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Original article

Comparative glycemic control, safety and patient ratings for a new 4 mm × 32G insulin pen needle in adults with diabetes

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Abstract

Objective:
Pen needles (PN) for subcutaneous insulin therapy have become smaller; 5 mm PNs are now the shortest in use. We evaluated the safety, efficacy and patient ratings of a new 4 mm × 32 gauge (G) PN.

Research design and methods:
Subjects with type 1 and type 2 diabetes and HbA1c 5.5% to 9.5% participated in a randomized non-inferiority cross-over trial, at four U.S. centers. Subjects used 4 mm × 32G PNs and either 5 mm × 31G PNs (4/5 mm) or 8 mm × 31G PNs (4/8 mm) in two, 3-week treatment periods; order of needle use was controlled. Subjects were either 'low dose' or 'regular dose' users (highest single insulin dose ≤ 20 units and 21–40 units, respectively). Percent absolute change in serum fructosamine (% |Δ Frul) was the primary endpoint; unexplained, severe hypo- or hyperglycemia was a secondary measure. Leakage at injection sites and pain measured by visual analog scale were tertiary measures. Equivalent glycemic control was defined *á priori* as % |Δ Frul (including 95% CI) within 20%; 40 subjects per subgroup provides 90% power at $\alpha = 0.05$.

Clinical trial registration:
The study was registered on clinicaltrials.gov (identifier: NCT00928057).

Results:
Of 173 subjects randomized, 168 completed the study, and 163 were included in the fructosamine analyses – 83 and 80 in the 4/5 mm and 4/8 mm groups, respectively. Subjects were 56% male, mean 52.6 yrs, 63% type 2. Baseline HbA1c = 7.5 ± 1.0% and fructosamine 301 ± 55.1 μmol/L. Mean % |Δ Frul was 4.9% (95% CI 3.8, 6.0) and 5.5% (4.5, 6.4), respectively, for the 4/5 mm and 4/8 mm groups, meeting glycemic equivalence criteria; results were similar in both dose groups. The median |Δ Frul was 11.0 μmol/L (8.0, 13.0) and 13.5 μmol/L (9.8, 18.0) for the 4/5 mm and 4/8 mm groups, respectively. Unexplained, severe hypo- and hyperglycemic episodes were infrequent and not different between PNs. The 4 mm PN was rated significantly less painful and preferred by approximately 2/3 of subjects ($p < 0.01$). All three PNs had similar reported injection site leakage.

Limitations:
The study was of relatively short duration, in adults in the U.S. Further trials in other patients (e.g., GLP-1 users, pediatrics, obese) should be performed.

Conclusions:
The 4 mm × 32G PN provided equivalent glycemic control compared to 31G, 5 mm and 8 mm PNs with reduced pain, no difference in insulin leakage and was preferred by patients.

Introduction

Since the first syringe designed specifically for insulin treatment in 1924, subcutaneous insulin delivery options have progressed from glass to disposable plastic syringes, thinner and shorter needles, insulin pens and pen needles (PNs), and insulin pumps. Insulin pens are available for many insulins and are reported to improve the ease, convenience and accuracy of insulin delivery[1–6]. As insulin pen use has expanded, shorter and thinner PNs – i.e. 5 and 6 mm, 31–33 gauge (G) – have been introduced. These smaller PNs reduce the discomfort and pain associated with subcutaneous injections compared with larger and/or longer needles[7,8]. Studies comparing only fine-gauge pen needles [31-33G] to each other have shown inconsistent patient ratings of relative pain and preference between such devices[9–11]. However, many educators and practitioners remain skeptical that short needles can be used in all of their patients, particularly those who are obese; the most commonly used PN length today – both in the U.S. and worldwide (nearly half of all patients) – remains 8 mm[12].

Injection technique is an important aspect of insulin injection therapy, for both consistent insulin delivery and to reduce patient discomfort[13–14]. It includes (but is not limited to) patient education and factors such as needle length, gauge and injection site; site rotation; use of angled or straight needle insertion; and possible use of a lifted skin fold by the patient. Today, the shortest PN available is 5 mm in length. This study evaluated a new 4 mm × 32G PN compared to two marketed PNs (5 mm × 31G and 8 mm × 31G) – all manufactured by BD (Becton, Dickinson & Co., Inc., Franklin Lakes, NJ). Outcomes include not only safety and efficacy but also subject-reported injection pain and leakage from injection sites, and overall preference between needles.

Subjects and methods

Subjects diagnosed with type 1 or type 2 diabetes and using an insulin pen at least once per day for two months or more were recruited at four clinical centers in the United States. Additional inclusion criteria were: BMI 18–50 kg/m^2, HbA1c 5.5–9.5%, and subjects being willing to monitor blood glucose at least four times per day and to maintain their non-insulin treatment regime during the study. Exclusion criteria were physical conditions which would make them unable to perform study procedures, recent history of unstable diabetes including ketoacidosis or hypoglycemic unawareness, bleeding disorders, or pregnancy.

Study conduct is outlined in Figure 1. At study Visit 1, subjects provided informed consent, and were screened including HbA1c. They were also assigned prospectively to an insulin dosing group (low or regular) based on their pre-study regimen to help ensure balance between the groups comparing the different size PNs: the largest single insulin doses allowed were ≤20 units for the low dose group, and 21–40 units for the regular dose group. There was no upper limit on total daily insulin dosage. At Visit 2, qualified subjects' baseline fructosamine was drawn. Subjects were randomized to either the 4/5 mm or 4/8 mm comparison group using an investigator site- and dose-group-specific computer-generated list of sequential numbers developed by BD Biostatistics, and were provided study PNs. The order of PN use was also randomized (no subject used all three PNs). After 21 ± 3 days, subjects returned for Visit 3 and received the alternate PNs. Three weeks later subjects returned for the fourth/final visit. When using the 4 or 5 mm PNs, subjects were advised to inject straight in (90°), with no pinch up. For the 8 mm PN, subjects were directed to use pinch-up at the abdomen and thigh. Actual injections were not observed. Fructosamine was again measured at study visits 3 and 4, where subjects also rated relative injection pain via a validated 150 mm visual analog scale (VAS)[15,16] (Figure 2A). All HbA1c and fructosamine tests were performed by Covance Central Laboratory in Indianapolis, IN.

The primary study objectives were to demonstrate equivalent glycemic control (as defined) with the 4 mm × 32G PN compared to 31G, 5 mm and 8 mm PNs. Secondary objectives were to evaluate A) % |Δ Fru| between the 4 mm × 32G and the other PNs in low dose and regular dose groups, and B) occurrence of severe, unexplained hypo/hyperglycemic events. Tertiary objectives were to evaluate A) occurrence of insulin leakage reported by subjects at injection sites, and B) perceived pain between the study PNs used by each subject, with the VAS. Additionally, a survey was administered at the end of the treatment periods regarding subjects' overall PN preference, ease of use, and pain.

