Faster pharmacokinetics and increased patient acceptance of intradermal insulin delivery using a single hollow microneedle in children and adolescents with type 1 diabetes


Objective: In an effort to improve compliance with insulin therapy and to accelerate insulin pharmacokinetics, we tested the hypothesis that intradermal insulin delivery using a hollow microneedle causes less pain and leads to faster onset and offset of insulin pharmacokinetics in children and adolescents with type 1 diabetes (T1DM) compared with a subcutaneous, insulin pump catheter.

Research design and methods: In this repeated measures study, 16 children and adolescents with T1DM received Lispro insulin by microneedle and subcutaneous administration on separate days. Subjects rated the pain of insertion and infusion using a visual analog scale. Blood specimens were collected over 4 h to determine insulin and glucose concentrations.

Results: Microneedle insertion pain was significantly lower compared with insertion of the subcutaneous catheter (p = 0.005). Insulin onset time was 22 min faster (p = 0.0004) and offset time was 34 min faster (p = 0.017) after hollow microneedle delivery compared with subcutaneous delivery.

Conclusions: In this study, intradermal insulin delivery using a single, hollow microneedle device resulted in less insertion pain and faster insulin onset and offset in children and adolescents with T1DM. A reduction in pain might improve compliance with insulin delivery. The faster onset and offset times of insulin action may enable closed-loop insulin therapy.

Two important goals for improving treatment of patients with type 1 diabetes (T1DM) are improving compliance and preventing long-term complications caused by hyperglycemia. To address these needs, we evaluated hollow microneedles <1 mm in length to administer Lispro insulin to children and adolescents with T1DM. We predict that patient compliance will improve because of reduced pain compared with subcutaneous administration. We also expect faster insulin pharmacokinetics with intradermal insulin delivery should improve closed-loop insulin therapy because of enhanced responsiveness to blood glucose levels.

Omission of insulin injections because of needlephobia is common in children and adolescents (1–4). Twenty-five percent admit to omitting or underdosing injections due to needlephobia (5, 6). Fear and omission of injections correlate with higher hemoglobin A1c levels (3, 7, 8), leading to more hospitalization and higher cost (9–11).

Pen devices, shorter needles, and injection ports have shown improvements in glycemic control and patient preference in adults and children (12–14), suggesting improved compliance. Microneedles are up to an order of magnitude shorter than these needles (15, 16), and
may be even more effective at reducing pain and apprehension. In blinded trials, microneedles were less painful than hypodermic needle injections (17, 18). In addition, physicians have agreed that microneedles would provide a beneficial option for patients on insulin therapy (19). These findings suggest that microneedles have potential to improve compliance through reduced needle pain and apprehension.

Microneedles may also enable closed-loop therapy by reducing the lag time for onset and offset of insulin action. Closed-loop therapy is currently limited by long lag times associated with insulin delivery and glucose measurements (20, 21), which do not exist in the normal pancreas. Microneedles may enable closed-loop therapy by reducing the lag time for insulin onset and offset, thereby allowing rapid changes in blood glucose levels and easing the requirement to predict insulin delivery needs. Studies in adults showed that intradermal infusion of insulin using microneedles leads to faster uptake (44–70% reduction in average time to peak insulin concentration) and faster subsequent clearance of insulin compared with subcutaneous delivery. This appears to be because of the enhanced venous and lymphatic access compared with the subcutaneous space (22–26).

Thus, microneedles offer two major routes to improved management of T1DM: (i) improving compliance, especially in children and adolescents with needle phobia and anxiety and (ii) accelerating insulin pharmacokinetics to enable more-responsive closed-loop therapy. Although data on intradermal insulin delivery exist for adults (17, 18, 23, 27), it is unknown if microneedles reduce pain or intradermal insulin delivery will lead to rapid uptake in children and adolescents. To the authors’ knowledge, this is the first study of microneedles in a pediatric population for any application (although two pediatric participants were included in another study by our team) (23).

We conducted this trial in a pediatric population to test the hypotheses that delivery of Lispro insulin using a microneedle results in (i) less needle insertion and infusion pain and (ii) faster pharmacokinetics compared with traditional subcutaneous insulin delivery.

Methods

Sixteen participants were recruited from the Emory Children’s Center. Subjects were aged 10–18 yr, had T1DM for at least 2 yr, used an insulin pump for at least 1 yr, and had a body mass index ≤85th percentile. Subjects were excluded if they were pregnant or nursing, had T2DM, acanthosis nigricans, major organ disease, a daily insulin requirement >150 U (1040 nmol), or cognitive impairment. On the study day, all subjects were healthy, with blood glucose levels between 100 and 200 mg/dL (5.5–11 mmol/L) (Table 1).

This repeated measures study involved microneedle and subcutaneous administration of insulin on separate days (8/16 had microneedle first). This study was approved by the Emory IRB.

Subjects fasted the night before, arrived at the study at 7 AM, and had an intravenous catheter inserted in the antecubital fossa. A 10-mL initial blood specimen was collected, after which, insulin Lispro (U50) was administered by either the microneedle or subcutaneous route using a syringe pump at 1.0 mL/min. The insulin dose was based on the subject’s insulin-to-carbohydrate ratio. Insulin dosing ranged from 10 to 20 U (i.e., 200–400 μL of a U50 solution, 70–140 nmol).

