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TECHNOLOGY REPORT

Comparison of Insulin Diluent Leakage Postinjection Using Two Different Needle Lengths and Injection Volumes in Obese Patients with Type 1 or Type 2 Diabetes Mellitus

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Abstract

Background:

Smaller gauge, shorter needles have been shown to be as safe and effective for insulin delivery as longer needles in many patients. However, in obese patients with diabetes, results have been inconsistent with regard to the impact of needle length on leakage of injectate.

Methods:

A single-blind, randomized, two-period, crossover study compared injections with 5 mm needles to 8 mm needles regarding leakage, pain, bleeding, and bruising at abdominal injection sites in obese patients with diabetes using 20- and 60-unit (U) volume equivalent injections of sterile insulin diluent.

Results:

Fifty-six patients (54% male; mean age 56 years; mean body mass index of 36 kg/m^2) with type 1 (n = 13) or type 2 (n = 43) diabetes participated. Median leakage (U) was similar for both needles [0.04 (5 mm/20 U) vs 0.02 (8 mm/20 U), P = .32; and 0.04 (5 mm/60 U) vs 0.02 (8 mm/60 U), P = .48]. Pain scores (mean) were similar [1.27 (5 mm/20 U) vs 1.14 (8 mm/20 U), P = .75, and 1.68 (5 mm/60 U) vs 0.95 (8 mm/60 U, P = .21)]. The proportion of injections with bleeding [10.8% (5 mm/20 U) vs 5.83% (8 mm/20 U), P = .23, and 4.92% (5 mm/60 U) vs 6.56% (8 mm/60 U), P = .73] and the proportion of patients with bruising [8.11% (5 mm/20 U) vs 10.81% (8 mm/20 U), p = .56, and 21.05% (5 mm/60 U) vs 26.32% (8 mm/60 U), p = .65] at injection sites were similar. Mean bruise size (mm) [0.73 (5 mm/20 U] vs 2.68 (8 mm/20 U), P = .23; and 1.11 (5 mm/60 U) vs 4.21 (8 mm/60 U), P = .08] at injection sites was similar.

Conclusions:

This study supports the suitability of the 5 mm needle for the injection of insulin in obese patients with diabetes.

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Abbreviations: (BMI) body mass index, (GEE) generalized estimating equation, (SAE) serious adverse event, (SD) standard deviation, (U) unit, (VAS) Visual Analog Box-21 Scale for Pain

Keywords: diabetes, leakage, needle length, obesity

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Introduction

Side effects of subcutaneous insulin injections can include leakage, pain, bleeding, and bruising at the injection site. These side effects may compromise insulin dose, increase patient discomfort, and compound the anxiety experienced by many patients toward insulin injections. Injection-related anxiety is thought to be a major contributor to "psychological insulin resistance."[1] When given the choice between a longer needle (12.7 mm) and a shorter needle (6 mm), most people would likely choose the shorter needle.[2] Smaller, shorter needles have been shown to be safe and effective for insulin delivery while reducing patient discomfort.[3] When 5 mm and 8 mm needles were compared in pediatric and adult populations, the 5 mm needle was found to be as efficacious and safe as an 8 mm needle.[4]

Obese patients with diabetes are often advised to use longer needles (≥8 mm) because of a clinical perception that longer needles are needed for a correct injection into a thicker layer of subcutaneous fat. However, there is no compelling clinical evidence that injecting deep into the subcutaneous fat produces superior efficacy to an injection into the superficial subcutaneous fat. Three studies have examined leakage of injectate in obese patients with diabetes.[2,5,6] In a study comparing 8 mm pen needles with 12.7 mm pen needles, obese subjects were significantly more likely to experience insulin leakage from their injection sites compared to nonobese subjects, regardless of needle length.[6] Among obese patients, although the use of 31 G × 6 mm vs 29 G × 12.7 mm needles produced comparable hemoglobin A1c values, double-blind pain and leakage scores, convenience, and ease of use; patients preferred the shorter needle.[2] A multicenter, open-label, crossover study in obese patients with type 1 and type 2 diabetes mellitus demonstrated equal efficacy and safety with 5 mm needles as compared with 8 mm needles.[5] Although two of the aforementioned studies supported use of shorter needles in obese patients with diabetes, the perception continues that longer needles should be used in obese patients. No studies to date have compared 5 mm needles with 8 mm needles using different injection volumes and pain assessments in obese patients with diabetes blinded to needle length.