For inclusion in the study, subjects were instructed to self-monitor blood glucose four times per day, primarily as a safety measure. They were also instructed to record all adverse events (AEs) in a log (including hypo- or hyperglycemic events and unusual injection pain) as well as any occurrences of insulin leakage from the skin with the date/time of the injection, dose, injection site and technique used (angle and pinch-up). A visual scale was provided for subjects to estimate size of leakage (Figure 2B). Study staff reviewed the contents of the log at each study visit and recorded AEs and leakage events on case report forms. Blood glucose levels <50 mg/dL and/or requiring assistance for treatment were categorized as severe, as were levels >450 mg/dL and/or requiring treatment in an emergency room or hospital. All of these events were also characterized as unexplained if there was no identifiable cause for the event (such as dosing error, skipping a meal, unplanned exercise, intercurrent illness, etc.).

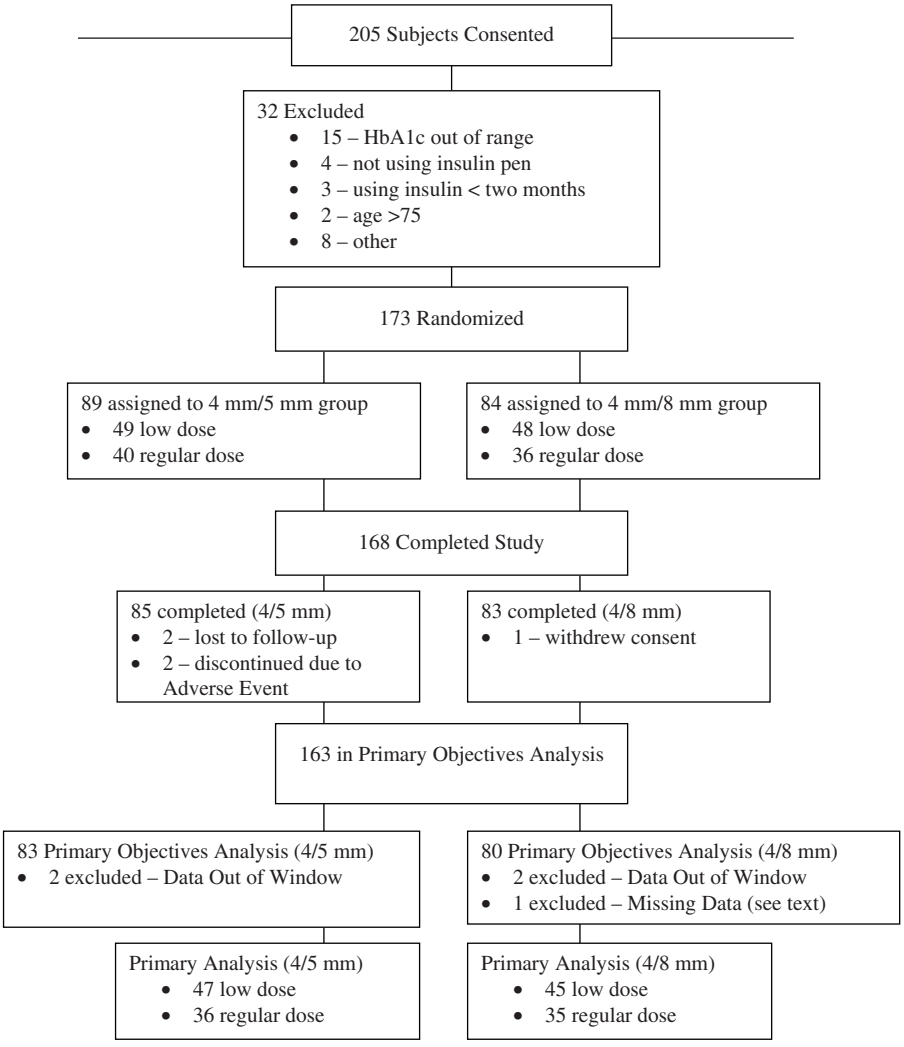

Figure 1. Study flow diagram. Subject flow in protocol, indicating screening, randomization, and follow-up.

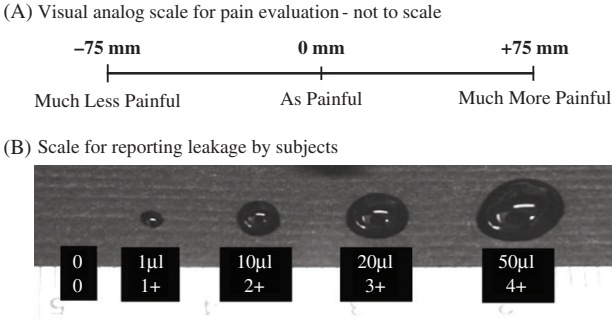

Figure 2. (A) Visual analog scale for pain evaluation – not to scale. VAS used to assess difference in pain between the pen needles used in the two study periods. Scale is 150 mm in length, and anchored at the mid-point with 'no difference' in pain between the two needles. Subjects were asked to mark the scale to indicate the difference (if any) they felt. Marks to the right indicate more pain and to the left, less pain. The order of needle use was adjusted for in the analysis. (B) Droplet size chart – not to scale. Visual scale provided to patients to estimate injection leakage: 0 = no leakage reported; 1 + ~1 µL volume; 2 + ~10 µL; 4 + ~50 µL. Ratings of 5 were entered if patients believed leakage exceeded 50 µL. 10 µL = 1 unit of U-100 insulin.

Power calculations and statistical methods

Fructosamine measurements reflect average blood glucose concentration during the past 2–3 weeks[17–19]. The principal endpoint is the percent absolute change in fructosamine, or % |Δ Fru|, calculated as:

$$100\% \frac{|Fru_{4\text{mm}} - Fru_{5\text{mm or }8\text{mm}}|}{Fru_{5\text{mm or }8\text{mm}}}.$$

Since this metric uses the absolute value of the bias, the average reflects both positive and negative differences between PNs, which add rather than cancel – it is a conservative indicator of BG stability. Dividing the bias by the fructosamine level with the comparator PN produces a relative measure. A related metric is the absolute change in µmol/L fructosamine, or |Δ Fru|, given by $|Fru_{4\text{ mm}} - Fru_{5\text{ mm or }8\text{ mm}}|$.

A previous BD study[20] showed the natural log of fructosamine had a standard deviation of 0.2. Assuming the

average Δ Fru would be 5%[20] and an equivalence acceptance criterion (including 95% CI) of 20%, 40 subjects were required to be in each subgroup (low and regular dose in 4/5 mm and in 4/8 mm groups) to provide 90% power for a non-inferiority test with $\alpha = 0.05$. Hence, there were about 80 subjects in each of the 4/5 mm and 4/8 mm groups, and 160 subjects in the entire study. Analysis of Variance (ANOVA) linear models were used to calculate the % |Δ Fru| for the 4 and 5 mm PNs, and for the 4 and 8 mm PNs, separately. The models were defined as the natural log of fructosamine adjusted for the effects of subject, dose group, investigator site and PN sequence to produce 95% CIs for the mean % |Δ Fru| between the 4/5 mm and 4/8 mm PNs, which were then compared to the equivalence criterion.