For microneedle administration, the microneedle was inserted into the subject’s abdomen to a length of 1.1 mm and retracted to 0.9 mm prior to infusion. Figure 1A, B compare a microneedle and a subcutaneous needle and catheter at the same magnification. Microneedles were made at Cartika Medical (Maple Grove, MN, USA) and mounted in a microneedle holder (Fig. 1C) described previously (22, 23). These microneedle devices are prototypes, intended for proof-of-principle studies.

After infusion, the microneedle was retracted slowly and a characteristic intradermal bleb was observed (Fig. 1D). For subcutaneous administration, a 9-mm MiniMed infusion set (Medtronic, Minneapolis, MN, USA) was used.

After insulin administration, subjects immediately ate a standard 75-g carbohydrate meal. Blood was collected from the intravenous catheter every 15 min for 2 h and then every 30 min for an additional 2 h. Data collection were stopped if subjects developed hypoglycemia or hyperglycemia defined as HbA1c >8.0–8.4%.

Table 1. Demographic and clinical characteristics of the participants

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Number enrolled n = 16</th>
<th>Number included in analysis n = 12</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male n = 6 (50%)</td>
<td>Female n = 6 (50%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11–12 n = 3 (25%)</td>
<td>13–14 n = 1 (8%)</td>
</tr>
<tr>
<td></td>
<td>15–16 n = 6 (50%)</td>
<td>17–18 n = 2 (17%)</td>
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<tr>
<td>Race/ethnicity</td>
<td>Caucasian/White n = 8 (67%)</td>
<td>African-American/Black n = 4 (33%)</td>
</tr>
<tr>
<td>HbA1c average</td>
<td>7.0–7.4% n = 6 (50%)</td>
<td>7.5–7.9% n = 4 (33%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17–19 n = 3 (25%)</td>
<td>20–24 n = 6 (50%)</td>
</tr>
<tr>
<td></td>
<td>24–29 n = 3 (25%)</td>
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HbA1c, hemoglobin A1c.
hypoglycemia (blood glucose < 60 mg/dL; 3.3 mmol/L) or symptomatic hyperglycemia. Blood was collected in EDTA-containing tubes, centrifuged, separated, and frozen immediately. The frozen plasma specimens were assayed for glucose concentration (Glucose Colometric Assay Kit, Cayman Chemical, Ann Arbor, MI, USA) and free Lispro insulin concentration (LisPro Insulin RIA, Millipore, Billerica, MA, USA). A blinded investigator measured insertion and infusion pain using a 100-mm slider as a visual analog scale (VAS).

Thirteen subjects were needed to detect a difference in $t_{\text{max}}$ of 15 min with a standard deviation of 15 at a power of 90% and $\alpha = 0.05$. Only seven subjects were needed to detect a difference in VAS of 15 mm with a standard deviation of 10 with insertion at a power of 90% and $\alpha = 0.05$. Therefore, assuming a 20% dropout or loss-to-follow-up rate, we enrolled 16 subjects.

A pharmacokinetic model with first-order insulin absorption and elimination was fit to all participants’ insulin curves using a standard compartment model equation and non-linear regression in SAS, PROC NLMIXED (25). $t_{\text{max}}$, offset time (time to return to half the peak concentration, $t_{1/2}$), and area under the insulin curve (AUC) were derived from the pharmacokinetic fit. Pain scores and time values were compared using paired t-tests; AUC and pharmacokinetic coefficients used ratio paired t-tests.

Results

Sixteen subjects enrolled in this study between February 2009 and January 2012. Four participants’ data sets were excluded from the analysis. One subject had an elevated insulin level at baseline, likely due to a bolus infusion for mild hyperglycemia. Three others received incomplete doses of insulin due to a mechanical issue with the microneedle holder. Three subjects developed hypoglycemia 3 h after both injections. No other clinically significant events occurred. The final analysis includes 12 subjects for 3 h. The need to remove some subjects from analysis due to the problems mentioned above only became clear after serological analysis. Even with this reduced number of subjects, key outcome measures showed significance, so we did not enroll additional participants.

Initially, pain was assessed using the VAS score after insertion of microneedles and subcutaneous catheters and after infusion of insulin solution. Microneedle insertion was significantly less painful than subcutaneous catheter insertion (Fig. 2, $\Delta\text{VAS} = -9.9$, $p = 0.005$). Ten of the 12 subjects rated microneedle insertion as less painful than catheter insertion. There was no significant difference between pain experienced by subjects after infusion of insulin using the microneedle and subcutaneous catheter delivery (Fig. 2, $\Delta\text{VAS} = 13.2$, $p > 0.05$), although pain scores associated with infusion using microneedles was higher than with subcutaneous catheters. Blebs absorbed within 2 h, with no reports of pain, itchiness, or pigment change.

