A comparison study of patient ratings and safety of 32- and 34-gauge insulin pen needles

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Abstract

Objective Our aims were to compare diabetic patients' evaluations of straight 32- and tapered 34-gauge 4-mm needles for usability and preference as well as the frequency of injection adverse events during insulin self-injection and to analyze the relationship between patients' preferences and their background characteristics including thumb force measured by manual muscle testing.

Methods We enrolled 60 insulin-treated patients and measured their maximum thumb force. Patients were randomized into two groups (32- and 34-gauge) with reverse order of needle use: 1 week with one type of needle and the next week with the other. The usability of and preference for the needles were measured using the visual analog scale (VAS), and the frequency of injection adverse events was evaluated.

Results Mean maximum thumb strength was 83.5 ± 25.4 N, tended to decrease with age and was significantly lower in females than in males. The mean VAS scores regarding smooth insertion and pain during insulin delivery were significantly different, favoring the 34-gauge needle. However, the mean VAS scores regarding ease of pushing an injection button and overall preference showed no significant difference between the two needles. There was no significant difference in the frequency of injection adverse events including breaking needles.

Conclusion Our patients had sufficient thumb force to push the injection button regardless of needle type. Although significant differences regarding smooth

insertion or pain during insulin delivery were perceived, there was no difference in overall preference between the two needles, indicating the usability and safety of the two needles are not different in clinical use.

Keywords Diabetic patients · Insulin pen needle · Patient ratings · Thumb force

Introduction

Daily multiple self-injections of insulin cause a substantial burden on diabetic patients. To improve the quality of life, specifically, to improve the ease of injection (ease of pushing an injection button) and reduce the pain during delivery, insulin delivery devices and needles have been modified in various ways [1–7]. Shorter and thinner needles have been developed as one way to improve insulin pens. The shortest and thinnest needle for insulin injection commercially available in Japan is 4 mm in length and tapered 34-gauge in diameter.

A short needle is expected to relieve pain and the fear caused by the needle's appearance, but there is a risk of failing to administer the full dose of insulin due to inadequate penetration of the subcutaneous tissue. Skin thickness in adults and children is reported to be approximately 2–2.5 mm at sites commonly used for insulin injection [8, 9], which suggests a needle length of 4 mm is long enough for subcutaneous injection in most patients. A study reported that the pharmacokinetics of insulin injected with a 4-mm needle was similar to those with 6- and 8-mm needles in young Japanese subjects [10]. These findings suggest that a 4-mm needle can be safely used in most patients. Other studies reported that glycemic control was improved by optimizing the injection technique [11] in

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addition to switching from a longer needle to a 4-mm needle [12]. A 34-gauge needle is expected to reduce the occurrence of perceived pain because it is less likely to stimulate the pain spots of the skin surface at the injection site. However, a thinner needle diameter requires an increased injection pressure. This may lead to various disadvantages including difficulty in pushing the button of an insulin pen, a longer time to deliver insulin and increased perceived pain during insulin delivery. Because many patients with type 2 diabetes are elderly, they often show a reduced manual dexterity because of impaired physical functions and comorbidities affecting their hands and fingers, such as osteoarthritis. Patients with diabetic complications may also show a reduced manual dexterity because of diabetic neuropathy. For those patients, ease of injection is an important factor in achieving appropriate glycemic control because ease of injection helps to ensure effective insulin delivery. A thinner needle may lower needle strength, which has raised concern about the possible increased frequency of breaking and bending needles.

At present, two 4-mm needles, 32 and tapered 34 gauge, are commercially available in Japan. A needle with an extra-thin wall and 32-gauge outer diameter that is the same as that of the original 4-mm, 32-gauge model but with an extra-thin cannula wall, giving an enlarged inner diameter, has been developed and marketed in the USA [13, 14]. A widened inner diameter can increase fluid flow and reduce injection pressure. Thus, such a needle requires less thumb pressure to push the buttons of insulin pens and is considered easier to use. Although the extra-thin wall 32-gauge needle has not been marketed in Japan, we had an opportunity to use this needle and compared its usability and safety with those of the 34-gauge, 4-mm needle, the thinnest one in Japan, focusing on the ease of pushing injection buttons.