Leakage incidents were summarized with counts, percentages and averages. Hypoglycemic events and AEs were summarized with counts of the number of subjects that experienced events and the overall number of events. Pain scores were graphically summarized and analyzed with one-sided *t*-tests, and responses to the subject survey were analyzed by a paired comparison *t*-test (same sample). For all analyses, $\alpha = 0.05$.

The study was conducted in compliance with Good Clinical Practices (GCP). The protocol was reviewed and approved by Copernicus Group IRB (Research Triangle Park, NC) and registered on clinicaltrials.gov (Identifier: NCT00928057).

Results

Subject flow

The study was conducted from June to November 2009. Subject flow is shown in Figure 1. Five of 168 subjects who completed Visit 4 were not included in the primary endpoint analysis – four due to data collected outside of defined time windows for fructosamine (±7 days). One additional subject's (#426) fructosamine level was reported at Visit 3 as 71 µmol/L – far below the physiological range. Both baseline (Visit 2) and Visit 4 levels for this subject were nearly the same – 226 and 232 µmol/L. The results implied a 70% decline in average blood glucose in the first treatment period, and a >200% increase in the second period – with no corresponding clinical events. These data indicate laboratory error so this subject was excluded from the Δ Fru analyses, but is included in all other analyses, as are the four subjects above.

Demographics

Subjects were 56% male, with mean age nearly 53 years (range 18 to 76); 78% were Caucasian and 63% type 2 diabetes. Overall, mean BMI was 31.0 kg/m^2 and ranged from 20 to 49 kg/m^2; 52% of subjects were obese (BMI >30 kg/m^2). Subjects' demographic characteristics were evenly distributed throughout all study subgroups, shown in Table 1. Regular dose subjects took twice as much insulin each day as low dose subjects, on average. Single insulin doses ranged between 2 and 40 units. Most subjects (65%) had been diagnosed with diabetes for ≥10 years and 58% were treated with insulin for ≥6 years; only 7% had used insulin <1 year. In addition to insulin, 68 (42%) subjects were treated with oral hypoglycemic agents and/or pramlintide or exenatide: 63% (65 of 103) of the type 2 subjects were treated with oral hypoglycemic agents and 12% were injecting pramlintide or exenatide.

The PNs used prior to the study were predominately from BD and Novo-Nordisk. The most frequent needle length was 8 mm (59%), followed by 5 mm (30%), 6 mm (8%) and 12.7 mm (2%). Baseline HbA1c in all subjects was 7.5 ± 1.0% (SD) and fructosamine 301 ± 55.1 µmol/L. These measures were similar across the two needle-length comparison groups and the two insulin dose subgroups, shown in Table 1.

Glycemic control

The mean % |Δ Fru| was 4.9% (95% CI 3.8, 6.0) between 4 and 5 mm PNs, and 5.5% (4.3, 6.4) between 4 and 8 mm PNs. There was no statistical difference between the two PN groups: the *p*-values were 0.878 and 0.927, respectively. Figure 3A displays these differences overall and for each subgroup compared to the 20% equivalence criterion. Similarly, Figure 3B shows median |Δ Fru| in µmol/L. The distribution of % Δ Fru (positive and negative) is shown in Figure 4. In the 4/5 mm group, approximately 67.5% of fructosamine changes were within ± 5%, and 89.2% within ± 10%. In the 4/8 mm group, 51.9% of these changes were within ± 5%, and 86.4% within ± 10%. For patients who used the 5 mm PN first followed by the 4 mm PN, fructosamine was 0.8% lower with the 4 mm PN; when used in the opposite order fructosamine was 0.3% lower with the 4 mm PN. For patients who used the 8 mm PN first then the 4 mm PN, fructosamine was 0.7% higher with the 4 mm PN; when used in the opposite order fructosamine was 3.5% higher with the 4 mm PN.

Correlation between insulin dose and change in glycemic control was evaluated by comparing Δ Fru following the first study period (Visit 3) with the greatest single daily dose at baseline (Visit 2) – no relationship was found (data not shown). Substantive changes in insulin doses during the study were infrequent – 21 subjects reported any change in insulin dosing, and only 13 had dose changes >10%. In an additional *post hoc* analysis, BMI did not correlate with Δ Fru in either the 4/5 mm or 4/8 mm PN groups, ($p = 0.719$ and 0.737, respectively), shown in Figure 5.

Table 1. Demographics – includes all subjects in primary outcome analyses.

	All Subjects	Subject Subgroups			
		4 mm/5 mm	4 mm/8 mm	Regular dose	Low dose
Number	164*	83	81	72	92
Age (Years) – Mean (SD)	52.6 (15.5)	54.4 (14.0)	50.8 (16.8)	51.3 (15.8)	53.6 (15.3)
BMI (kg/m^2) – Mean (SD)	31.0 (6.1)	31.0 (6.0)	30.1 (6.3)	32.3 (6.1)	29.2 (5.9)
Gender, Male – Number (%)	92 (56%)	46 (55%)	46 (57%)	37 (51%)	55 (60%)
Race/Ethnicity – Number (%)					
Asian	7 (4)%	3 (4%)	4 (5%)	4 (6%)	3 (3%)
Black/African American	24 (15%)	14 (17%)	10 (12%)	12 (17%)	12 (13%)
Hispanic/Latino	3 (2%)	2 (2%)	1 (1%)	1 (1%)	2 (2%)
White/Caucasian	128 (78%)	63 (76%)	65 (80%)	55 (76%)	73 (79%)
Other	2 (1%)	1 (1%)	1 (1%)	0 (0%)	1 (2%)
Diabetes Type					
Type 1 Number (%)	61 (37%)	31 (37%)	30 (37%)	27 (38%)	34 (37%)
Insulin Doses – Mean (units)					
Total Daily	46.6	47.4	45.7	64.8	32.3
Largest Single	20.5	21.3	19.6	29.0	13.8
HbA1c (%)					
Mean (SD)	7.5 (1.0)	7.6 (1.0)	7.4 (1.0)	7.7 (1.0)	7.3 (1.0)
Min/Max	5.6/9.6	5.7/9.5	5.6/9.6	6.0/9.5	5.6/9.6
Fructosamine (μmol/L)					
Mean (SD)	301 (55.1)	303 (60.8)	299 (49.0)	303 (54.8)	299 (55.7)
Min/Max	207/465	209/465	207/422	209/432	207/465

mm = millimeters; SD = standard deviation; BMI = body mass index.
*includes subject #426 – see Methods.

