**Journal of Diabetes Science and Technology**
Volume 6, Issue 2, March 2012


ORIGINAL ARTICLE

# Improving Patient Acceptance of Insulin Therapy by Improving Needle Design

James J. Norman, B.S., and Mark R. Prausnitz, Ph.D.

## Abstract

Improved needle designs could increase patient compliance with insulin therapy. In this issue of *Journal of Diabetes Science and Technology*, Hirsch and colleagues assessed patient pain and preference for a 5-bevel needle design among diabetes patients. A blinded comparison with traditional 3-bevel needles yielded no significant difference, but patients preferred the 5-bevel needle in unblinded home injection and clinical insertion studies. This suggests that important subjective/contextual factors contribute to preference in conjunction with the fundamental needle design change. While 5-bevel needles may increase patient acceptance, more dramatic changes of needle design, such as microneedles, could enable still greater patient acceptance through reduced pain as well as improved insulin pharmacokinetics.

*J Diabetes Sci Technol 2012;6(2):336-338*

One third of patients in a survey on insulin therapy said they dread their daily injections.[1] Nearly half the patients said they would improve compliance with insulin therapy if they knew how to ease their pain and discomfort. Toward that end, manufacturers are developing improved needles and injection devices and then assessing patient pain and preference in clinical studies. Becton, Dickinson, and Company has developed a 5-bevel needle that is sharper, has a thinner profile, and requires 23% less force to insert into skin compared with a traditional 3-bevel needle.[2] In one study, Hirsch and colleagues[3] assessed pain and preference for this device with three tests in diabetes patients: a blinded needle insertion test comparing 5- and 3-bevel needles, a home insulin injection test using only the 5-bevel needle, and a follow-up unblinded comparative insertion test.

In the blinded comparison, the 5-bevel needle showed no significant difference for pain, preference, ease of insertion, or comfort compared with 3-bevel needles. This is consistent with an earlier blinded study showing no significant pain reduction with 5-bevel needles compared with conventional 3-bevel needles.[2] In another study, 5-bevel, 29 G needles were found to be less painful than 3-bevel, 27 G needles;[4] however, the fact that the 5-bevel needles were also of smaller gauge size confounds the possible role of increased beveling on pain.

Altogether, these studies suggest that the reduction of insertion force, which was shown to be statistically significant for 5-bevel needles compared with 3-bevel needles,[2–4] may not be easily distinguished by patients as a reduction in pain. Moreover, deep needle insertion

**Author Affiliation:** School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia

**Keywords:** bevel, hypodermic needle, insulin injection, microneedle, pain, patient preference

**Corresponding Author:** Mark R. Prausnitz, Ph.D., School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, 311 Ferst Dr., Atlanta, GA 30332; email address *prausnitz@gatech.edu*

into the subcutaneous space may be equally painful and override the perception of reduced insertion force, which is governed primarily by forces applied at the surface of the skin.

Given that patient needle preference is most important for insulin injection in daily use, these blinded studies are limited because they (1) tested needle insertion instead of insulin injection; (2) used an artificial, clinical environment rather than a realistic use environment; and (3) used the abdomen and thigh, which are among the least sensitive areas for tactile discrimination.[5]

The home injection test was done in a more realistic use environment, but it was not blinded. Patients were aware that they were using a new device. In addition, they did not use a 3-bevel needle for parallel comparison but instead were asked to compare the new, 5-bevel needle to their historical experience with 3-bevel needles. In this study, patients rated the 5-bevel needle device as significantly easier to insert, more comfortable, more preferred, and less painful compared with the 3-bevel needles they traditionally used.

This preference for 5-bevel needles may be because of the more realistic use scenario and cumulative experience of patients over multiple injections. However, it may also be due to effects of unblinding, such as altered expectations[6] and reactivity to the investigator when rating pain and preference.[7] Thus the objective effects of the 5-bevel needle design are confounded with the subjective effects of the patients' unblinded knowledge that they were using a new device.

In the third phase of the study, the insertion test was repeated, but the patients were unblinded this time and knew which insertion was with the 5-bevel needle and which was with the 3-bevel needle. In this unblinded scenario among now-experienced users, the 5-bevel needles were preferred. The change in use scenario and use frequency, the change in expectations, and the reactivity to a third party probably all played a role in the results shift, and each effect may be important in understanding compliance with a new drug delivery device.

The reduced insertion force and possible patient preference of 5-bevel needle geometry may have additional benefits beyond the measures of this study. The 5-bevel design could be applied to other medical devices inserted into tissue, such as biopsy needles and microneedle patches, for which the effect of design on insertion force is an actively studied and critical topic.[8,9] The authors of the original study also mentioned the potential for reduced lipohypertrophy due to reduced injection trauma when using 5-bevel needles.[3]

Building on the premise of this study that smaller, sharper needles are preferred by patients, more dramatic reduction in needle size may have even greater benefits. While the 5-bevel needles used in this study were just 31–32 G in width (i.e., 235–260 μm) and 4–8 mm in length, recent advances in microfabrication have yielded much smaller needles. These microneedles are an order of magnitude shorter, typically measuring less than 1 mm in length and having a diameter often of the order of 100 μm.[10] Such dramatic reductions in needle size might be able to boost patient compliance with insulin therapy beyond what is achievable with hypodermic needles.

Studies with microneedles have shown that needle length exhibits a strong inverse correlation with pain reported by blinded human subjects, such that microneedles have been shown to cause less pain than hypodermic needles in a number of studies.[11,12] In these studies, the reduction in pain by microneedles was significant enough that they could be readily discerned by blinded subjects.

Because microneedles are so short, they administer insulin into the skin rather than into the subcutaneous space, which has pharmacokinetic benefits. Human studies have shown that postprandial bolus insulin delivery with microneedles exhibits insulin uptake and time to peak concentration that occur much faster than with conventional subcutaneous delivery.[13,14] This increased rate of uptake is presumably due to rapid insulin absorption by vascular and lymphatic capillaries found at high density in the skin compared with the sub-cutaneous space.[15]

To conclude, improved patient compliance with insulin therapy is important and may be achieved by improved needle design. The 5-bevel needle exhibited objectively reduced force to be inserted into the skin and was subjectively strongly preferred by patients in unblinded studies where numerous factors may have contributed to patient preference. More radical departures from current needle design, such as microneedles, could engender still greater patient acceptance through reduced pain as well as improved insulin pharmacokinetics.

**Funding:**

This work was supported in part by the Thrasher Research Fund.

**Disclosure:**

Mark Prausnitz founded two companies: Clearside Biomedical and Microneedle Systems. He is a consultant for many companies and his patents have been licensed to many companies, most of which are confidential.

**Acknowledgments:**

We thank Eric Felner for helpful discussions.

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