Methods

Study design

This was a prospective, randomized, open-label, controlled home-use crossover study that was carried out at a single center and conducted between December 2013 and March 2014 at the Diabetes Center, Kitasato Institute Hospital, Tokyo, Japan. The study was conducted in accordance with the Ethical Guidelines for Clinical Studies (21 July 2008) and Declaration of Helsinki (22 October 2008). The study was approved by the Research Ethics Committee of Kitasato Institute Hospital (study no. 13058).

Study subjects

Eligible subjects were outpatients with type 1 or 2 diabetes, 20 years of age or older, who had been treated with insulin self-injection at least twice a day using an insulin pen device over 1 year. Patients using NovoRapid® FlexTouch® (Novo Nordisk Pharma Ltd., Tokyo, Japan), pregnant or breastfeeding females or females with a suspicion of pregnancy, and patients with severe neurological disorder were excluded. The investigators provided a written explanation to all the subjects, and their informed consents were obtained in writing.

Study materials

We compared the BD Ultra-Fine™ Nano™ 4-mm pen needle with Easy Flow™ technology (Becton-Dickinson and Co., NJ, USA; not marketed in Japan; hereafter referred to as UF32G) with the NANOPASS® NEEDLE II (Terumo Corp., Tokyo, Japan; hereafter referred to as NP34G). The UF32G needle is a straight, 4-mm-long and 32-G needle with a 5-bevel needle tip and extra-thin wall design. Except for the extra-thin wall design, this needle is identical to the BD Micro-Fine™ Plus 32G × 4 mm (Nippon Becton-Dickinson, Ltd., Tokyo, Japan; hereafter referred to as MFP). Meanwhile, the NP34G needle is a double-tapered, 4-mm-long and 34-G needle with an asymmetric and 3-bevel needle tip.

Enrollment

Eligible subjects were assigned to either group 1 or group 2 with a central registration system according to the randomization table generated by SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Subjects in group 1 used the NP34G needles for the first week of the total 2-week needle evaluation period and then the UF32G needles for the second week in their routine insulin injections. Subjects in group 2 used these two kinds of pen needles in the reverse order: the UF32G needles for the first week and then NP34G needles for the second week.

Clinical data, measurement and evaluation

Prior to the needle evaluation, the maximum thumb force of the dominant hand was measured with the Micro FET2™ (Hoggan Health Industries, West Jordan, UT, USA) [15]. Each subject was instructed to sit in a chair, hold the device between the thumb and other fingers of the dominant hand, keep the device still on the opposite-side

Table 1 Evaluated items for usability and preferences as well as injection events during self-injection

(a) Usability and preference for pen needles	
Ease of pushing an injection button	
Penetration pain	
Smooth insertion of the needle	
Pain during insulin delivery	
Overall preference	
(b) Injection events during self-injection	
Needle bend/breakage at needle insertion	
Pain or resistance at removing the needle	
Insulin leakage from the skin	
Insulin leakage from the needle tip after needle removal	
Needle bend/breakage after needle removal	

thigh and push the attachment part of the device with the thumb of the dominant hand at maximum force for 3–5 s. The subject's thumb force was measured three times in total with 1-min intervals between the first and the second measurement and between the second and the third one. The investigators or study coordinators recorded the measurement results together with the subject's age, sex, diabetic type, body mass index (BMI), history of diabetes, duration of insulin therapy, insulin dose per injection and stage of chronic kidney disease in the case report form.

The subjects used each needle for 1 week according to the assigned order. They recorded any injection adverse events including needle breakage for every insulin injection in a diary during the 2-week period (Table 1b). After both needles had been used for 1 week respectively (i.e., 2 weeks after using both needles), the usability of the needles was evaluated in terms of ease of pushing an injection button, penetration pain, smooth insertion of the needle, pain during insulin delivery and overall preference (Table 1a). The subjects evaluated the two needles for each item using a 150-mm visual analog scale (VAS) (Fig. 1) [16, 17].