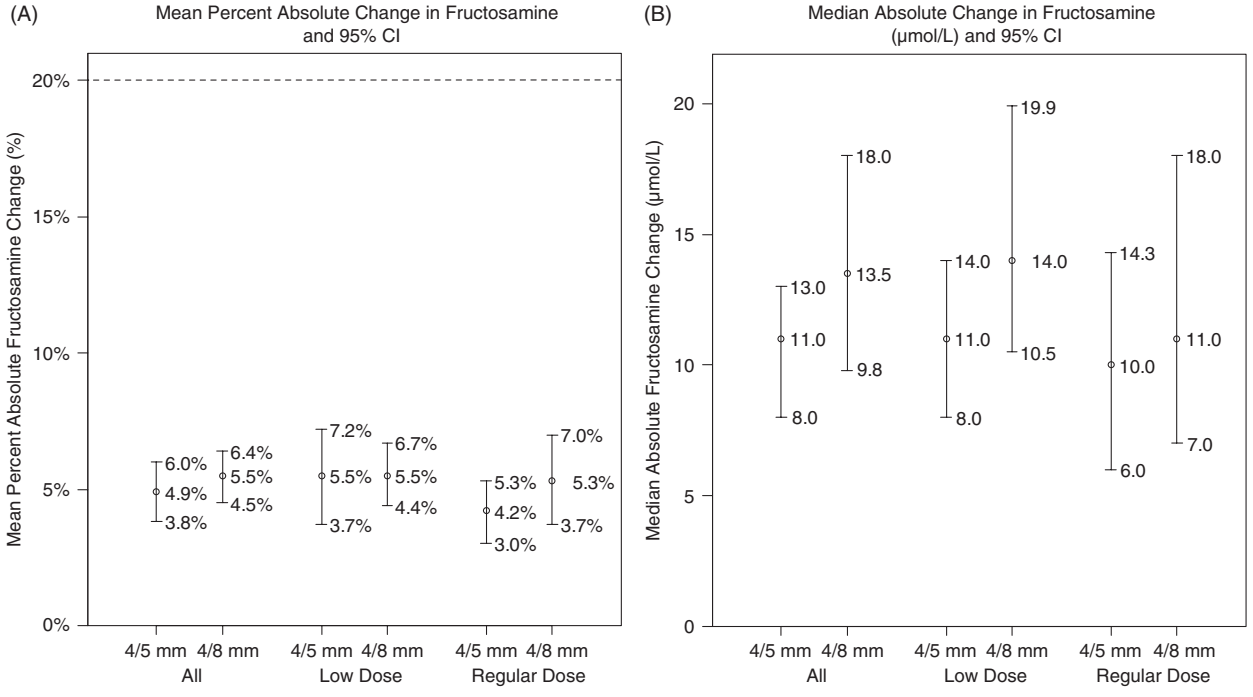

Figure 3. (A) Mean of percent absolute changes in fructosamine for 4 vs 5 mm ($N = 83$) and 4 vs 8 mm ($N = 80$) subjects. Left: All subjects, $N = 163$. Middle: low dose group, $N = 92$. Right: regular dose group, $N = 71$. Glycemic equivalence for pen needles was defined as percent absolute fructosamine changes including CIs within 20% (dashed line). (B) Median of absolute changes in fructosamine for 4 vs 5 mm ($N = 83$) and 4 vs 8 mm ($N = 80$) subjects. Left: All subjects, $N = 163$. Middle: low dose group, $N = 92$. Right: regular dose group, $N = 71$.

Pain

VAS scores were available for 68 subjects in the 4/5 mm group, and 69 in the 4/8 mm group – a number of ratings were collected outside the study visit ± 3-day time window. The VAS pain score was 11.9 mm less for the 4 mm PN vs the 5 mm PN, and 23.3 mm less for the 4 mm PN vs the 8 mm PN. Both differences are statistically significant, $p < 0.02$, in Table 2.

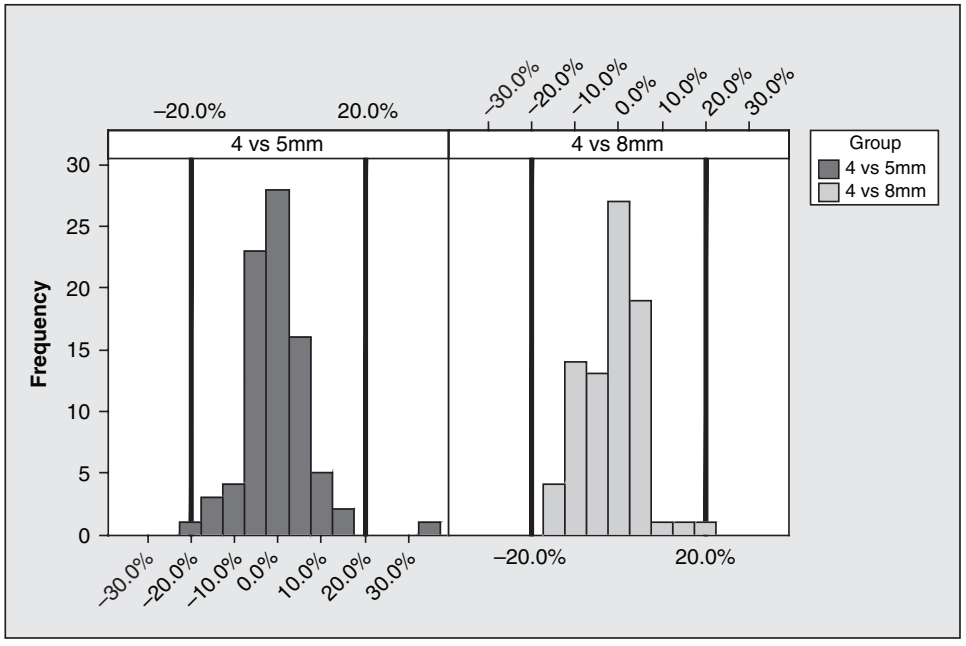

Figure 4. Frequency distribution of relative fructosamine differences by study group. Distribution of changes in fructosamine, whether positive or negative, for 4 vs 5 mm, and for 4 vs 8 mm comparison groups.

