Lack of Pain Associated with Microfabricated Microneedles

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Hypodermic needles are effective at bolus delivery of drugs, but cause pain during insertion and are not ideally suited for delivery over extended periods. Transdermal patches address these shortcomings (1), but are extremely limited in application because most drugs are unable to cross skin at therapeutic rates (2,3).

As a novel alternative, we have used microfabrication technology to make microneedles that pierce into the skin far enough to permit drug delivery, but are short and thin enough to avoid causing pain. The skin's stratum corneum provides the greatest barrier to drug transport into the body (4). Because this layer contains no nerves, a microneedle that crosses stratum corneum without going much deeper should be capable of delivering drugs into the permeable regions of skin without stimulating nerves found deeper in the tissue. Previous work has demonstrated that microneedles of the same design used in this study are capable of piercing human skin and increasing skin permeability by orders of magnitude to small molecules and proteins for many hours *in vitro* (5,6).

Our objective was to test the hypothesis that silicon microneedles are small enough to avoid causing pain by comparing sensation associated with microneedle application to the forearm of human subjects to that caused by a 26-gauge needle (positive control) and a smooth silicon surface (negative control).

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MRP and MGA have a significant financial interest in a company called Redeon, Inc., which is developing products related to this study. The terms of this arrangement have been reviewed and approved by Georgia Institute of Technology and Emory University in accordance with their conflict of interest policies.

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Methods

Microneedle arrays were fabricated as described previously (5) by using microfabrication technology adapted from the microelectronics industry (7). Each array contained a total of 400 microneedles in an area of 3 × 3 mm (Fig. 1). The height of each microneedle was approximately 150 μm, the base diameter was approximately 80 μm, and the tip had approximately 1-μm radius of curvature.

A 26-gauge hypodermic needle (Becton Dickinson, Franklin Lakes, NJ) was used as a positive control and a smooth (unetched) piece of silicon wafer was the negative control. The microneedle arrays and smooth pieces of silicon were each mounted onto a rubber septum (12-mm diameter) by using double-sided tape, and sterilized in an autoclave.

To control depth of insertion, the hypodermic needle was inserted into an ethylene oxide-sterilized needle sheath, which was supplied with the needle and from which the end had been cut off so that only 2 mm of the needle tip protruded.

After obtaining approval from the Georgia Institute of Technology and the Emory University human investigations committees, 12 male and female healthy volunteers between 18 and 40 yr of age were recruited. After giving informed consent, subjects laid on an examination table and extended one arm onto a Mayo stand and under a curtain, which prevented viewing of the object placed on the subject's arm.

All treatments were performed with sterile materials after the treatment site was cleaned with ethanol and allowed to dry. The three treatments included pressing a smooth piece of silicon, a microneedle array, or a hypodermic needle against, or into, the skin.

For each test, the subject was informed that the test was about to begin, the skin was treated, and then the subject was asked to rate the pain on a 100-mm visual analog scale with anchors at one end reading "no pain" and the other reading "worst pain." Each test was separated by a 1-min "recovery" time.

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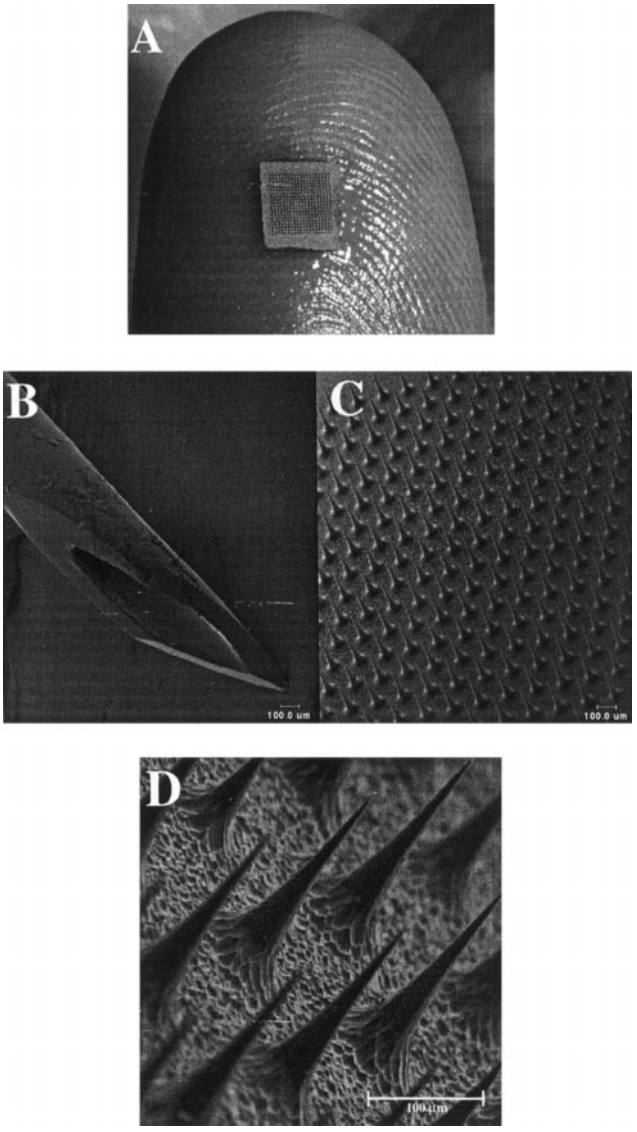