Microneedle administration resulted in a faster onset and offset of insulin action (Fig. 3A). The average time to peak insulin concentration (onset time) was $30 \pm 2$ min after microneedle
Fig. 2. Pain associated with microneedle and subcutaneous insulin administration. Participants scored pain associated with insertion into skin and associated with insulin solution infusion using microneedles and subcutaneous catheters. The data represent average values from 12 participants. Error bars represent the standard error of the mean. *p = 0.005.

administration and 52 ± 4 min after subcutaneous infusion (Fig. 4A). The onset time for microneedle delivery was 22 min faster, a reduction of more than 40% (p = 0.0004). The offset time was also faster for microneedle administration by 34 min, a reduction of 24% (p = 0.017).

The absorption coefficient was 3.7 times higher for microneedle administration (Fig. 4B), consistent with the faster onset and offset times. The elimination coefficients were not significantly different (Fig. 4B), indicating that once insulin reaches the bloodstream by either route, it is eliminated at the same rate. Finally, the AUC values were statistically indistinguishable between the two groups (Fig. 4B).

The pharmacodynamic response to insulin delivery after ingestion of a standard carbohydrate meal is shown in Fig. 3B. After insulin administration by either route, plasma glucose level rose over the course of 30 min, which is expected after consuming food. After microneedle delivery, glucose levels plateaued for the remainder of the study, whereas glucose levels decreased and returned to baseline in subjects receiving subcutaneous insulin.

Discussion

This study tested the hypothesis that insulin delivery using microneedles causes less pain in children with T1DM compared with conventional subcutaneous injection. We found that children rated insertion of microneedles as significantly less painful than introduction of a subcutaneous catheter. This is consistent with the earlier studies of microneedles in adults (17, 18, 23). This first study of microneedles in children also suggests the use of microneedles for therapy in other pediatric indications for improved compliance.

Insulin delivery using microneedles did not cause less infusion pain compared with the subcutaneous route, also consistent with earlier results (23, 25). Some strategies to reduce infusion pain associated with microneedles include: lowering flow rate, adding hyaluronidase, and increasing the size of the needle lumen to reduce infusion pressure (28). Adopting these strategies may also reduce the likelihood of incomplete insulin delivery with microneedles.

This study also tested the hypothesis that intradermal insulin delivery using microneedles leads to faster onset and offset of insulin pharmacokinetics compared with subcutaneous injection. We found that insulin administered with microneedles had significantly faster onset and offset of insulin action, consistent with previous studies in adults (23, 24).

We believe that the reason for accelerated pharmacokinetics after insulin administration using microneedles involves intradermal targeting, enabled by the small size of microneedles. Skin delivery may target the rich capillary bed found in the superficial dermis or via lymphatic drainage (26, 29).

In the microneedle group, postprandial glucose levels initially increased by approximately 30 mg/dL, then plateaued. A similar pharmacodynamic profile occurred in a study of adults all receiving an insulin dose at 0.125 U/kg (0.89 nmol/kg) (25) and in the 30% under-dosed arm of a multi-arm study where participants received individualized doses (27). The optimally dosed arm in contrast, had a small but significant improvement in postprandial glucose levels for intradermal insulin delivery. This suggests that optimizing the dose for intradermal delivery is important for controlling postprandial glucose levels and our subjects may have been under-dosed overall.

Microneedle administration to the skin, with faster onset and reduced persistence of insulin, may be better suited to rapidly responsive, closed-loop insulin therapy rather than standard subcutaneous insulin injections. Delivery with faster pharmacokinetics could prevent rapid rises in postprandial glucose, glucose peaks above acceptable ranges caused by slow insulin onset, hypoglycemia caused by systemic insulin persistence (20, 21).

To improve closed-loop control, further reductions in onset and offset with microneedles could be explored. For example, statistical analysis of our data showed that the time to peak insulin concentration was significantly shorter in subjects receiving smaller insulin doses delivered with the microneedle (p < 0.02). A similar
correlation was previously observed for subcutaneous insulin delivery (30). It is possible that increasing insulin concentration (e.g., to 500 U/mL) or switching from a single injection on the order of 100 μL to multiple injections on the order of 10 μL (using an array of multiple microneedles) could accelerate the uptake of intradermal insulin. Other strategies exist for accelerating the pharmacokinetics of insulin uptake including injecting hyaluronidase (31), warming the injection site (32, 33), and creating a more soluble insulin formulation (34). Combining these methods with microneedles may synergistically result in ultra-fast insulin uptake.

Limitations of our study include small sample size with limited demographic distribution and single-injection timeframe. To move toward clinical adoption, additional studies are needed with larger pediatric trials and application of multiple injections to assess reproducibility as well as long-term safety, tolerability, compliance and glycemic control. While the microneedles used in this study were made of borosilicate glass, we have also made similar microneedles from stainless steel (35) and believe these will be more suitable for use in clinical practice.

Conclusions

This is the first study of intradermal insulin delivery using microneedles in children and adolescents with...
T1DM. Microneedle administration of insulin resulted in less needle insertion pain and faster insulin onset and offset. The reduction in pain may increase compliance with insulin therapy, especially in needlephobic children. The accelerated pharmacokinetics may also improve closed-loop insulin therapy, which requires rapidly responsive insulin delivery to maintain tight glycemic control.

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References