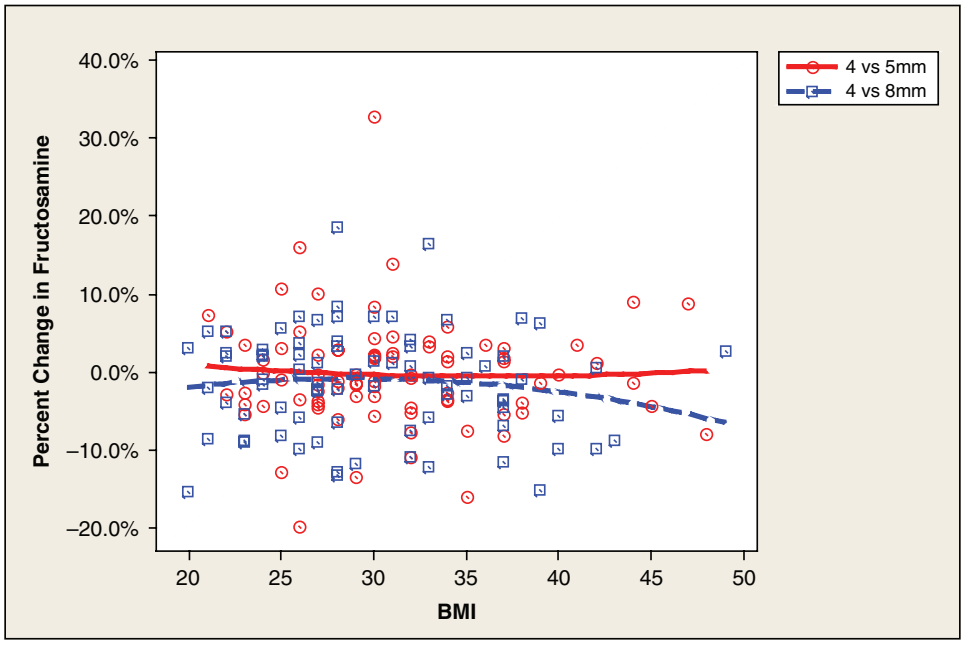

Figure 5. Relative percent change in fructosamine as a function of subject BMI. Percent change in fructosamine for 4 vs 5 mm group (open circles, solid red line) and for 4 vs 8 mm group (open squares, dashed blue line) is not significantly related to subject BMI (body mass index, kg/m^2).

Table 2. Visual analogue scale (VAS) scores for pain.

Group	*N*	Mean Difference (mm)	SD	SEM	95% Upper Bound	*p*-value (compared to 0 mm)
4 mm vs 5 mm	68	−11.91	46.27	5.61	−2.55	0.019
4 mm vs 8 mm	69	−23.26	35.25	4.24	−16.18	<0.001

SD = standard deviation; SEM = standard error of the mean.

Table 3. Leakage from injection sites for the 4, 5 and 8 mm pen needles.

Needle Length	Subjects (Number)	Subjects Reporting Leakage (%)	Total Number of Events	Mean Number of Leakage Events Reported
4 mm	164	72 (44)	650	9.0
5 mm	83	39 (47)	481	12.3
8 mm	81	45 (56)	357	7.9

Patient-reported events of leakage during both treatment periods of study. All subjects used the 4 mm needle in one treatment period; about 50% of subjects used either the 5 mm or 8 mm needle in the other period. Mean number of leakage events reported was calculated using the number of subjects who reported any leakage, only.

Table 4. Number (%) of randomized subjects with non-serious adverse events (AEs) while using the pen needle indicated*.

Non-Serious AEs	4 mm ($N=173$)	5 mm ($N=89$)	8 mm ($N=84$)
Hypoglycemia	36 (20.8)	21 (23.6)	22 (26.2)
Injection Site Pain	27 (15.6)	11 (12.4)	11 (13.1)
Hyperglycemia	7 (4.0)	7 (7.9)	4 (4.8)

*Adverse events that occurred in single patients are not shown in table – these included ligament sprain, needle breakage, nevus, osteoarthritis, skin cosmetic procedure, and urinary tract infection.

Leakage

Insulin leakage or 'backflow' data are shown for each individual PN length, with the events reported expressed in both absolute numbers and as a rate per subject, in Table 3. The average rates reported do *not* include the injections for which patients did not report any leakage – such information was not collected prospectively. For all the PNs, 1488 leakage events were reported; 838 (58%) when using the 5 and 8 mm PNs. A numerically smaller proportion of patients using the 4 mm PN reported leakage than with the 5 mm and 8 mm PNs. The mean reported droplet sizes for all needle lengths at the abdomen, arm and thigh injection sites were <2+ (< 1 unit of insulin), and did not differ between the three PNs. Nearly all leakage reports were with injections at 90° – about 20% of events reported with 4 mm and 5 mm injections were with pinch-up, and 80% as instructed, without pinch-up (data not shown).

Safety

Eighty-eight subjects experienced 413 AEs in the study. The most common AEs reported were hypoglycemia followed by injection site pain and hyperglycemia; these accounted for 98% of all reported AEs. Rates for these were not significantly different between the three PNs – see Table 4. Unexplained severe hyper- and hypoglycemic events are summarized in Table 5 – these were infrequent and occurred at similar rates with all three PNs.

Table 5. Severe unexplained hypoglycemic and hyperglycemic events (see Methods for definition) among randomized subjects.

Needle Length (Number Randomized)	4 mm ($N=173$)	5 mm ($N=89$)	8 mm ($N=84$)
Event			
Hypoglycemia (%)	9 (5.2)	5 (5.6)	4 (4.8)
Hyperglycemia (%)	0 (0)	2 (2.2)	1 (1.2)

Number (%) of subjects with one or more events, by needle used at time of event.

Two subjects discontinued the study due to AEs unrelated to product usage. There were five serious adverse events (SAEs) reported in the study, three of which occurred while subjects used the 4 mm needle (one each of dyspnea, hypoglycemia, and hypoglycemic seizure), and two that occurred during use of the 8 mm needle (one case of dyspepsia and one myocardial infarction). None of these SAEs was considered device-related by the investigators.

Preference survey

At Visit 4, subjects were asked which of the two study PNs they preferred overall; responses are available for 140 (85%) subjects. Subjects preferred the 4 mm PN significantly more than either the 5 mm or 8 mm PNs ($p<0.05$; Figure 6). Approximately four times as many subjects preferred the 4 mm PN 'a lot more' as did subjects who preferred either of the other two PNs similarly.

Specific attributes of study PNs such as insertion pain, ease of use or of delivering their insulin were also evaluated by subjects at Visit 4. The 4 mm PN was significantly preferred over the 5 and 8 mm PNs for nearly all attributes tested ($p<0.05$; Figure 7).

Discussion

In adults with type 1 and type 2 diabetes, the 4 mm × 32G pen needle provides equivalent glycemic control to 31G, 5 and 8 mm PNs. Percent absolute changes in fructosamine were small, averaging 5 to 5.5% (median 11–13.5 µmol/L), and there was no suggestion of any trend in directional change in blood glucose levels with the new pen needle. The 4 mm × 32G PN was reported to be less painful, easier to use, caused no additional leakage and was preferred to the larger, longer needles by the study subjects.

