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ORIGINAL ARTICLES

Does Needle Size Matter?

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Abstract

Hypodermic needles are in widespread use, but patients are unhappy with the pain, anxiety, and difficulty of using them. To increase patient acceptance, smaller needle diameters and lower insertion forces have been shown to reduce the frequency of painful injections. Guided by these observations, fine needles and microneedles have been developed to minimize pain and have found the greatest utility for delivery of vaccines and biopharmaceuticals such as insulin. However, pain reduction must be balanced against limitations of injection depth, volume, and formulations introduced by reduced needle dimensions. In some cases, needle-free delivery methods provide useful alternatives.

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Hypodermic Needles

The hypodermic needle was invented independently by Charles Gabriel Pravaz in France and by Alexander Wood in England in 1853.[1] Since then, needles have become the most widely used medical device, with an estimated 16 billion injections administered worldwide.[2] Currently, needles are available in a wide range of lengths and gauges (i.e., diameters) either to enable delivery of drugs, vaccines, and other substances into the body or for extraction of fluids and tissue (**Figures 1 and 2**). The appropriate needle gauge and length are determined by a number of factors, including the target tissue, injection formulation, and patient population. For example, venipuncture requires the use of needles typically as large as 22–21 gauge inserted to depths of 25–38 mm to withdraw milliliters of blood.[3] In contrast, vaccines usually require injection of less than 1 ml of fluid and, therefore, 25- to 22-gauge needles with a length of 16–38 mm are adequate.[4] Insulin delivery, which involves even smaller volumes and is typically carried out by patients in diverse everyday settings, benefits from still smaller needles, usually of 31–29 gauge inserted to a depth of 6–13 mm.[5]

Although hypodermic needles are effective, the pain, anxiety, needle phobia, and difficulty of use have made them widely unpopular with children and adults alike.[6,7]

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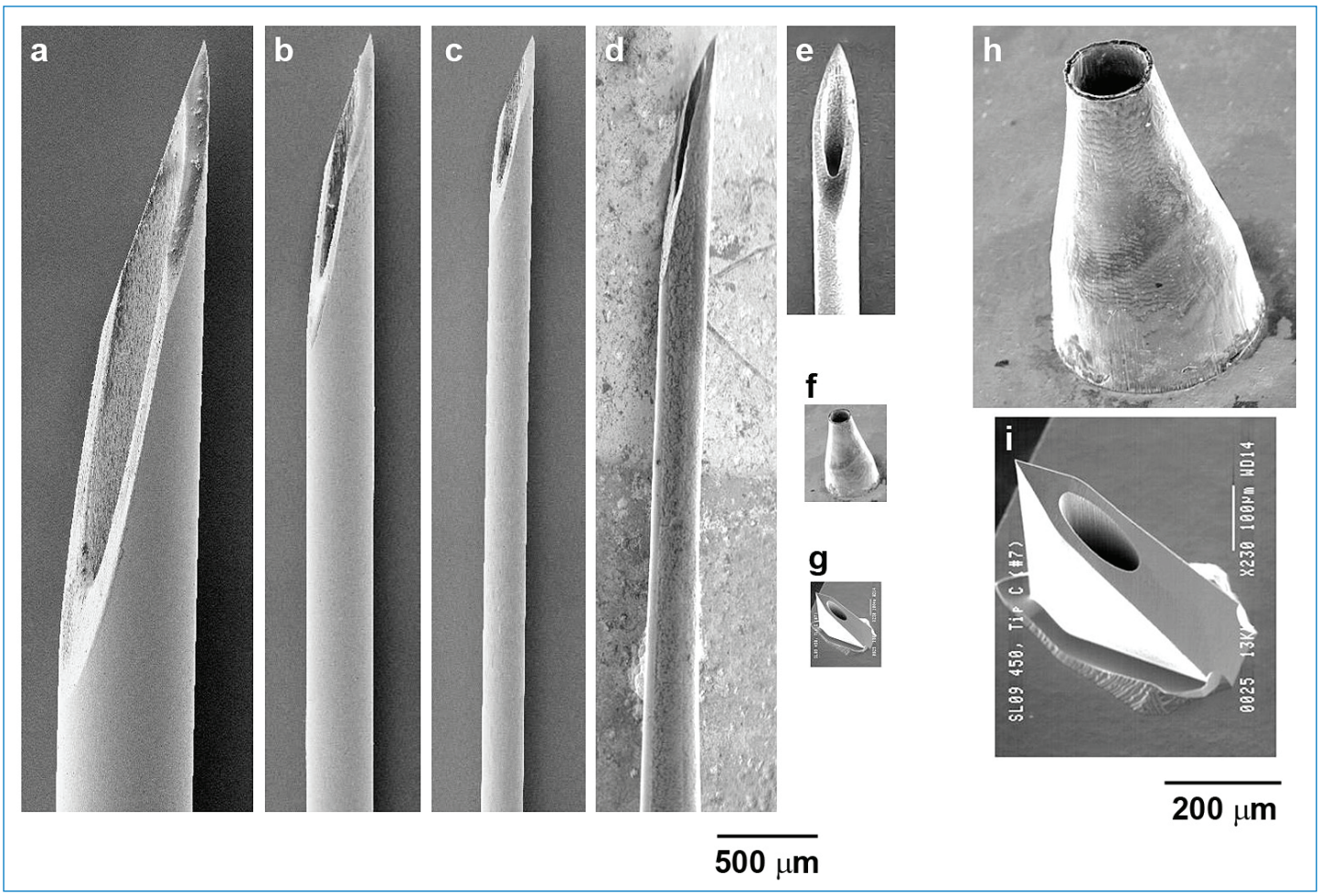