This study compared investigator-administered injections of 20- and 60-unit (U) equivalent volumes of preserved sterile insulin diluent using 5 mm needles with similar injections using 8 mm needles regarding leakage, pain, bleeding, and bruising at abdominal injection sites in obese patients with diabetes.

Methods

Patients

Eligible patients were men and women ≥18 years of age with type 1 diabetes or type 2 diabetes and a body mass index (BMI) ≥30.0 kg/m^2, who were injecting insulin at least once daily for at least 6 months prior to screening procedures. Patients were excluded if they had more than two abdominal surgical scars longer than 2 inches within the provided injection grid area, had self-perceived dullness or loss of sensation on either side of the abdomen, had known hypersensitivity or allergy to preserved sterile insulin diluent or insulin, were taking anticoagulants or antiplatelet medications other than aspirin, had a diagnosis or past history of a significant bleeding disorder, or had significant weight change (± 10% body weight) within 6 weeks prior to screening procedures.

Study Design

This study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical review boards approved the study protocol for each study site, and investigators obtained subjects' written informed consent before any study procedures. This was a randomized study conducted at two outpatient centers in the United States. Patients were blinded to needle length. Patients were randomly assigned to one of eight sequence groups in order to reduce bias during study execution. A two-period crossover design was used to compare both 20 U (200 µl) and 60 U (600 µl)-equivalent volume injections of preserved sterile insulin diluent administered with both 5 mm and 8 mm needles using the HumaPen® Memoir™ (Eli Lilly and Company, Indianapolis, IN) insulin pen injector.

The primary objective of this study was to compare injections with 5 mm and 8 mm needle lengths with respect to leakage at the injection site. The secondary objectives were to compare injections with 5 mm and 8 mm needle lengths with respect to pain intensity, bleeding, and bruising at the injection site.

Patients were randomized by dose and abdominal quadrant (left and right lower) to receive either 20 U (200 μl) or 60 U (600 μl)-equivalent volume injections of preserved sterile insulin diluent. Once randomized, all patients were injected at least three times (and up to five times) per series with a HumaPen Memoir insulin pen injector fitted with either a 5 mm or 8 mm needle. The goal was to achieve three successful injections for each series. A successful injection was defined as an injection with no visible bleeding—the presence of blood at the injection site would have interfered with accurate measurement of leakage.

Leakage was assessed using filter paper and a tared, calibrated analytical balance. After completion of the injection, filter paper was laid on the injection site to absorb any postinjection leakage. The filter paper was then placed on the analytical balance to obtain the weight (in mg) of insulin diluent leaked from the injection site. Leakage data were converted to volume using the following conversion formula: 10,000 μg = 1000 μg/mg × 10 mg = 10 μl = 1 U.

Pain measurements were assessed using the validated Visual Analog Box-21 Scale for Pain (VAS).[7–11] Only the first injection with each needle length was assessed for pain to reduce the possibility of pain fatigue. Immediately following the injection, the participant was asked to rate the pain associated with each injection on a scale of 0 to 20. All injection sites were observed immediately postinjection by the investigator or designee, and the presence of visible bleeding was recorded (yes/no). All injection sites were assessed for bruising 1 to 3 days following each series of injections.

Statistical Methods

P-values for comparison of leakage medians were calculated using the sign test. Type one errors were controlled by a gatekeeping strategy. The incidence of bruising and bruise size were analyzed using the McNemar test and Student's *t*-tests, respectively. The incidence of bleeding was analyzed using a generalized estimating equation (GEE) model. *P*-values for comparison of pain scores were calculated using Student's *t*-tests.

Results

Patient Characteristics

Fifty-six patients entered the study and were randomly assigned to treatment, and all patients completed the study. Patients were generally middle-aged [mean ± standard deviation (SD) 55.75 ± 9.77 years], male (53.57%), had a mean (± SD) BMI of 35.63 ± 5.54 kg/m^2, and the majority had type 2 diabetes (76.79%) (**Table 1**) and had diabetes of long duration (mean ± SD 15.67 ± 8.65 years). Most patients (98.21%) originated from the United States.