Factors affecting patient perceptions of pain with injection therapy include needle diameter and length, tip sharpness including bevel angularity, polishing and smoothness of the cannula, as well as cannula lubrication. External cannula diameter has been shown to be especially important in several studies[21,22] (and Hofman P. – personal communication). There is good evidence that larger needle diameter triggers greater nocireceptor reaction, meaning

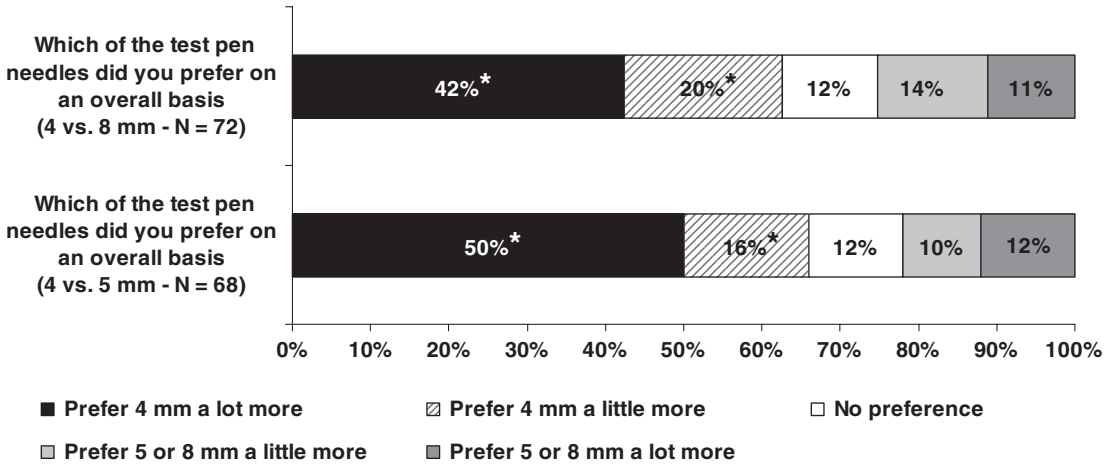

Figure 6. Survey question – 'Which of the test pen needles did you prefer on an overall basis, the ones you tried first or the ones you tried second?' *Combined ratings of 'Prefer 4 mm a lot more' and 'Prefer 4 mm a little more' – subjects prefer 4 mm over other test pen needle at 95% confidence level.

greater pain, with other factors held constant[21,22]. A single study in children did not support such findings, but was conducted with all larger-diameter needles[23].

The VAS evaluation in this study clearly showed significantly less pain with the 4 mm × 32G PN: subjects rated the new PN nearly 12 mm less painful than the 5 mm needle, and 23.3 mm less painful than the 8 mm needle – a nearly two-fold larger change. Using the VAS described with a center point anchor of 'No difference,' the maximum difference demonstrable would be 75 mm between two devices/needles: the VAS score differences are nearly 16% and 31%, respectively, of the maximum, implying changes that can be appreciated by the subjects. Other studies[16,24] and our prior investigations suggest that a 10 mm difference is clinically meaningful. The mean differences seen with the 4 mm × 32G needle vs the 31G, 5 mm and 8 mm needles both exceed this threshold, although the upper bound of the 95% CI fell within 10 mm for the comparison to the 5 mm PN. Studies comparing insulin delivery devices using a VAS measuring absolute pain (e.g., without a central anchor) are more prone to inaccurate findings[9,10], since the absolute degree of pain with today's shorter length, smaller diameter (higher gauge) needles is small[25].

These VAS findings were also strongly supported by the survey responses regarding needle attributes: the 4 mm × 32G PN was rated significantly more comfortable and less painful, both for needle insertion and when injecting insulin (Figure 7). In a previous study comparing a 29G, 12.7 mm PN with a 31G, 6 mm PN, patients rated the smaller PN as more comfortable and causing less pain, yet when double-blinded vehicle injections were performed as part of that study with the same PNs, VAS pain scores did not differ[26]. In aggregate, these findings indicate the importance of psychological and perceptual dynamics in pain assessments. Patients see the PN they use every day in real world use, and these attributes influence patient reaction to the needle and their acceptance of insulin injection therapy.

Injection technique is also important for patient perceptions of pain and overall satisfaction[13–14]. For the new PN, subjects were instructed to inject straight in (i.e., at a 90° angle) without using pinch-up (raising a skin fold). Skin (epidermis + dermis) thickness has been shown to be ≤2.8–3.0 mm in nearly all adults, including obese diabetics at injection sites[27,28]; therefore, when inserted as recommended in adults, the 4 mm PN will penetrate the skin and enter the subcutaneous tissue reliably, with virtually no risk of IM injection. In the accompanying paper, calculations indicate that a 4 mm PN inserted at a 90° angle should deposit insulin in the SC space >99.5% of the time – confirmed with magnetic resonance imaging[27]. An angled injection, i.e. 45°, may result in inadvertent intradermal medication delivery in some cases, which has been associated with accelerated insulin absorption[29]. The 'straight-in' technique without skin fold should be easy for patients to perform and for health care providers to instruct patients – including those just starting insulin therapy – and may allow more flexibility for use of certain sites, such as the upper outer arm.

Although not studied directly, it appears that children and adolescents can also use this 4 mm PN and injection technique. Prior work has shown similar or slightly lower skin thickness in younger populations vs adults[30,31], and one brief report demonstrated insulin delivery subcutaneously with a 4 mm PN inserted at 90° without pinch-up in the thigh in children, adolescents, and lean adults[32]. It is logical to assume the 4 mm PN will further reduce the risk of inadvertent IM injection vs a 5 mm or 6 mm PN[27]. Nevertheless, use of a lifted skin fold with the 4 mm PN *may* be appropriate for some younger lean patients,

