Objective: To assess the safety of a novel microneedle device on facial skin of healthy individuals of all Fitzpatrick skin types.

Design: Subject- and live rater–blinded, sham-controlled, randomized trial.

Setting: University-based ambulatory dermatology service providing both primary and referral care.

Participants: Healthy adults recruited from postings.

Intervention: Device or sham applied with finger pressure to the right or left sides, respectively, of the participants’ lateral forehead, temple, and nasolabial fold. At the 24-hour visit, a larger area (3 × 3 matrix) at the central forehead was treated with the device, and the participants applied the device to their chins.

Main Outcome Measure: Live blinded rater determination of local skin reaction scores (SRSs).

Results: At the 5-minute skin assessment, the median SRS was 1 for all skin type and age groups. There was no median pain score higher than 1 for any age or skin type group. For the sham device, median SRSs were 0 at all time points for all age and skin type groups. Mean SRSs for the device and sham were significantly different only for the lateral forehead at 5 and 30 minutes (P = .04).

Conclusions: The microneedle device appears to be safe and well tolerated in both sexes and various skin types and ages. Facial skin application of the device elicits mild, self-limited, and rapidly resolving erythema marginally greater than that associated with the sham control.

Trial Registration: clinicaltrials.gov Identifier: NCT01257763


Many of the medications used in dermatology practice are administered topically; however, cutaneous absorption is significantly impaired by the stratum corneum. Solid microneedle devices (MNDs) may facilitate transepidermal transport of drugs by creating microchannels through the stratum corneum. Pretreatment with microneedles has been shown to increase absorption of 5-amino-levulinic acid, naltrexone, charged macromolecules, and plasmid DNA. Modern microfabrication technology has led to devices with a large number of closely juxtaposed microneedles long enough to penetrate the stratum corneum. Despite the promising potential therapeutic benefits of microneedles, there have been only a few small studies evaluating their safety and associated skin irritation. In this study, we assessed the safety and tolerability of a novel MND used on the facial skin of adults.


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Methods

Study Design

This was a single-center subject- and rater-blinded, sham-controlled, balanced (1:1 ratio), parallel-site randomized trial conducted in the United States. The study was approved by the Northwestern University Institutional Review Board and registered as a clinical trial before recruiting began.

Study Participants

Participants were recruited from the Northwestern University community and nearby downtown Chicago through postings. Eligible individuals were healthy adults, with enrollment limited to a first-come basis to en-
sure an equal number of persons in the age groups 18 to 35, 36 to 60, and 61 to 74 years. Each age group was also constrained on the same basis to equal numbers with Fitzpatrick skin types I and II, III and IV, and V and VI. Total enrollment was limited to 54 participants. Individuals with significant inflammatory skin disease (eg, moderate to severe acne, seborrheic dermatitis, and moderate to severe rosacea) that could be exacerbated by device application or interfere with study assessments were excluded. All data were collected in the clinical offices of the Department of Dermatology of Northwestern University in Chicago, Illinois.

STUDY DEVICE

The study device (Microchannel Skin System; 3M Company) used in this study was molded from a commercial medical-grade polymer and consisted of a disposable rectangular array of 351 pyramidal, 700-µm-long, solid microneedles spaced in a pattern of consistent density on a 2.3 × 1.0-cm oval plastic backing designed to attach to a reusable handle (Figure 1 and Figure 2).

The device is designed to be applied to the skin via stamping with gentle pressure. Coverage of a larger surface area than the device area entails lifting, repositioning, and restamping the device on adjacent areas until the targeted total area is treated.

To maximize the likelihood of successful patient blinding with regard to whether the study device or the control device was being applied, a sham device identical in all ways to the study device, except for the absence of microneedles, was produced by the same manufacturer for the conduct of this study. Like the study device, the sham device was applied with a gentle stamping pressure. With the exception of patient self-applications of the device to the chin area, all device and sham applications were performed by a single investigator (F.J.H.).