Statistical analysis

Based on results from a previous report [18], we estimated that a sample size of 23 subjects per group was necessary to achieve 80 % power at a 5 % significance level in order to detect the mean difference of 0.5 with the standard deviation of 0.8. Assuming that seven subjects per group would be withdrawn, we determined the target sample size to be 60 in total. The intention-to-treat (ITT) set was defined as subjects from whom the survey questionnaires were retrieved. The full-analysis set (FAS) was defined as subjects other than those who violated the study procedure. The one-sample *t* test and binominal test were used for the data analysis on the usability evaluation. The χ^2 test was

used for the safety evaluation. A *p* value <0.05 was considered statistically significant. Multiple regression was used to analyze the relationship between subjects' preferences and their background factors with the preference for needles as the dependent variable and 12 background factors (age, gender, BMI, diabetes type, stage of chronic kidney disease, other complication disease, daily insulin dose, daily number of insulin injections, medical history of diabetes, history of insulin treatment, thumb force and assigned group) as the independent variables. All analyses were conducted using SAS version 9.3.

Results

Study subjects

A flow diagram of the study subjects is shown in Fig. 2. A total of 60 eligible subjects were enrolled in the study, and one subject was excluded from all the analyses because the case report forms (CRFs) could not be collected. The safety evaluation was analyzed in the remaining 59 subjects, who were included in the ITT set. From these 59 subjects, 1 subject who injected insulin only in the thigh and another who used each needle for only 3 days were excluded; thus, the remaining 57 subjects were defined as the FAS. The usability evaluation was analyzed in the FAS. One subject in the FAS had only used for 6 months before the study, but was judged to be reliable and therefore included in the FAS analyses.

Baseline characteristics

The subjects' baseline characteristics are shown in Table 2. The mean age was 65.6 ± 10.6 years old. Forty-five subjects (76 %) were male. Fifty subjects (85 %) had type 2 diabetes. The mean BMI was 24.6 ± 4.4 kg/m². The mean insulin dose per injection was 8.1 ± 6.2 U (median of 6 U). Fifty-eight of the ITT set's 59 subjects used the Novo Fine 32G $\times$ 6-mm tapered needle (Novo Nordisk Pharma Ltd., Tokyo, Japan) and the other one the MFP for their routine practice. Subjects with stage 2 (53 %) or stage 3 (32 %) chronic kidney disease account for 85 %.

Thumb force

The mean maximum thumb force was 83.5 ± 25.4 N in the ITT set (Table 3). The mean maximum thumb force was 91.7 ± 22.3 N in males and 57.4 ± 14.9 N in females, indicating a significantly lower force in females than in males ($p < 0.001$, *t* test). The maximum thumb force tended to decrease with age ($r = -0.3963$, Pearson correlation coefficient).

Fig. 2 Study design of this cross-over study

Subjects' evaluation for usability and preference

In the subjects' evaluation, the mean VAS scores were significantly different for the two items, namely smooth insertion of needles and pain during insulin delivery, favoring the NP34G ($p = 0.017$ for smooth insertion of needles and $p = 0.041$ for pain during the insulin delivery; t test). There were no significant differences between the two needles in VAS scores for ease of pushing an injection button, penetration pain or overall preference (Table 4). Further, the binomial test was conducted by dividing the subjects into the two groups depending on which needle they preferred, which was determined by each VAS score they marked in evaluating both needles. The NP34G was regarded as 'preferred' if the VAS score was negative; the UF32G was regarded as 'preferred' if it was positive. The preference for the NP34G and UF32G was regarded as 'same' if it was zero. The binomial test result showed a significant difference only in smooth insertion ($p = 0.011$), but no differences in the other items between the two needles (Table 5).

Frequency of injection adverse events

The frequencies of injection adverse events including breaking needles were calculated with the total number of insulin injections as denominator. No significant differences were shown in the frequencies of injection adverse events between the two needles (Table 6).

Relationship between needle preference and subjects' background

The multiple regression analysis showed no association between the needle preferences and the 12 subject background factors analyzed.