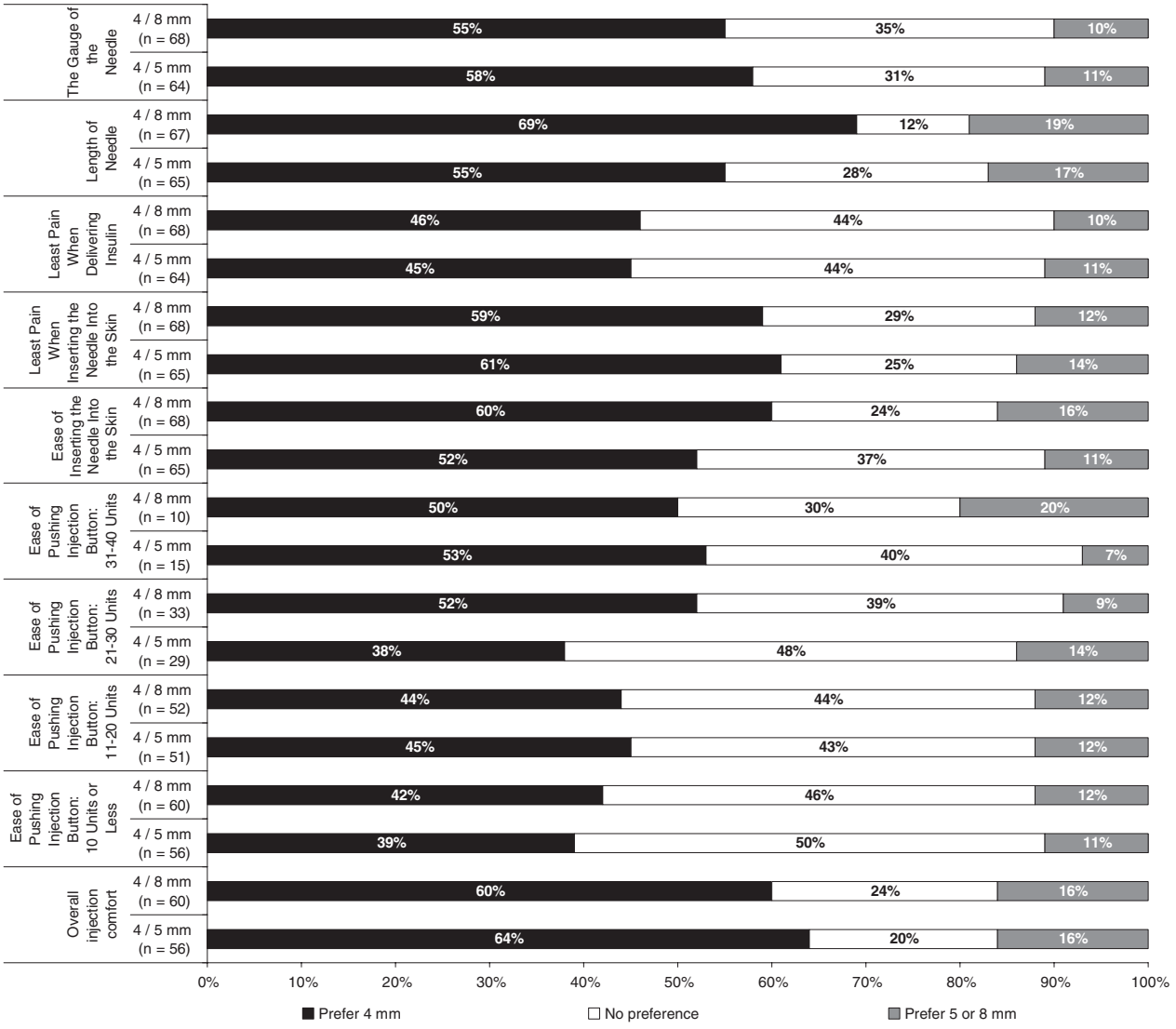

Figure 7. Summary of subjects' preference on various pen needle attributes. 4 mm significantly preferred over other test pen needle at 95% confidence level for all attributes except for Ease of Pushing Injection Button: 31–40 Units (*N* too small for testing).

especially in the limbs, and should be studied. This is important because Hofman *et al*. raised some questions about use of lifted skin folds in children and adolescents. Specifically, they found that lifting a horizontal skin fold in the abdomen increased subcutaneous thickness nearly two-fold (192 ± 16%), but pinching the thigh increased it by only 22 ± 6% – and in some subjects with <10 mm of thigh subcutaneous fat, actually *reduced* fat depth – leading them to recommend angled injections with pinch-up for 6 mm PNs[31]. Use of the thigh for insulin injection therapy may carry a higher risk of inadvertent IM injection, especially in thinner males.

There was no indication of increased skin leakage with the new 4 mm × 32G PN. In fact, a numerically smaller percentage of subjects reported leakage with the 4 mm needle than with either the 5 mm or 8 mm needles. Subjects indicated they injected at 90° with pinch-up in about one-fifth of leakage events they reported with the 4 mm and 5 mm PNs; nearly all of the other reports were with injections at 90° without pinch-up, as advised. It appears there was no clear relation between reports of leakage and use of lifted skin folds with the short PNs – but further study of injection site leakage (including the relationship with BMI) is warranted. The percentage of subjects reporting leakage events was much higher than occurs in clinical use – doubtless reflecting the training the participants received as part of the study to report such events. The reports should not be assumed to be accurate in terms of leakage volume – injections were not observed and gravimetric measurement was not performed. However, there is no reason to believe the reports were biased among the three PNs. Overall, there is no evidence

of any clinically untoward effect of the leakage events reported.

A common perception is that obese patients 'need' longer needles for optimal subcutaneous insulin treatment, although the evidence belies this[26,33]. If this were valid, there should be a relationship between patient BMI and change in glycemic control – which was clearly *not* the case (Figure 5). No relationship (either by linear or quadratic modeling) was found for Δ Fru and BMI with either the 4/5 mm or the 4/8 mm comparisons. Two controlled crossover studies in obese patients evaluated 6 mm versus 12.7 mm needles[26], and 5 mm versus 8 mm needles[33]. Both showed equivalent glycemic control (HbA1c) with the different needle lengths tested, and little if any differences in leakage or bleeding. Patients preferred the 6 mm needle (which was also a finer gauge) to the 12.7 mm PN; there were smaller (non-significant) differences in preference favoring the 5 mm versus 8 mm PNs[26,33]. Shorter-length pen needles appear to be safe and effective for insulin therapy in obese diabetic patients.

Several previous studies evaluated different length needles for insulin therapy in other groups of patients. When 8 mm needles were first introduced, they were found to provide unchanged glycemic control as the then-prevalent 12.7 mm needles[20]. Similar outcomes were obtained when the 5 mm PN was first compared to 8 mm needles in both adult and pediatric patients[8]. Insulin uptake (using ^{125}I-labeled human [regular] insulin) was previously shown to be similar when injected at superficial and deep levels in the subcutaneous tissue, in both abdominal and thigh locations[34]. Taken together, these studies indicate consistency of insulin kinetics and effects when injected at different depths within the SC space. Analogue insulin absorption appears less variable than with human (regular, NPH) insulin, both by anatomic site and injection depth, but inadvertent IM injection should be avoided[35].

In terms of insulin flow through the needle, subjects did not report negative perceptions of the ease of delivering their insulin with the thinner 32G needle. This may be partially explained by laboratory tests that show it only takes about one additional second for the 4 mm × 32G PN to deliver the same dose as the 31G × 5 mm PN, up to 80 units (BD Data on File). This difference is nominal and was apparently of no concern to study subjects, who still rated the 32G PN similar or easier to use (Figure 7). The new PN uses the same 'thin-wall' technology as the 5 mm and 8 mm needles, which has been shown to be preferred by patients when compared to other, 'regular-wall' PNs[36].

Conclusions from the study are strongly supported by the data, but some limitations exist. The study was conducted in adults in the U.S. for relatively short duration (3 weeks for each treatment period) and was not blinded; both investigators and subjects knew which PN they were using. This may have influenced some subjective measures, but not the fructosamine values. (Blinding in fact is not possible in such a study). The subjects had to have injected insulin with a pen for several months prior to participation – they were not questioned if they had previously used syringes, nor was prior use of any particular length needle required. The distribution of pen needle lengths used by the subjects is similar to that in the overall U.S. market, and we believe the population studied reasonably represents those taking insulin with pens. Further studies should be conducted in other groups including children and adolescents, and prospectively in obese patients injecting higher insulin doses. Additional trials might investigate variations in injection technique (use of skin pinch/lifted skin fold), particularly in lean, younger patients. The new 4 mm × 32G needle should also be evaluated for other diabetes medications given subcutaneously, like GLP-1s (incretin agonists) or amylin agonists.

Conclusion

This study has demonstrated equivalent glycemic control with a new 4 mm × 32G pen needle versus two marketed pen needles (5 mm × 31G and 8 mm × 31G) in a diverse group of adult, insulin-requiring patients with diabetes. Absolute changes in fructosamine were small, about 5–5.5% on average (median 11–13 μmol/L) between the 4 mm and each of the other PNs, and relative changes were distributed evenly around zero. The shorter needle was safe and well tolerated, rated easier to use, did not increase skin leakage, and was preferred by the majority of patients. These findings support use of a 4 mm × 32G pen needle for subcutaneous insulin injection therapy.