Figure 1. Images of microneedles. A, Light micrograph of an array of microneedles resting on a forefinger. This 20 × 20 array contains 400 microneedles in an area <0.1 cm^2. Also shown are scanning electron micrographs of (B), a 26-gauge hypodermic needle, and at the same magnification, (C), a section of an array of microneedles (reproduced from Reference (6), with permission). This comparison shows that microneedles are much smaller than even the tip of a conventional needle. D, Scanning electron micrograph of microneedles measuring approximately 150 μm in length, 80 μm in width at their base, and 1 μm at the tip.

Each subject was first blindly exposed once to each of the three treatments to help the subject calibrate subsequent pain scores. The pain scores reported by the subjects on these first three tests were not used in subsequent data analysis. For the remaining 12 tests, four tests of each treatment type were conducted in a random order. After all of the tests had been performed, the treatment sites were visually examined and compared with neighboring untreated skin. The subjects were also asked to inform the investigators if they experienced any pain or irritation at the treatment site.

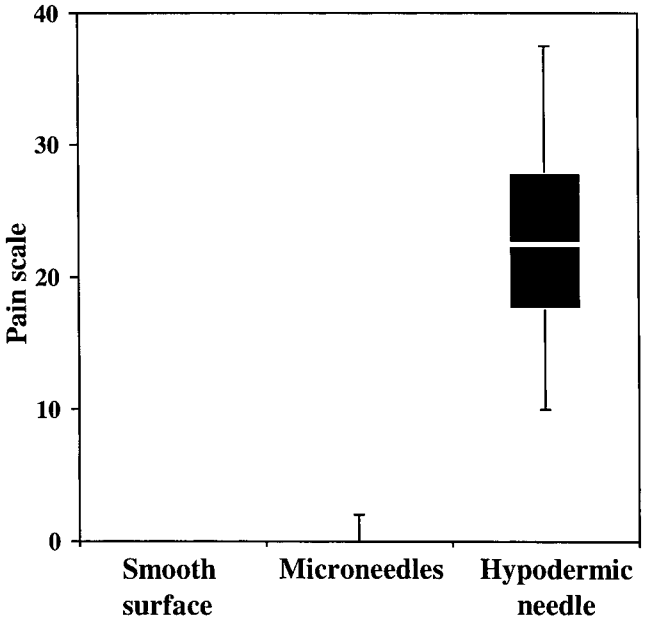

Figure 2. Box plot showing visual analog pain scores from a blinded comparison between (i) a smooth silicon surface, (ii) a 400-microneedle array, and (iii) a 26-gauge hypodermic needle inserted into the forearm of human subjects. For each treatment, the 5th, 25th, 50th, 75th, and 95th percentiles are shown. Microneedles were reported as being painless.

To analyze the data, the four tests of each treatment type for each subject were averaged to obtain the mean pain score. The mean pain scores of the 12 subjects were analyzed for statistical significance between each treatment by using the Wilcoxon's signed rank test (8).

Results

As shown in Figure 2, sensation caused by microneedles (mean value = 0.67) was statistically indistinguishable ($P = 0.09$) from a smooth surface (mean = 0.42), with the 95% confidence interval of the difference between means ranging from −0.10 to 0.60. In contrast, pain caused by a hypodermic needle (mean = 23.9) was substantially more ($P = 0.001$) than microneedles (mean = 0.67), with the 95% confidence interval of the difference in means ranging from 14.4 to 30.1. Despite our small sample size ($n = 12$), these results are significant, because power calculations indicated that a 5-U difference in mean pain scores, with a standard deviation of 2.5 U, would be detected 99% of the time in this study.

The areas to which microneedles were applied were visually inspected after the study. No redness or swelling was observed, suggesting that the microneedles had not caused damage or irritation. Minor

bleeding was sometimes seen at sites treated with a hypodermic needle. None of the subjects reported any adverse reactions.

Discussion

We hypothesized that very small needles previously shown to make skin permeable to small drugs and macromolecules could be inserted into skin without causing pain. This hypothesis is supported by this study, which indicates that microneedles are painless, as well as previous studies, which show dramatic increases in skin permeability *in vitro* (5,6). When scaled up to mass production, microneedles are likely to be inexpensive enough to be used as disposable devices and therefore provide a viable alternative to hypodermic needles for some indications. Although additional safety and efficacy studies are needed, these results suggest that microneedles may provide a useful clinical tool for minimally invasive drug delivery.

Possible clinical uses of microneedles include rapid local delivery of a local anesthetic before inserting an IV catheter; long-term variable-rate delivery of opioids, if coupled with a programmable pump; and "blood" chemistry monitoring if microneedles are used to facilitate transport of interstitial fluid components out of the body.

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