STUDY PROCEDURES

Treatment of Facial Skin

All experimental treatments were in facial skin for several reasons: (1) the facial skin was considered to be a likely target of future therapeutic interventions; (2) the facial skin was considered to be among the more sensitive skin surfaces on the body, and hence a promising substrate on which to detect local site reactions; and (3) even mild local site reactions on facial skin would be clinically significant, since such skin is socially salient and rarely covered by clothing. When in routine clinical use, this device may be applied at physician discretion on facial skin or on other skin surfaces. Future applications may include topical drug delivery, direct induction of collagen remodeling, or other functions that may or may not occur on facial skin.

Baseline Visit

A designated member of the research staff (F.J.H.) applied the device using consistent finger pressure for 10 seconds to the lateral forehead, temple, and nasolabial fold 3 times at adjacent sites at each location for a total of 9 applications. The side not receiving application of the device at each location received applications of a sham device without microneedles but with the same plastic backing. Participants reported pain using a standardized 0 to 10 pain scale immediately after each device application. Skin assessments were then performed at 5 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours after application by live blinded raters.

24-Hour Visit

Twenty-four–hour skin assessments were performed for all application sites. In addition to the ongoing skin measurements at 6 sites per participant, 2 sites were treated at the 24-hour visit. Specifically, the device was applied by study personnel 9 times in the shape of an adjacent, nonoverlapping 3 × 3 matrix to the central forehead and self-applied by the participants 3 times to the chin after standardized instruction. The purposes of these 2 additional applications were to assess outcomes associated with treatment of a larger surface area and self-application. Pain and skin assessment data were collected as for the baseline visit. Participants completed a multiple-choice questionnaire assessing the ease of application and whether they would be comfortable using the device in their home.

48-Hour Visit

Forty-eight–hour skin assessments of the lateral forehead, temple, and nasolabial fold areas were conducted. In addition, 24-hour skin assessments of the central forehead and chin were performed.

PRIMARY OUTCOME MEASURE

All skin assessments included evaluation for skin irritation using a local skin reaction score (SRS) at each site of device application. The SRS is designed to detect both acute and chronic irritation and has demonstrated high interobserver and test–retest reliability. The SRS has been shown to be sensitive to the effects of various skin irritants, including topical corticosteroids, topical antifungal agents, and topical antiseptics.

Figure 1. Global and magnified views of the microneedle application surface.

Figure 2. Reusable application handle.
Table 1. Description for Local SRSs

<table>
<thead>
<tr>
<th>SRS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of inflammation</td>
</tr>
<tr>
<td>1</td>
<td>Minimal erythema, barely perceptible</td>
</tr>
<tr>
<td>2</td>
<td>Definite erythema, readily visible, minimal edema or minimal papular response</td>
</tr>
<tr>
<td>3</td>
<td>Erythema and papules</td>
</tr>
<tr>
<td>4</td>
<td>Definite edema</td>
</tr>
<tr>
<td>5</td>
<td>Erythema, edema, and papules</td>
</tr>
<tr>
<td>6</td>
<td>Vesicular eruption</td>
</tr>
<tr>
<td>7</td>
<td>Strong reaction spreading beyond test site</td>
</tr>
</tbody>
</table>

Abbreviation: SRS, skin reaction score.

Table 2. Number of Participants Enrolled by Age Range and Fitzpatrick Skin Type Grouping

<table>
<thead>
<tr>
<th>Fitzpatrick Skin Type</th>
<th>Age, y 18-35</th>
<th>36-60</th>
<th>61-74</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II</td>
<td>6 (2)</td>
<td>6 (1)</td>
<td>6 (3)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>III and IV</td>
<td>6 (5)</td>
<td>6 (2)</td>
<td>6 (3)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>V and VI</td>
<td>6 (2)</td>
<td>6 (4)</td>
<td>6 (1)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (9)</td>
<td>18 (7)</td>
<td>18 (7)</td>
<td>54 (23)</td>
</tr>
</tbody>
</table>

*Data presented as number of participants (number of men).

SECONDARY OUTCOME MEASURES

Pain was verbally reported by the participant using a visual analog (0-10) pain scale. Pain scores were recorded by study staff immediately after each device application.