Transparency

Declaration of funding

BD (Becton, Dickinson and Company) provided funding for this study and manufactures all the pen needles tested.

Declaration of financial/other relationships

L.J.H., M.A.G., J.A. and S.Q. have disclosed that they are employees of BD. T.S.B. and L.K. have disclosed that they were investigators in the study and received payments for their work.

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References

1. Kortykowski M, Bell D, Jacobsen C, et al. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injections in patients with type 1 or 2 diabetes mellitus. Clin Ther 2003;11:2836-48
2. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther 2004;9:1498-505
3. Stocki K, Ory C, Vanderplas A, et al. An evaluation of patient preference for an alternative insulin delivery system compared to standard vial and syringe. Curr Med Res Opin 2007;23:133-46
4. Rubin RR, Peyrot M. Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diab Care 2004;27:2495-7
5. Bohannon NJV, Ohannesian JP, Burdan AL, et al. Patient and physician satisfaction with the Humulin/Humalog pen, a new 3.0-mL prefilled pen device for insulin delivery. Clin Ther 2000;22:1049-67
6. Rosak C, Burkard G, Hoffmann JA, et al. Metabolic effect and acceptance of an insulin pen treatment in 20,262 diabetic patients. Diab Nutr Metab 1993;6:139-45
7. McKay M, Compion G, Lytzen L. A comparison of insulin injection needles on patients' perceptions of pain, handling, and acceptability: a randomized, open-label, crossover study in subjects with diabetes. Diab Tech Ther 2009;11:195-201
8. Strauss K, Hannet I, McGonigle J, et al. Ultra-short (5 mm) insulin needles: trial results and clinical recommendations. Pract Diab Intl 1999;16:218-22
9. Miyakoshi M, Kamoi K, Iwanaga M, et al. Comparison of patient's preference, pain perception, and usability between Micro Fine Plus® 31-gauge needle and microtapered NanoPass® 33-gauge needle for insulin therapy. J Diab Sci Technol 2007;1:718-24
10. Iwanaga M and Kamoi K. Patient perceptions of injection pain and anxiety: a comparison of NovoFine 32-gauge tip 6 mm and Micro Fine Plus 31-gauge 5 mm needles. Diab Tech Ther 2009;11:81-6
11. Fujimoto R, Okeda T, Nobuyuki A, et al. Study on penetration pain of pen needles for insulin injection. Practice 2009;26:95-9
12. De Coninck C, Frid A, Gaspar R, et al. The 2008–2009 insulin injection technique questionnaire survey: results and analysis. 2010 [In press]
13. Hansen B, Kirketerp G, Ehlers G, et al. Evidence-Based Clinical Guidelines for Injection of Insulin for Adults with Diabetes Mellitus, 2nd edn. Dansk Sygeplejeråd (Danish Nurses Organization), 2006
14. Frid A, Hirsch L, Gaspar R, et al. New injection recommendations for patients with diabetes. 2010 Manuscript submitted for publication
15. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue scale for evaluating pain. Anaesthesia 1976;31:1191-8
16. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. Ann Emerg Med 2001;37:28-31
17. Hom FG, Ettinger B, Lin MJ. Comparison of serum fructosamine vs glycohemoglobin as measures of glycemic control in a large diabetic population. Acta Diabetol 1998;35:48-51
18. Hom F. Fructosamine, hemoglobin A1c, and measures of diabetic control. Diab Tech Ther 1999;1:443-5
19. Smaldone A. Glycemic control and hemoglobinopathy: when A1c may not be reliable. Diab Spectrum 2008;21:46-9
20. Ross SA, Jamal R, Leiter LA, et al. Evaluation of 8 mm insulin pen needles in people with type 1 and type 2 diabetes. Pract Diab Intl 1999;16:145-8
21. Egekvist H, Bjerring P, Arendt-Nielsen L. Pain and mechanical injury of skin following mechanical needle insertions. Eur J Pain 1999;3:41-9
22. Arendt-Nielsen L, Egekvist H, Bjerring P. Pain following controlled cutaneous insertion of needles with different diameters. Somatosens Mot Res 2006;23:37-43
23. Hanas R, Lyzten L, Ludvigsson J. Thinner needles do not influence injection pain, insulin leakage or bleeding in children and adolescents with type 1 diabetes. Pediatr Diab 2000;1:142-9
24. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153-7
25. Karges B, Muche R, Moritz M, et al. Low discomfort and pain associated with intensified insulin therapy in children and adolescents. Diab Res Clin Pract 2008;80:96-101
26. Schwartz S, Hassman D, Shelmet J, et al. A multicenter, open-label, randomized, two-period crossover trial comparing glycemic control, satisfaction, and preference achieved with a 31 gauge × 6 mm needle versus a 29 gauge × 12.7 mm needle in obese patients with diabetes mellitus. Clin Ther 2004;26:1663-78
27. Gibney MA, Arce CH, Byron KJ, et al. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin 2010;26:1519-30
28. Laurent A, Mistretta F, Bottigioli D, et al. Echographic measurement of skin thickness in adults by high frequency ultrasound to assess the appropriate microneedle length for intradermal delivery of vaccines. Vaccine 2007;25:6423-30
29. Heinemann L, Hompesch M, Kapitza C, et al. Intra-dermal insulin lispro application with a new microneedle delivery system led to substantially more rapid insulin absorption than subcutaneous injection. Diabetologia 2006;49(S1):620
30. Seidenari S, Giusti G, Bertoni L, et al. Thickness and echogenicity of the skin in children as assessed by 20-MHz ultrasound. Dermatology 2000;201:218-22
31. Hofman PL, Lawton SA, Peart JM, et al. An angled insertion technique using 6-mm needles markedly reduces the risk of intramuscular injections in children and adolescents. Diabet Med 2007;24:1400-5
32. Birkebaek NH, Solvig J, Hansen B, et al. A 4-mm needle reduces the risk of intramuscular injections without increasing backflow to skin surface in lean diabetic children and adults. Diab Care 2008;31:e65
33. Kreugel G, Keers JC, Jongbloed A, et al. The influence of needle length on glycemic control and patient preference in obese diabetic patients. Diabetes 2009;58(S1):440-P
34. Frid A, Linde B. Intraregional differences in the absorption of unmodified insulin from the abdominal wall. Diabet Med 1992;9:236-9
35. Frid A. Fat thickness and insulin administration, what do we know? Infusystems International 2006;5:17-19
36. Siegmund T, Blankenfeld H, Schumm-Draeger P-M. Comparison of usability and patient preference for insulin pen needles produced with different production techniques: 'Thin-wall' needles compared to 'Regular-wall' needles: an open-label study. Diab Tech Ther 2009;11:523-8