Discussion

The UF32G needle with a wider inner diameter than that of the MFP needle was expected to improve the ease of pushing an injection button because of increased fluid flow and reduced insulin injection pressure. However, this study showed no significant difference in the mean VAS score for ease of pushing an injection button between the UF32G and the NP34G. Toraishi et al. [19] reported that 6–17 N was needed to deliver 10 U of insulin using various insulin injection devices with a 30-gauge needle. Kato [20] reported that the maximum load was approximately 30 N when 10 U of insulin was delivered at a speed of 400 mm/min with the Lantus® SoloSTAR® (Sanofi K. K., Tokyo, Japan) or NovoRapid® 30 Mix FlexPen® (Novo Nordisk Pharma), combined with the MFP or the NP34G needle. In this study, the minimum value of the subjects' maximum thumb forces was 40 N, and the mean dose per injection was 8.1 U. Combining these data with the previous two studies' results, it can be said that the subjects in this study had enough thumb force to push an injection button for

Table 2 Baseline characteristics of the subjects (ITT)

Characteristic	Value
Age (years)	
Mean (SD)	65.6 (10.6)
Median (range)	66.0 (35–86)
Sex, <i>n</i> (%)	
Male	45 (76 %)
Female	14 (24 %)
Type of diabetes, <i>n</i> (%)	
Type 1	9 (15 %)
Type 2	50 (85 %)
BMI (kg/m ²)	
Mean (SD)	24.6 (4.4)
Median (range)	24.2 (16.1–39.9)
History of diabetes (years)	
Mean (SD)	15.5 (9.4)
Median (range)	14.0 (1.1–45.0)
History of insulin treatment (years)	
Mean (SD)	8.0 (5.3)
Median (range)	7.1 (0.5–31.0)
Insulin dosage (U/injection)	
Mean (SD)	8.1 (6.2)
Median (range)	6.0 (2–38)
Stage of chronic kidney disease	
Stage 1	6 (10 %)
Stage 2	31 (53 %)
Stage 3	19 (32 %)
Stage 4	2 (3 %)
Stage 5	1 (2 %)

ITT intention to treat, BMI body mass index

routine insulin injection; therefore, they might not have been able to detect the difference in ease of pushing an injection button between the UF32G and NP34G. In this regard, future studies may be needed to evaluate the ‘ease of pushing an injection button’ by focusing on a special population such as elderly diabetic patients, female patients or diabetic patients with impaired manual coordination due to diabetic neuropathy.

In the usability evaluation, significant differences were shown in both the mean VAS score and the result of the binominal test regarding smooth insertion, favoring the NP34G. A significant difference was shown in the mean VAS score but not in the binominal test result regarding pain during insulin delivery. Considering that a significant difference was shown in the results concerning penetration pain between the two needles and that smooth insertion is strongly correlated with overall preference ($r = 0.8647$, correlation coefficient), the study result indicates that the patients’ most important criterion for choosing the needle was smooth insertion. Prior to the study implementation,

Table 3 Thumb force (ITT)

Category	Value (<i>N</i>) ^a
All	83.5 (25.4), 84.2 (40.0–129.0)
Sex ^b	
Male	91.7 (22.3), 92.9 (44.3–129.0)
Female	57.4 (14.9), 54.3 (40.0–97.5)
Age (years) ^c	
<50	104.3 (24.0), 117.5 (76.6–118.6)
50–59	103.7 (18.3), 101.9 (70.2–128.3)
60–69	81.4 (23.1), 82.9 (40.0–123.2)
70–79	72.4 (24.3), 72.3 (43.0–129.0)
≥80	74.0 (25.7), 74.0 (51.4–96.6)

ITT intention to treat, *N* Newton

^a Mean (SD), median (range)

^b $p < 0.001$, *t* test

^c $p = -0.3963$, Pearson correlation coefficient

we expected that penetration pain would be the most important factor for patients in selecting a needle. However, probably because both needles used in the study are 4 mm long, or the shortest marketed needles, and have substantially thin diameters (32 and 34 gauge), the subjects may have shifted the focus of attention from painlessness to smooth insertion.