Leakage Analysis

A summary and analysis of leakage is presented in **Table 2**. There was no significant difference between the 5 mm needle and the 8 mm needle with respect to median leakage with either the 20 U or 60 U equivalent volume.

Table 1.
Patient Characteristics

Characteristic	Total (*N* = 56)
Age (years), mean ± SD	55.75 ± 9.77
Sex, *n* (%)	
Male	30 (53.57)
Female	26 (46.43)
BMI (kg/m^2), mean ± SD	35.63 ± 5.54
Diabetes type, *n* (%)	
Type 1	13 (23.21)
Type 2	43 (76.79)
Origin, *n* (%)	
Mexico	1 (1.79)
United States	55 (98.21)

(*n*) number of patients, (*N*) total number of patients.

Table 2.
Analysis of Leakage

Needle length (mm)	5	8	5	8
Injection volume (U)	20	20	60	60
N	37	37	18	19
Mean (U)	0.07	0.06	0.14	0.06
Median (U)	0.04	0.02	0.04	0.02
SD	0.08	0.09	0.20	0.08
90% CI (U)[a]	(0.02, 0.06)	(0.02, 0.04)	(0.01, 0.13)	(0.01, 0.04)
P value[b]	.32		.48	

(*N*) total number of patients
[a] The CI was calculated for median using exact order statistics.
[b] *P* values for comparison of medians were calculated using the sign test.

Pain Scores

There was no significant difference between the 5 mm needle versus the 8 mm needle with respect to pain score with either the 20 U or 60 U equivalent volume (**Figure 1**). Mean ± SD differences (5 mm minus 8 mm) in pain score for 20 U and 60 U equivalent volumes were 0.14 ± 2.56 and 0.74 ± 2.49, respectively.

Bruising

A summary of the incidence of bruising and bruise size by injection volume is provided in **Table 3**. There were no significant differences between the 5 mm and 8 mm needles with respect to incidence of postinjection bruising at the injection site with either injection volume. In addition, there were no significant differences between the 5 mm and 8 mm needles with respect to bruise size. The mean (± SD) differences (5 mm minus 8 mm) in bruise size (mm) for 20 U and 60 U equivalent volumes were -1.95 ± 9.79 mm and -3.11 ± 7.38 mm, respectively.

Bleeding

There were no significant differences between the 5 mm and 8 mm needles with respect to the incidence of post-injection bleeding at the injection site. A summary of bleeding by injection volume is provided in **Table 4.**

Safety

There were no serious adverse events (SAEs) reported during this study.

Discussion

Smaller needles may reduce patient discomfort and have a positive impact on psychological insulin resistance. In this single-blind, randomized trial of obese patients with type 1 or type 2 diabetes, there were no observed differences between the 5 mm needle and the 8 mm needle with respect to insulin diluent leakage, pain intensity, bleeding, or bruising at injection sites with 20 U- or 60 U-equivalent volumes. There were no SAEs reported during study execution. The study results suggest that the 5 mm needle does not pose any additional risk for use in the obese population with diabetes compared with the 8 mm needle. This study provides evidence supporting the suitability of the 5 mm needle for the injection of insulin in obese patients with diabetes.

Similar to the results of the study by Kreugel and coworkers,[5] we found no difference between the 5 mm and 8 mm needles with respect to bruising and pain. However, in contrast to the Kreugel study, where