Figure 1. Size comparison among hypodermic needles and microneedles. Scanning electron micrographs of **(a)** 21-gauge, **(b)** 27-gauge, and **(c)** 31-gauge hypodermic needles (BD Technologies) and **(d)** tapered 33-gauge Terumo NanoPass hypodermic needle (image courtesy of Kyuzi Kamoi). Scanning electron micrographs of microneedles at the same magnification as hypodermic needles: **(e)** stainless steel microneedle with a total length of 1.5 mm (image courtesy of John Mikszta, BD Technologies), **(f)** nickel microneedle with a length of 500 μm, and **(g)** silicon microneedle with a length of 450 μm (image courtesy of NanoPass Technologies). Higher magnification scanning electron micrographs of **(h)** nickel microneedle and **(i)** silicon microneedle for the needles shown in f and g, respectively. (Note that although they have the same name, the NanoPass 33-gauge hypodermic needle by Terumo and the company NanoPass Technologies are unrelated.)

Consequently, there is poor compliance in initiating and adhering to needle-dependent therapies, such as insulin administration.[8] Therefore, less painful needles and more convenient delivery systems are being developed.

Factors Affecting Pain from Needle Insertion

To mitigate pain from hypodermic injections, the effect of needle geometry on pain has been investigated. Needle gauge has been shown to significantly affect the frequency of pain during needle insertion into the skin of human subjects.[9] For example, insertion of a 27- or 28-gauge needle (**Figure 1b**) had an approximately 50% chance of being reported as painful, which was significantly greater than insertion of a 31-gauge needle (**Figure 1c**), which had a 39% chance of causing pain.

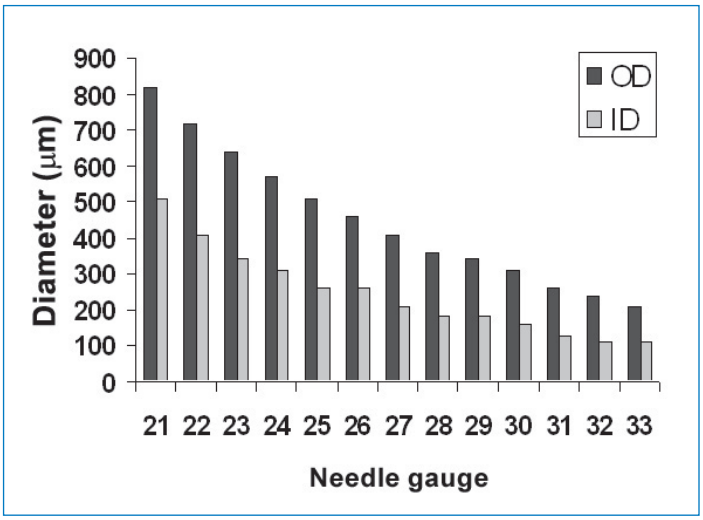

Figure 2. Outer and inner diameters of conventional hypodermic needles as a function of needle gauge.

The likelihood of bleeding was also observed to decrease with decreasing needle diameter. Increasing needle length is also expected to increase pain, although to our knowledge the literature does not contain formal studies specifically demonstrating this effect.

In addition, the mechanics of needle insertion has been found to significantly affect pain. Both the force and the mechanical workload (i.e., area under the force-displacement curve) of hypodermic needle insertion have been found to positively correlate with the frequency of pain.[10,11] Thus, needle tip sharpness and other factors, such as lubrication, which can reduce the force of insertion and mechanical workload,[12] are important parameters that can be optimized to reduce pain from needle insertions.

Development of Less Painful Needles

Motivated to make less painful needles, there has been growing interest in fabricating smaller needles that should be less painful. Progress in this field has been limited by the need for small needles to reliably insert into the skin, to have sufficient mechanical strength, and to be manufactured in a cost-effective manner.

Fine Needles

By scaling down conventional manufacturing processes, a number of companies have developed fine needles smaller than 30 gauge that are used largely for insulin delivery. Examples include 31-gauge Micro Fine Plus® needles (Becton Dickinson, Franklin Lakes, NJ) and 33-gauge NanoPass® needles (Terumo, Tokyo, Japan), both of which measure 5 mm in length (**Figures 1c and 1d**). A significant reduction in pain and bleeding from use of a 33-gauge needle compared to a 31-gauge needle has been demonstrated.[13] However, patient satisfaction was improved only after application of a suitable lubricant to the 33-gauge needle, which presumably reduced insertion force and workload.

Microneedles

To further minimize pain during injection, 31-gauge needles have been manufactured to be just 1–3 mm long (**Figure 1e**). These needles are further designed to remain within the skin and thereby facilitate intradermal vaccination, which may be facilitated by targeting antigen delivery to the skin's Langerhans and dermal dendritic cells. A number of vaccines have been delivered in this way to animal models and human clinical trials are well under way.[14,15] These short needles also have potential for delivery of other therapeutics into the dermis, which is well vascularized[16] and can thereby enable rapid uptake of drugs into systemic circulation with improved pharmacokinetics.

Even submillimeter needles can be effective, because the primary barrier to delivery of drugs into the skin is its topmost layer called the stratum corneum, which is just 10–20 µm thick.[17] Recognizing this fact, micrometer-scale needles have been developed to deliver drugs into the skin (**Figures 1f–1i**).[18–21] These microneedles are sufficiently long to penetrate through the stratum corneum, yet small enough to cause little or no pain. Delivery of insulin using microneedles has been demonstrated in diabetic animal models[19–21] and, more recently, in diabetic human subjects.[22] Because of their very small size, novel microfabrication methods have been adapted from the microelectronics industry to produce these microneedles using methods suitable for inexpensive mass production.

Confirming the hypothesis that microneedles can avoid pain, a study in human volunteers found that 150-µm-long microneedles were reported as painless.[23] More recent results from our laboratory examined the effect of microneedle geometry on pain in greater detail and concluded that microneedle length and the number of microneedles are the most important geometric parameters affecting pain and that 500- to 750-µm-long needles can cause 10 to 20 times less pain than a 26-gauge hypodermic needle (data not shown).

How Small Is Small Enough?

Reducing needle size reduces pain and generally increases patient acceptance. The increasing popularity of the short, 31-gauge pen needle is a notable example.[24] However, smaller needles are not suitable for all applications. For example, rapid delivery of large volumes and administration of formulations with large particulates require larger needles. Furthermore, scaling down needle length also prevents injection into deeper tissues. Microneedles are just long enough to deliver into the skin, which may be an advantage in some scenarios, but is a drawback in others. Moreover, as needle size approaches the dimensions of skin surface topography and mechanical deformation, microneedle insertion into the skin becomes more difficult and may, in some cases, require specialized insertion devices.[25,26] Thus, there is a trade-off between pain and other delivery considerations when smaller needles are used. The correct balance must be obtained for each application. Based on current literature and applications, delivery of vaccines and

protein biotherapeutics appears to be most suitable to benefit from the use of smaller needles.

Needle-Free Delivery Methods

In some cases, the limitations of hypodermic needles can be addressed by eliminating the needle altogether. However, these needle-free alternatives each have limitations of their own. For example, jet injectors accelerate liquid droplets across the skin at high velocity and are used clinically to administer insulin, vaccines, and other drugs, but have had limited impact because of their size, cost, and inability to reduce pain and injury.[27] Transdermal patches have also been developed to passively deliver drugs across the skin, but this approach has been limited to hydrophobic and small molecules.[17] Skin pretreatment methods such as ultrasound, electric fields, solid microneedles, and thermal ablation are being investigated to increase the permeability of skin for protein and vaccine patches.[17,28] New approaches, such as pulmonary, oral, and nasal delivery routes, are increasingly being studied for the systemic delivery of compounds that currently require injections.[29] Notably, pulmonary delivery of insulin (Exubera®, Pfizer, Groton, CT) is already approved by the Food and Drug Administration.[30]

Conclusion

In conclusion, smaller needles can reduce pain and provide other advantages that can increase patient compliance. Fine needles of 33–31 gauge have already gained clinical acceptance and still smaller microneedles are under development. However, smaller needles are not suitable for all applications and, in some cases, needle-free delivery systems provide useful alternatives.

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