According to two past clinical studies, the MFP needle, the original type of UF32G needle, was compared with the Novo Fine 32G × 6 mm tapered needle, which has the same gauge as and a longer needle than the MFP, in one study [21], and with the NANOPASS 33G × 5 mm needle (Terumo Corp., Tokyo, Japan), which is thinner and longer than the MFP by 1 mm, in the other study [18]. Both studies showed that the MFP was superior to any of these needles with respect to penetration pain, smooth insertion and overall evaluation. These results suggest that needle lengths considerably influence patients’ decision making in needle selection. Meanwhile, in the present study, both needles had the same length of 4 mm. This may help explain why no significant differences were shown regarding penetration pain and overall preference. Thus, patients’ usability evaluations for the two needles were not very different, and the thinner NP34G was preferred because of its smoother insertion.

The multivariate analysis was conducted with needle preference as the dependent variable and the 12 background factors as the independent variables. No associations were shown in any of the factors, suggesting that these factors are unlikely to influence decisions about needle selection in patients who have been accustomed to insulin therapy. However, it would be a rash decision to apply the same logic to patients who are newly initiating insulin therapy. It may still be necessary to consider the

Table 4 VAS scores for the subjects' evaluations of needle usability and preference (FAS)

Questionnaire	VAS ^a	<i>p</i> value ^b
Ease of pushing an injection button	−0.13 (−6.3, 6.0), −50 to 72.5	0.966
Penetration pain	−6.84 (−14.8, 1.1), −67.5 to 60.0	0.090
Smooth insertion of the needle	−9.17 (−16.6, −1.7), −70.0 to 60.0	0.017
Pain during insulin delivery	−6.45 (−12.6, −0.3), −72.5 to 37.5	0.041
Overall preference	−8.29 (−18.2, 1.7), −72.5 to 72.5	0.100

FAS full analysis set, VAS visual analog scale

^a Mean (95 % confidence interval), range; negative mean values indicate preference for NP34G^b *t* test**Table 5** Distribution of the subjects' preference (FAS)

Questionnaire	Distribution ^a			<i>p</i> value ^b
	NP34G	UF32G	Same	
Ease of pushing an injection button	28	15	14	0.066
Penetration pain	30	16	11	0.054
Smooth insertion of the needle	35	16	6	0.011
Pain during insulin delivery	26	14	17	0.081
Overall preference	34	19	4	0.053

FAS full analysis set

^a Number of preferences^b Binomial test**Table 6** Frequency of injection adverse events based on the number of all injections (ITT)

Injection adverse events	NP34G (%)	UF32G (%)	<i>p</i> value ^a
Needle bend/breakage at needle insertion	0.4 (5/1214)	0.2 (3/1205)	0.726
Pain or resistance at removing the needle	2.4 (29/1214)	2.5 (30/1205)	0.896
Insulin leakage from the skin	3.6 (44/1214)	5.2 (63/1205)	0.060
Insulin leakage from the needle tip after needle removal	4.2 (51/1214)	4.2 (51/1205)	1.000
Needle bend/breakage after needle removal	0.5 (6/1214)	0.5 (6/1205)	1.000

ITT intention to treat

^a Fisher's exact test

patients' various backgrounds, and letting patients themselves decide which type of needle they will use after actually testing different types of needles may also need to be considered.

The UF32G needle has a feature that contributes to reducing injection pressure because of its enlarged inner diameter. However, this feature was not detected in the subjects in the present study, probably because all of them had more than enough thumb force to easily push an injection button. To investigate advantages of using needles with extra-thin walls, further studies should be conducted in diabetic patients with lower finger force and more impaired manual dexterity. Moreover, if insulin delivery-supporting devices equipped with new function to require less force to press an injection button, such as the NovoRapid® FlexTouch [22], become more popular, it is

expected that the needle type will have less impact on the injection pressure that patients would feel.

In conclusion, although significant differences were found between the two usability items, smooth insertion and pain during insulin delivery, there was no significance in overall preference between the two needles. Furthermore, no significant differences were shown in the frequencies of injection adverse events including breaking needles. Considering the above, the two needles are regarded as not being different for clinical use for patients who have enough thumb force.

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Compliance with ethical standards

Conflict of interest This study was conducted with sponsorship of Nippon Becton-Dickinson Co., Ltd. There is no other relevant conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for being included in the study.

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