Active surveillance of harms was performed using a brief structured interview format after each treatment visit and at the last follow-up visit. Patients were asked at the end of each study visit whether they had experienced any adverse events before or during that visit. To capture adverse events between study visits, participants completed a standardized questionnaire at the beginning of the 24- and 48-hour visits. This questionnaire asked whether they had noticed rash, redness, discomfort, or itching. If they had noted these reactions, they were asked to describe the appearance and symptoms, the anatomic distribution, severity on a 3-point scale (mild, moderate, and severe), and time of onset and resolution. They were not asked about any adverse events after their last visit but were instructed to contact study staff if they experienced problems likely related to the device.

At each visit, investigators visually inspected the application sites to detect harms, such as blistering, bleeding, visible marks and indentations, ulceration, hypopigmentation, and hyperpigmentation.

After completing self-application of the device, patients were asked whether they found this easy or difficult on a 5-point scale (very easy to very difficult). They were also asked whether they would feel comfortable using this device in their home.

RANDOMIZATION PROCEDURE

All participants served as their own control. For each of the 3 anatomic areas treated on their faces, there were left and right sides. Randomization assigned 1 side per anatomic site per participant to the study arm and 1 to the control (sham device). Randomization was such that no patient received the study device only on one side and was stratified so that each age group and skin type had a balanced design (3 device applications on the right and 3 on the left for each site). Sequence generation was performed by the study statistician (M.K.), who provided randomization codes. Allocation concealment was ensured by placement of the codes in consecutively numbered sealed opaque envelopes. Another investigator (F.J.H.) enrolled the volunteers, and yet another (N.P.) assigned treatment sites to detect harms, such as blistering, bleeding, visible marks and indentations, ulceration, hypopigmentation, and hyperpigmentation.

BLINDING

All participants and all 4 raters assessing outcomes were blinded regarding assignment to interventions, as was the study statistician. Some participants were likely able to differentiate the...
side treated with the device vs the sham because the former was imbedded with microneedles, which may have induced mild discomfort on application.

The device and sham were otherwise similar in shape, size, and material of manufacture. Moreover, the application of the device and the sham were in the same manner, with similar pressure, location of application, and spacing.

STATISTICAL ANALYSIS

Because there were multiple applications per location, the maximum SRS per location was used to compare treatment devices, time, location, and demographics. Wilcoxon signed rank tests, without adjustments for multiple comparisons, were used to detect significant differences in maximum SRS or pain scores between device and sham at the various locations. A Friedman test was used to evaluate differences in maximum pain scores from the study device at the 5 locations. The SRSs were compared across sex using Wilcoxon rank sum tests. No formal comparisons were made between skin type or age groups because the study was not powered to detect significant differences in SRSs or pain scores between device and sham at the various locations. The group with skin types III and IV and the age group 36 to 60 years had median SRSs of 1 through the 30-minute assessment and 0 for all subsequent assessments; all other skin types and age groups had median SRSs of 0 subsequent to the 5-minute assessment. There was no median pain score higher than 1 for any age or skin type group, and the median SRSs for men and women were similar at each location and time point, with the exception of the central forehead at 1 hour and the chin at 5 minutes, where women had marginally higher SRSs (P < .048 and P < .03, respectively).

For the sham device, median SRSs were 0 at all time points for all age and skin type groups, and there were only 10 nonzero SRSs across all participants, with no SRS higher than 1.

There were significant differences (Table 4) in median maximum (because there were multiple applications per location, the maximum SRS at each location was used) and in SRSs (combining all age groups) between the device and sham at the lateral forehead from 5 minutes (P < .001) through 4 hours (P < .001), at the temple from 5 minutes (P < .001) through 4 hours (P < .004), and at the nasolabial fold from 5 minutes (P < .001) through 1 hour (P < .004). The mean SRSs for device and sham were significantly different only for the lateral forehead at 5 and 30 minutes (P < .04). Notably, there were no significant differences between mean SRS at the chin (subject self-applied) and at the other sites of device application (investigator applied), with overlap of the 95% CIs at all time points.

At the central forehead, the median SRS (all participants combined) was 1 from 5 minutes after application through 1 hour and 0 for all subsequent time points. The median SRS (all participants combined) at the chin was 1 from 5 minutes after application through 30 minutes and 0 for all subsequent time points.

