. Lidocaine produces a measurable anesthetic effect and can serve as a surrogate to examine the effectiveness of medicine delivery. This method did not require a tissue biopsy to measure lidocaine or another drug’s absorption and assimilation through the skin.

The advantage of delivering medicine by iontophoresis is that it can be applied directly to a specific location such as an injury site, resulting in a local effect of treatment. Similar to an injection, this local effect allows treatment in the area of the patient’s injury. Local application of medication has benefits compared with systemic delivery such as oral ingestion, which is delayed in reaching the site of interest for treatment. Once a pill is ingested, there is an initial metabolic breakdown from the liver. Then the medicine needs to be absorbed into blood serum to be transported to the injury site. This process decreases the bioavailability (potency) of the medicine that is available to treat the injury. On the other hand, iontophoresis does not decrease the bioavailability of the medicine because it is delivered directly to the localized area, avoiding the bloodstream and uptake by the liver. For example, buprenorphine, a medicine similar to morphine, has been studied when administered orally and via iontophoresis. Only 10% to 15% of the medicine was available when administered orally, compared with an increase in uptake when delivered by iontophoresis. Similar to iontophoresis, an injection can be used to administer medicine locally. However, this form of delivery is invasive and painful and carries a higher risk of infection. There is also the potential of damage to the tissue from the needle penetration or the formation of a subcutaneous bolus. Iontophoresis decreases these risks, as well as providing a consistent delivery of medicine.

Iontophoresis has limitations that may hinder the ability to quantify medicine absorption and transmission, such as the anatomical properties of the stratum corneum, diameter of the sweat glands and pores, polarity, molecular size of the medicine, and pH of the skin. In addition to those limitations, clinicians have the ability to alter parameters of current amplitude and treatment duration that affect the dosage, and in the literature there is no general consensus on the optimal settings. A clinician chooses a dose, then typically sets the current amplitude at a level comfortable and tolerable to the patient. The treatment duration is increased depending on the current amplitude. The equation “milliampere-minutes (mA-min) = current × treatment time” is the dose, so either component can be changed without affecting the chosen dose. Clinical trials have examined a wide range of medicines and settings for iontophoresis treatments, but the studies used inconsistent parameters and a variety of medicines. Most research focuses on qualitative measures rather than quantitative outcomes. The qualitative studies report reductions in pain and patient satisfaction, and the quantitative studies measure the improvement in range of motion rather than the quantity of subcutaneous medicine absorption. This inconsistency in treatment application has created uncertainty as to which dose is most effective or whether there is sufficient evidence to support the use of iontophoresis to treat musculoskeletal pathologies.
Recent published reports by Gurney et al\textsuperscript{5,17} demonstrated evidence of subcutaneous absorption of dexamethasone via semitendinosus or gracilis autograph tissue analysis, suggesting that the modality is effective at delivering the medicine through the skin. There is inconclusive evidence in clinical trials, so is the therapeutic modality ineffective, or are the most optimal parameters yet to be determined? Previous commercial iontophoresis units were capable of delivering a maximum of 40 mA-min. Recently, manufacturers have begun marketing units that deliver up to 80 mA-min after empirical observations suggested that running sequential treatments were tolerated and may be beneficial. To date, no studies have been conducted comparing a higher dose with a traditional dose.

The purpose of this stage 1 study was to investigate the effect of 40- and 80-mA-min doses of iontophoresis on lidocaine delivery by measuring skin anesthesia. We hypothesized that the 80-mA-min dose would have a larger and longer anesthetic effect than the 40-mA-min dose, both 80- and 40-mA-min doses would have a larger and longer anesthetic effect than either sham treatment, and there would be no difference between the sham treatments.

Methods

Design

We used a double-blind crossover design with counterbalanced randomization. The independent variables were the treatment condition—40 mA-min with lidocaine, 80 mA-min with lidocaine, 40-mA-min treatment with saline (saline sham), or a 40-min lidocaine treatment with no current (lidocaine sham)—and time, consisting of baseline and posttreatment (0, 20, 40, 60 min). The dependent variable was the Semmes-Weinstein monofilaments (SWM) score.

Skin anesthesia was measured using SWMs, which are nylon filaments frequently used in research evaluating the threshold of sensation.\textsuperscript{18,19} They have been repeatedly tested and proven to have intertester and intratester reliability of 92\% and 89\%, respectively\textsuperscript{20-22}; sensitivity of 73\%; and specificity of 90\%.\textsuperscript{23} There are 20 different SWMs ranging in score from 1.65 to 6.65. There is no unit for the SWM, just a numeric score. Each value is a logarithm of force produced expressed in tenths of a milligram.\textsuperscript{22,24} The SWM is applied perpendicularly with just enough force for the monofilament to buckle, forming the shape of a crescent moon.\textsuperscript{25}

Participants

Fifteen healthy subjects (5 men and 10 women: age 24.1 ± 2.1 y, height 169.7 ± 8.3 cm, weight 72.5 ±14.2 kg; 2 right-nondominant and 13 left-nondominant arms) volunteered to enroll in this study. They were recruited via e-mail and flyers, and interested subjects contacted the investigator. Subjects were screened for allergies to lidocaine or adhesive materials, any neurological pathology of the upper body that might influence sensory capabilities, and skin irritations in the area of testing; if any of these were present the subject was excluded from the study. All subjects read and signed an informed-consent form approved by the Institutional Review Board for Health Science Research (IRB:HSR 13383).
Procedures

Subjects entered the laboratory and completed a general health questionnaire, as well as an upper extremity questionnaire, to determine eligibility and arm dominance. All subjects had their nondominant arm inspected for skin irritations or rashes that could alter the sensation threshold and affect the iontophoresis treatment. The volar surface of the nondominant arm was cleaned with an alcohol prep pad to remove dead skin and debrided 4 cm above and 4 cm below the cubital fossa. We chose the volar surface of the arm for consistency and because there are fewer hair follicles and less dry skin. Hair follicles are a route for iontophoresis transport, and contact with them by the SWM may affect the score.

Marks were drawn at the cubital fossa and 4 cm above and below to denote the placement of the edge of the cathode and anode electrodes, respectively. A circle was drawn where the bladder of the anode electrode was to be placed (Figure 1). A template from the electrode bladder was used as a stencil and lined up to the superficial tick mark on the volar arm to denote the area of sensory testing. The primary investigator conducted baseline SWM measurements on all subjects, recorded the values, and then left the laboratory.

To test skin sensation, the smallest-diameter monofilament was used to begin the SWM test (Figure 2). The subjects were then asked if they could feel the filament. With a “no” response, the monofilament diameter was increased by 2 sizes. With a “yes” response, the monofilament diameter was decreased by 1 size. If that monofilament received a “yes,” that diameter was recorded. If there was a “no” response, the diameter of the previous monofilament was recorded. Subjects placed their arms into a draped cart to prevent them from seeing the monofilament applied to their arm. The primary investigator would sporadically not always touch the skin with an SWM to prevent subjects from thinking they were always being

Figure 1 — Template for anode and cathode placement 4 cm above and below cubital fossa. Circle is Semmes-Weinstein monofilament testing area.
touched with one and illicit the point when SWM sensation was truly felt for the first time. Measurements were recorded at baseline and 0, 20, 40, and 60 minutes posttreatment for all treatment conditions.

Subjects were randomly assigned by one investigator to a counterbalanced order of treatment interventions, and the assignment was written down and placed in an opaque envelope. Another investigator entered the laboratory, opened the envelope, and applied the designated treatment. Because the 80-mA-min dose, saline sham, and lidocaine sham required a 40-minute treatment time (because the current intensity was set at 2 mA for all subjects), the start of application was delayed 20 minutes for the 40-mA-min condition to ensure blinding for the assessment. This resulted in all treatments concluding in the same duration of time. The subjects were unaware of which treatment was applied but did acknowledge that the treatment did not feel the same when there was no current (lidocaine sham).

The treating investigator injected 2.5 ml of 2% lidocaine HCl or saline solution into the anode electrode and placed the electrode directly over the circle marked on the arm (4 cm below the cubital fossa). The cathode electrode was placed 4 cm above the cubital fossa (Figure 3). The interventions of 40 mA-min, 80 mA-min, and saline sham were applied at a current intensity of 2 mA, influenced by previous research suggesting no significant difference between a high-amplitude short-duration treatment and low-amplitude long-duration treatment. The current intensity was well tolerated by all subjects. The lidocaine sham condition had no current applied, and a stopwatch was used to time the treatment. At the conclusion of the treatment, the treating investigator removed the pads and wires from the subject and put away the equipment. The primary investigator was informed to enter the

Figure 2 — Semmes-Weinstein monofilament in testing area.
laboratory to conduct the monofilament testing. This was done immediately and at 20, 40, and 60 minutes posttreatment. The same technique was applied as in the pretesting. Treatments were separated by a minimum of 24 hours and a maximum of 12 days. Most treatments were separated by 48 hours. Participants were monitored for any erythematous or irritated skin before all treatments. Most of them presented with minor irritation and mildly inflamed skin after both true iontophoresis treatments, as well as the saline sham, but these resolved before their next laboratory visit. The only condition that did not cause reddening of the skin was the lidocaine sham, for which the machine was not turned on. Although the primary investigator may have known when that treatment was performed, the subjects were blinded during the SWM testing.

**Statistical Analyses**

A 4-by-5 analysis of variance with repeated measures on time was used to examine the effects of dose and time on the SWM scores. Statistics were calculated using SPSS version 15 (SPSS Inc, Chicago, IL). The independent variables were treatment (40 mA-min, 80 mA-min, saline sham, and lidocaine sham) and time (baseline and 0, 20, 40, and 60 min posttreatment). The dependent variable was SWM score (1.65–6.65). The a priori alpha level was set at $P < .05$, and Tukey’s honestly significantly different post hoc tests were conducted to explain specific significant differences.

**Results**

A significant interaction between treatment and time ($F = 4.137$, $P < .001$) was identified (Figure 4). Tukey’s post hoc tests determined that the 40-mA-min group and the 80-mA-min group were not significantly different from each other at baseline or 0, 40, and 60 min postintervention. There was a significant difference at 20
Skin Anesthesia After Iontophoresis

193

min postintervention with the 40-mA-min treatment, indicating a greater amount of skin anesthesia than with the 80-mA-min treatment. The 40-mA-min condition created significantly more anesthesia than either sham at all posttreatment times. The 80-mA-min group created significantly more anesthesia than the saline sham condition for all posttreatment times. There was also a significant difference between the 80-mA-min group and the lidocaine sham condition at 0 minutes posttreatment (Figure 4). The saline sham and the lidocaine sham conditions were not significantly different from each other at any of the time points. There was no significant difference between treatments at the baseline.

Discussion

Iontophoresis is a noninvasive method of delivering medications transcutaneously. With multiple parameters that can alter an iontophoresis treatment, clinicians have many options to choose from, which might explain why the current research on iontophoresis is currently inconclusive. Dose and medication are 2 variable parameters, with dose the focus of this study. Our results show that the 40- and 80-mA-min treatment conditions are not significantly different when using lidocaine as a
model for medicine absorption at baseline or 0, 40, or 60 minutes posttreatment. Both the traditional low and high doses resulted in higher SWM scores, indicating a decrease in skin-perception threshold compared with either of the 2 sham groups at different time periods. Because there was no benefit of the high dose, the 40-mA-min treatment may be more time efficient for both clinicians and patients.

Iontophoresis proved to be an effective method of delivering the lidocaine across the stratum corneum and creating decreased skin sensation in this study. Both the 40- and 80-mA-min treatment groups had a decrease in skin sensation, whereas the 2 sham groups did not. These results agree with those of previous studies examining the effectiveness of lidocaine delivered via iontophoresis for topical anesthesia.27,28 This also suggested that passive diffusion does not result in transmission of lidocaine across the skin.

Although both true iontophoresis groups had a decrease in skin sensation, there was only 1 time point at which one true treatment was more significant than the other. After 0 minutes posttreatment, the threshold of sensation for those in the 80-mA-min group declined rapidly and even resulted in a significant difference from the 40-mA-min group at the 20-minute posttreatment measure. Although this is the only point of significance between the 2 true treatments, one must consider the duration of treatment between the 40- and 80-mA-min groups. Iontophoresis provides a constant delivery of medicine; therefore the 80-mA-min group received the lidocaine for twice as long as the-40 mA-min group. Although it would be implausible to begin testing the skin sensation of the 80-mA-min group before the treatment had concluded, it should be noted that the half-life of lidocaine is approximately 90 minutes, and there is a chance that the greatest decrease in skin sensation could have occurred while the subject was still receiving the treatment. This might explain the quick drop in sensation threshold for the 80-mA-min group after the initial posttest measurement. This concept is supported in the literature, suggesting that the longer the treatment time, the greater number of ions should transfer to the tissue.12

Lidocaine was used as a model in this study because the effects of the medicine could be examined in a noninvasive manner. To achieve an anesthetic effect on the skin, the medicine would have to pass through the stratum corneum to elicit its action. The degree of anesthesia could be measured quantitatively using a standard monofilament examination for skin sensation.20,21,24 Monofilaments have been used in a variety of research studies to test sensation, with conditions ranging from diabetes 29 to peripheral nerve pathologies.30 The SWMs have also been used to examine the validity of other sensation devices such as 2-point discrimination,25 pin prick,25 and vibration-perception threshold29 and are considered a gold standard in touch-pressure threshold.18 This tool has utility in testing alteration of skin sensation because significant differences were found in this study.

Manufacturers recently programmed iontophoresis units to use higher doses, up to 80 mA-min, theorizing that increased treatment time would add more energy and ultimately deliver more medicine to the treatment area.31 Several iontophoresis devices offer the higher dose, and the FDA has increased the maximum dose to 80 mA-min. Our results do not support the need for higher doses when using lidocaine, but we did not test a pathological population, which would have supplied results more clinically relevant to the altered dose. This does warrant additional research examining changes in dose with a pathological patient population. No significant
difference was measured between 40 and 80 mA-min when applied at a rate of 2 mA-min. The increase in energy did not increase the anesthetic effect of lidocaine. This may be a result of sweat glands and pores becoming clogged with ions over a longer treatment time.\textsuperscript{32}

The predetermined rate of 2 mA-min was selected for all patients, with the support of past research examining the influence of duration and amplitude on direct current delivering lidocaine iontophoresis.\textsuperscript{26} That study observed no statistically significant differences between a high amplitude (4 mA) with a short duration (10 min) and a low amplitude (2 mA) for a long duration (20 min).\textsuperscript{26} Although patient tolerance is the clinically acceptable method for determining amplitude, that study showed no difference between the 2 and influenced our decision to eliminate the variable of amplitude and standardize a 2-mA rate for all patients in our study.

Other factors may explain why there was no significant difference between the 80- and 40-mA-min conditions. The 80-mA-min group might have had a deeper penetration of the medicine because the increased time may have permitted further diffusion into the dermis. The high dose had a very high peak immediately after the treatment concluded, then a drop in skin anesthesia as the time posttreatment increased. Lidocaine blocks transmission from the superficial mechanoreceptors; if the medication penetrated beyond these receptors, the effectiveness in producing skin anesthesia may have been lessened. If the lidocaine was delivered deeper into the subdermal tissues, the vasculature may have removed the medicine from the testing site. If this were the case, this model for testing the effectiveness would not be ideal; a direct measure of tissue biopsy or serum measures would be more appropriate.

There was no significant difference between the lidocaine sham and the saline sham in SWM scores. This finding allows either option to serve as a control for future studies. The saline sham showed no difference in skin anesthesia from only a direct current, and the lidocaine sham showed no difference from passive diffusion of lidocaine. It should be noted that most of our subjects had more skin irritation after the saline sham treatment. All subjects were erythematic and had mildly inflamed skin that resolved within 48 hours. No subject asked that the current amplitude be decreased. Saline is not pH balanced, and the direct current created a physiochemical reaction, possibly resulting in skin irritation.

This study examined the standard dose of iontophoresis (40 mA-min), a higher dose (80 mA-min), a treatment of just direct current (with saline), and a treatment of lidocaine with no direct current. Although the 4 groups were compared to determine changes in skin anesthesia, there has been no research to date examining the difference between the true treatment groups and the gold standard via localized lidocaine injection.

This study did have its limitations. Although crossover designs are typically used to allow each subject to serve as his or her own control, this affected the blinding of the subjects. All subjects received all 4 treatments, so if they received a true treatment before the lidocaine sham condition, they were aware that they did not receive direct current. They were also never asked their awareness of the purposed effects of lidocaine. If subjects were aware, they might have had a bias.

This study supports the use of iontophoresis to deliver lidocaine in an effort to create local anesthesia, but generalizations to injured, inflamed, or painful conditions cannot be made. The use of healthy subjects permitted comparisons in a controlled...
environment. This study also does not indicate the effectiveness of iontophoresis with lidocaine to treat pain, nor other common medicines such as dexamethasone.

**Conclusion**

This study was a stage 1, mechanistic study to help advance the evidence-based practice of using iontophoresis in sports medicine. The fundamental concepts such as optimal parameter setup need to be explored before clinical trials. Both the traditional dose of 40 mA-min and the higher dose of 80 mA-min effectively produced skin anesthesia, indicating effective transmission of lidocaine by iontophoresis. There were no added benefits of using the higher dose in healthy people, so this study should be replicated in an injured population to determine whether a 40-mA-min dose should be recommended so that treatment time can be shortened and more time can be spent on other rehabilitative techniques.

**References**