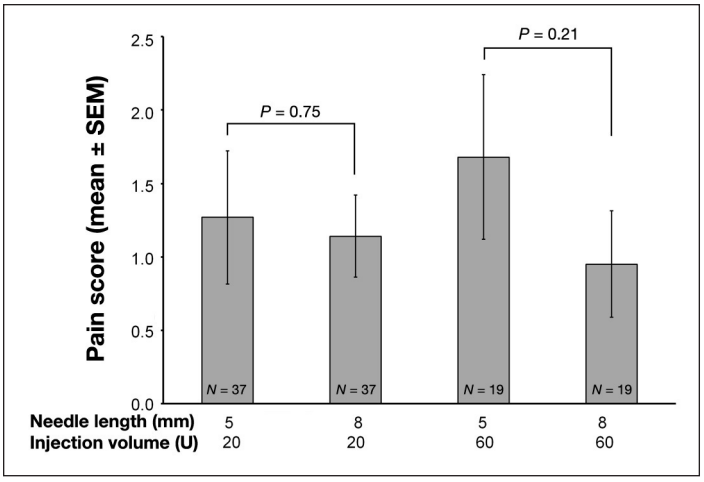

Figure 1. Pain scores using VAS 0–20 point scale. *P* values were calculated using Student's *t*-test. (*N*) total number of patients, (SEM) standard error of the mean.

Table 3.
Incidence of Bruising and Bruise Size

Needle length (mm)		5	8	5	8
Injection volume (U)		20	20	60	60
Bruising	*N*	37	37	19	19
	Yes, *n* (%)	3 (8.11)	4 (10.81)	4 (21.05)	5 (26.32)
	P value[a]	.56		.65	
Bruise size (mm)	*N*	37	37	19	19
	Mean	0.73	2.68	1.11	4.21
	SD	3.36	9.61	2.51	8.54
	P value[b]	.23		.08	

(*n*) number of patients, (*N*) total number of patients
[a] *P* values were calculated using the McNemar test
[b] *P* values were calculated using a *t*-test

Table 4.
Incidence of Bleeding

Needle length (mm)		5	8	5	8
Injection volume (U)		20	20	60	60
Bleeding	*N*	124	120	61	61
	Yes, *n* (%)	13 (10.48)	7 (5.83)	3 (4.92)	4 (6.56)
	P value[a]	.23		.73	
	P value[b]	.39			

(*N*) total number of observations, (*n*) number of observations
[a] Comparison of 20 U (5 mm vs 8 mm) and 60 U (5 mm vs 8 mm). A GEE model was used to calculate *p* values and included the following factors: needle length, injection site, and injection sequence.
[b] Comparison of 5 mm needle (20 U + 60 U) versus 8 mm needle (20 U + 60 U). A GEE model was used to calculate the *p* value and included the following factors: needle length, injection site, injection sequence, injection volume, and aspirin use.

patients reported less bleeding with the 5 mm needle and less insulin leakage with the 8 mm needle, we found no differences between the needle lengths with respect to bleeding and leakage. There are some important design differences between the Kreugel study and the present study, which may explain the different results. Patients in the Kreugel study administered their own injections, whereas all injections were administered by the investigator in the present study. The majority of endpoints in the Kreugel study, including leakage and bleeding, were patient-reported. In contrast, leakage was measured and bleeding was recorded by the investigator in the present study.

A unique feature of this study design was the use of two different injections volumes given with both needle lengths for all endpoints. A single injection volume was used in two reported studies.[5,6] Injection volumes vary depending on dose of insulin required. The injection volumes [20 U (200 µl) and 60 U (600 µl) equivalent] used in this study were representative of a relatively large mealtime dose of insulin and the maximum dose of several insulin pen injectors.

A potential limitation of this study is that all injections were investigator-administered. While blinding was necessary for assessment of pain scores, the study design did not replicate "real life," in which most insulin injections are self-administered. The assessment of pain, where patients were blinded to needle length, may not accurately reflect the psychological perception of injection discomfort as compared with a self-administered injection. Another limitation of the present study was that glycemic endpoints were not examined. Finally, all pen injections were randomized to the left and right lower quadrants of the abdominal area. The exclusion of other injection sites limits the conclusions of this study.

Conclusion

In summary, the 5 mm needle was similar to the 8 mm needle with respect to insulin diluent leakage postinjection in obese patients with type 1 or type 2 diabetes. In addition, the 5 mm needle was similar to the 8 mm needle with respect to pain intensity, bleeding, and bruising at injection sites with 20 U (200 µl) or 60 U (600 µl) equivalent volumes. The results of this study provide further evidence supporting the suitability of the 5 mm needle for the injection of insulin in obese patients with diabetes.

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Disclosures:

Haoda Fu and Debra Ignaut are employees and stockholders of Eli Lilly and Company.

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