SRSs AND PAIN SCORES

Pain and SRS data were collected for 1110 device and 486 sham applications. The median and range of SRSs at each time after device applications at the lateral forehead, temple, and nasolabial fold combined for each skin type and age group are presented in Table 3. At the 5-minute skin assessment, the median SRS was 1 for all skin type and age groups. The group with skin types III and IV and the age group 36 to 60 years had median SRSs of 1 through the 30-minute assessment and 0 for all subsequent assessments; all other skin types and age groups had median SRSs of 0 subsequent to the 5-minute assessment. There was no median pain score higher than 1 for any age or skin type group, and the median SRSs for men and women were similar at each location and time point, with the exception of the central forehead at 1 hour and the chin at 5 minutes, where women had marginally higher SRSs (P < .048 and P < .03, respectively).

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At the central forehead, the median SRS (all participants combined) was 1 from 5 minutes after application through 1 hour and 0 for all subsequent time points. The median SRS (all participants combined) at the chin was 1 from 5 minutes after application through 30 minutes and 0 for all subsequent time points.
Among all device applications performed, there was no SRS higher than 2, with the exception of an SRS of 3 at 5 minutes for a single application at the lateral forehead. No participant had an SRS higher than 1 for any site at the 2-hour assessment or beyond. Barely perceptible erythema (SRS, 1) was present in only 6 of 52 participants at 24 hours, and there were no ongoing reactions at 48 hours. At the 2-hour assessment, only 6% of participants (n=1) with skin types V and VI had an SRS higher than 0 at 1 or more application sites compared with 61% of participants (n=11) for skin types I and II and 61% of participants (n=11) for skin types III and IV.

Significantly more pain was reported at the lateral forehead, temple, and nasolabial fold when the MND was compared with the sham using median maximum pain scores at each location (all \( P < .001 \), combining all age groups). There was no significant difference in the maximal pain reported from the MND at the 5 locations (\( P = .07 \)).

The frequencies of each pain score, separating device and sham and combining all applications, are summarized in Figure 4. Approximately 97% of the pain scores reported for a total of 1110 device applications were 3 or less (mild or no pain) on a 10-point scale.

**PARTICIPANT QUESTIONNAIRE AND SAFETY**

The questionnaire regarding ease of device use was administered to 49 participants. Three could not be reached and 2 dropped out of the study. Thirty-eight participants (78%) rated the device self-application as “very easy” and 11 (22%) rated it as “easy.” All indicated that they would be comfortable using the device in their homes.

No adverse events were serious, and all were mild. A summary of adverse events is given in the following tabulation:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild stinging/irritation</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Mild pruritus</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Mild bleeding</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Mild headache</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Mild open microcomedones</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*The modifier preceding each adverse event describes severity: mild indicates no interference with usual activities.

Sensation of stinging or irritation was the most frequent reaction (9 participants [17%]), and it usually resolved within 10 to 90 minutes after the application. Mild pruritus (4 participants [7%]) at the application sites was also short-lived.

One participant developed several sites of barely perceptible pinpoint bleeding after self-applying the device.
to the chin. The individual was observed to use appropriate application technique, and there was no residual erythema or other clinical finding at this site following the 2-hour assessment.

A different participant developed small, open comedones on the central forehead in a device pattern at several sites of device application. These resolved without treatment within 9 days.

The adverse events that were detected by the investigators and participants were not temporally clustered in that they did not occur around a particular day or days. Adverse events were not detected disproportionately often by 1 or more of the 4 blinded assessors.

This study showed that an MND applied to facial skin was associated with minimal discomfort on application and minimal, self-limited, and rapidly resolving erythema thereafter. This MND appeared to be well tolerated across the study sample, which included both sexes and different ages and ethnicities.

Solid silicon microneedles were first reported to increase drug delivery in 1998, when Henry et al. demonstrated a 25,000-fold increase in calcein permeability across in vitro human epidermis. Recent advances in microfabrication technique have led to microneedle designs that optimize skin permeability. Yan et al. found that acyclovir flux across the skin was highest when pre-treated with microneedles 600 µm or more in length, with needles longer than this failing to result in significant increases in drug penetration. Microneedles 700 µm long can penetrate approximately 200 µm below the skin surface, thus entering the viable epidermis without reaching deep dermal structures at most locations. Although increased needle density creates more channels for the drug, densities of 400/cm² have been shown to be more effective than very high-density configurations that may actually hinder needle penetration. The device evaluated in this study therefore has needles of moderate density and sufficient length to maximize skin permeability while reducing the risk of blood vessel or nerve injury.

The purpose of our study was to demonstrate the safety and tolerability of the MND. That the MND evaluated does form microchannels has been demonstrated on live pig skin. In this earlier study, the depth of penetration into skin was determined by measuring the distance from the tip of the microneedle to where the rhodamine B coating had been wiped from the microneedle after insertion into the skin. The depth of penetration was imaged and measured using a microscope with digital image analysis software. The mean depth of penetration for each array was determined by averaging measurements from 66 of the 225 microneedles per array in 4 predetermined areas of the array. The observation of microbeads of blood in humans treated with the microneedle array supports the contention that this occurs in humans as well.

Creating microchannels in the stratum corneum facilitates absorption. This technique has implications for localized delivery of drugs, such as topical anesthetics, topical photosensitizers, or opioid patches, and for systemic applications ranging from insulin administration to vaccination.

In our study, except for a mild papular dermatitis that was observed at 5 minutes for 1 of the 1110 MND applications, skin reactions were generally limited to transient, barely perceptible erythema, peaking at 5 minutes and resolving within 1 hour. Only 1 of 16 participants with skin types V to VI had any ongoing skin reaction beyond 1 hour, compared with 11 individuals in each of the 2 other skin type groups. This may be a result of difficulty detecting very faint erythema in darker skin, although decreased susceptibility to skin irritation in this group may also play a role. Although the device caused more pain than the sham, 97% of pain scores were from 0 to 3 of 10, correlating to no pain or mild “annoying” pain. The remaining pain scores were 4 to 5 (moderate “uncomfortable” pain). Median (1) and maximum (5) pain scores reported in our study are comparable to those reported by Bal et al. for microneedles 400 µm and 550 µm in length. Kaushik et al. found that microneedles 150 µm in length were perceived as painless by 12 healthy volunteers, which may be explained by the shorter needles. Interestingly, 73 of the 483 of sham device applications (15%) resulted in pain scores higher than 0. Application pressure may have been interpreted as pain or pain may have been elicited when the sham device was pressed over bony or gingival structures. Higher pain values may also have been associated with known significant variation among individuals in the subjective reporting of pain in response to an identical stimulus. It was our general observation that participants did not exhibit noticeable signs of physical discomfort (eg, withdrawing or flinching) during any of the device applications.

A limitation of our study is that topical medications were not used with the device; thus, no data were gathered regarding device efficacy or skin irritation when used with topical products. The population did not include individuals with underlying skin conditions and thus was not highly representative of patients with facial dermatosis seen in a dermatology practice.

In conclusion, the MND was safe and well tolerated in adults of all skin phototypes, causing only marginally...
more skin irritation and pain than the sham. Skin reactions typically consisted of barely perceptible erythema that resolved quickly and spontaneously. Participants found the device easy to apply and were observed to use proper application technique. This device appears to offer a safe and practical mechanism by which to potentially enhance cutaneous absorption of topically applied medications. Additional studies with concomitant use of substances such as topical anesthetics and cosmeceuticals may better delineate the clinical utility of this novel MND.

Accepted for Publication: January 10, 2012.
Published Online: March 19, 2012. doi:10.1001/archdermatol.2012.280

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Financial Disclosure: Dr Alam has been principal investigator on research grants from Medicis and Allergan to Northwestern University. However, Dr Alam does not receive any remuneration directly or indirectly from these companies, nor does he receive any salary support or residuals into a research fund that he controls. Dr Alam receives book royalties of less than $5000 annually from Elsevier.

Funding/Support: This study was supported in part by 3M Company, the manufacturer of the device examined in this study. None of the investigators or authors received any direct support or payment in kind from 3M, which provided support to Northwestern University and not specifically to any of the authors or investigators.

Role of the Sponsor: The sponsor had no role in the design or conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES