Brief report
Glycemic control, reported pain and leakage with a 4 mm × 32 G pen needle in obese and non-obese adults with diabetes: a post hoc analysis

Laurence J. Hirsch
Michael A. Gibney
Lingzhi Li
Julie Bérubé
Becton, Dickinson & Company Inc., Franklin Lakes, NJ, USA

Address for correspondence:
Laurence J. Hirsch MD, 1 Becton Dr., MC 378, Franklin Lakes, NJ 07417, USA.
laurence_hirsch@bd.com

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Abstract

Objective:
The shortest pen needle (PN) for subcutaneous insulin therapy is 4 mm. Clinicians may hesitate to use it in obese patients. We report a post hoc analysis of a previously published study of the 4 mm × 32 G PN, evaluating responses in obese (≥30 kg/m²) and non-obese (<30 kg/m²).

Methods:
Subjects (BMI 20 to 49 kg/m², 52% obese) with diabetes used 4 mm × 32 G PNs and either 5 mm or 8 mm PNs (both 31 G) in two, 3-week treatment periods in a randomized noninferiority cross-over trial. Percentage absolute change in fructosamine (%ΔFru) was the primary endpoint. Equivalent glycemic control was defined as %ΔFru within 20% (including 95% CI). The impact of obesity on change in fructosamine, pain and reported insulin leakage from the skin is described.

Clinical trial registration:
Clinicaltrials.gov – identifier: NCT00928057.

Limitations:
This report is a post hoc analysis of two BMI subgroups resulting in smaller sample sizes.

Results:
Of 168 who completed the study, 163 were included in the fructosamine analyses — 83 and 80 in the 4/5 mm and 4/8 mm groups, respectively. For the 4/5 mm group, mean BMI ± SD in non-obese and obese groups were 25.9 ± 2.3 and 35.0 ± 4.9 kg/m², respectively; 4/8 mm group 25.2 ± 2.6 and 35.6 ± 4.2 kg/m². BMI group was not significant for %ΔFru for either 4/5 mm or 4/8 mm. Between BMI groups, the difference of the means in %ΔFru was 0.4% (4/5 mm) and 0.3% (4/8 mm). The 4 mm PN was significantly less painful in all subject groups, except non-obese in 4/5 mm. Regardless of needle size, obese subjects reported more leakage events. For both BMI groups, there were fewer total reported leakage events when using the 4 mm vs 5 mm and 8 mm needles.

Conclusions:
The 4 mm pen needle provided equivalent glycemic control in both obese and non-obese patients compared to 5 mm and 8 mm needles with no increase in reports of skin leakage, in this post-hoc analysis. These findings should be confirmed in a prospective randomized controlled trial.
Introduction

Insulin therapy has dramatically changed for the better over the decades – for patients who may take up to seven or eight injections daily. Needles for subcutaneous (SC) injections for insulin and other medication have progressively become shorter and thinner over the last 25 years. This is especially true for pen needles (PNs) that are now as short as 4 mm and as thin as 32 gauge (G), nominally 0.23 mm diameter. Insulin syringes, limited by the ability to draw up insulin from vials, have progressed from 12.7 mm to 8 mm, 31 G. Despite the availability of smaller needles, clinicians frequently continue to believe that many patients, especially those who are obese, still require longer needles. A recent survey of >4300 insulin-taking patients showed that an 8 mm length needle is – by far – the most commonly used worldwide for insulin injection therapy\(^1\). But what is the supporting evidence for this common practice? Using radio-labeled regular human insulin, Frid reported 20 years ago that in normal-weight subjects, injections that were given superficially or deep in subcutaneous tissue resulted in nearly identical rates of disappearance of radioactivity at injection sites\(^2\). In a subsequent study of obese subjects with type 2 diabetes, no difference in HbA1c levels was seen when the subjects used a 6 mm 31G PN vs a 12.7 mm 29G PN\(^3\).

We previously demonstrated equivalent safety and efficacy, and reduced pain of a 4 mm \(\times\) 32 G PN compared to 5 mm and 8 mm PNs, both 31 G, in adults with diabetes\(^4\). This report further explores injection depth and the impact for subjects with different BMIs. It provides results of a secondary, post hoc analysis comparing the outcomes between obese (BMI \(\geq\) 30 kg/m\(^2\)) and non-obese (BMI < 30 kg/m\(^2\)) subjects in that trial.

Subjects and methods

The methods and main study results have been previously reported\(^4\). This was a prospective, randomized, open label, two-period cross-over investigation of different PNs with two study groups: 4 mm \(\times\) 32 G vs 5 mm \(\times\) 31 G PNs (4/5 mm), and 4 mm \(\times\) 32 G vs 8 mm \(\times\) 31 G PNs (4/8 mm). Adults with type 1 or type 2 diabetes with HbA1c 5.5–9.5%, BMI 18–50 kg/m\(^2\), and who used an insulin pen for \(\geq\) 2 months were recruited at four clinical centers in the United States from June to November 2009. Study periods were 3 weeks long to assess change in fructosamine levels. The primary study objectives were to show equivalent glycemic control (fructosamine) within the 4/5 mm and 4/8 mm study groups. Reports of insulin leakage and comparisons of pain between the study PNs, the latter via a 150 mm pain visual analogue scale (VAS), were also assessed. Study conduct is outlined in Figure 1. The study was conducted in compliance with the Declaration of Helsinki and with Good Clinical Practices. The protocol was approved by Copernicus Group IRB (Research Triangle Park, NC, USA) and registered on clinicaltrials.gov (Identifier: NCT00928057). All subjects provided written, informed consent.

Original statistical methods

Fructosamine measurements convey the average blood glucose concentration during the past 2–3 weeks. The principal endpoint was the percentage absolute change in fructosamine, or % \(\Delta\) Fru, calculated as: 

\[
100\% \frac{Fru_{t_{	ext{end}}} - Fru_{t_{	ext{start}}}}{Fru_{t_{	ext{start}}}}
\]

This is a conservative measure that uses the absolute value of the bias and reflects both positive and negative differences between PNs, which add rather than cancel. Dividing the bias by the fructosamine level with the comparator PN produces a relative measure of change\(^4\). A second control measure was used, % \(\Delta\) Fru, calculated as: 

\[
100\% \frac{Fru_{t_{	ext{end}}} - Fru_{t_{	ext{start}}}}{Fru_{t_{	ext{start}}}}
\]

in order to detect directional trends.

New statistical analysis

A re-analysis of data from the previous study has been performed to evaluate the impact, if any, of obesity (defined as BMI \(\geq\) 30 kg/m\(^2\)) on the main results. Specific endpoints assessed are change in fructosamine, pain perception, and leakage of insulin from the skin in the 4/5 mm and 4/8 mm groups.

The mean relative absolute difference of fructosamine, % \(\Delta\) Fru and 95% CIs were calculated for the 4/5 mm and 4/8 mm PN study arms. The CIs were compared to the equivalence acceptance criterion (including 95% CI) of 20%.

Pain scores via a 150 mm visual analogue scale (VAS) were graphically summarized and analyzed with one-sided t-tests. Mixed effect Poisson models were used to calculate impact of needle length and BMI on reported number of leakage events. For all analyses, \(\alpha = 0.05\).

Results

Of the 173 subjects randomized, 168 completed the study, and five were excluded from the primary endpoint analysis of change in fructosamine – four due to data collected outside of defined time windows and one due to a laboratory error. For the primary analysis there were 83 and 80 subjects with in the 4/5 mm and 4/8 mm groups, respectively. Overall, mean BMI was 31.0 kg/m\(^2\) (range, 20 to 49 kg/m\(^2\)) with 52% of subjects (\(N = 84\)) considered obese (BMI \(\geq\) 30 kg/m\(^2\)). The original analysis showed equivalence in % \(\Delta\) Fru; pain was significantly less for the 4 mm than 5 and 8 mm PNs, the number of reported
leakage events was lower for the 4 mm needle, and it was preferred overall.

Demographics
Detailed demographic data for the two PN groups (4/5 mm and 4/8 mm) within each BMI group (<30 kg/m² vs ≥30 kg/m²) in this post hoc analysis appear in Table 1. At baseline, in both PN groups those with BMI <30 kg/m² tended to be slightly younger (4/5 mm \( p = 0.043 \), 4/8 mm NS), more type 1 diabetes (4/5 mm \( p = 0.021 \), 4/8 mm \( p < 0.001 \)), lower weight (both \( p < 0.001 \)), lower daily insulin dosage (both \( p < 0.001 \)) and slightly higher baseline mean fructosamine (\( p < 0.01 \), both pen groups). Baseline mean HbA1c was 0.44% less in those with BMI <30 kg/m² in the 4/8 mm group but was NS (\( p = 0.06 \)).

Glycemic control
For subjects with BMI <30 kg/m, the mean % [Δ Fru] was 4.7% (95% CI 3.5, 7.1%) between 4/3 mm, and 5.6% (4.4, 7.3%) between 4/8 mm. For subjects with BMI ≥30 kg/m, the mean % [Δ Fru] was 5.1% (95% CI 3.8, 7.6%) between 4/5 mm and 5.2% (4.0, 7.1%) between 4/8 mm.

Box-plots of % Δ Fru for each BMI category within each PN group (4/5 mm and 4/8 mm) are shown in Figure 2. There was no suggestion of any trend in directional change in blood glucose levels with the new PN. Out of the 163 subjects none had a % Δ Fru below −20% and only one had a % Δ Fru above 20%.

Pain
Sixty-seven subjects in the 4/5 mm and 68 subjects in the 4/8 mm groups were included in the analysis of relative pain scores by VAS. For both BMI groups, a significant reduction in relative pain was found for the 4 mm vs 8 mm needle, and for subjects with BMI ≥30 kg/m² in the 4/5 mm group. However, in the 4/5 mm group, VAS pain differences were NS for subjects with BMI <30 kg/m² (Table 2).

Figure 1. Study conduct.
Leakage
Eighty-five subjects in the 4/5 mm and 83 subjects in the 4/8 mm groups (e.g., all completers) were included in the analysis of leakage events. More leakage events (878 [59%] vs 610 [41%]) were reported by those with BMI/C21 > 30 kg/m² – who comprised 51% of total subjects – for all three PN lengths (Table 3). For both BMI groups, there were fewer total reported leakage events when using the 4 mm needle vs 5 mm and 8 mm needles. The majority of reported estimated droplet sizes for all needle lengths was 0.1 unit of insulin; 64% in BMI group and 54% in ≥30 BMI group.

Discussion
This post hoc analysis demonstrates very similar outcomes in terms of maintenance of glycemic control with a 4 mm needle and glucose control in obese diabetes. Hirsch et al., in a controlled prospective crossover study of 62 obese patients with mean BMI 39 kg/m² (range 30–64 kg/m²), evaluated 6 mm vs 12.7 mm needles and reported no differences in HbA1c. The shorter needle was preferred with similar reports for pain, leakage, convenience, and ease of use. In a second, similar crossover study, Kreugel et al. reported on 126 obese subjects with mean BMI 36.4 kg/m² (range, 30.1–62.5 kg/m²), comparing 5 mm and 8 mm needles, both 31 G. No within-group differences were demonstrated with HbA1c, fructosamine, 1,5-anhydroglucitol (post-prandial glycemia measurement), hypoglycemic events, bruising, pain or preference. Pooling data for all 126 subjects showed HbA1c was about 0.1% lower with the 5 mm needle than the 8 mm needle (p = 0.02). Less bleeding was reported with the 5 mm needle (p = 0.04) and less insulin leakage from the skin with the 8 mm needle (p = 0.01). Other studies demonstrated similar efficacy between longer and shorter needles; 12.7 mm vs 8 mm needles in obese and non-obese adults (n = 106), and 8 mm vs 5 mm in both adults (n = 46) and children (n = 54).

Table 1. Baseline demographics – pen needle (4 vs 5 mm, 4 vs 8 mm) and BMI groups (<30 and ≥30 kg/m²). N = 163 in primary efficacy analysis.

<table>
<thead>
<tr>
<th>Pen needle group</th>
<th>4 vs 5 mm</th>
<th>4 vs 8 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI group (kg/m²)</td>
<td>&lt;30</td>
<td>≥30</td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>Age (years) Mean (SD)</td>
<td>50.7 (15.1)</td>
<td>57.1 (12.5)</td>
</tr>
<tr>
<td>Min/max</td>
<td>22.3/72.4</td>
<td>22.7/76.2</td>
</tr>
<tr>
<td>Gender – female number (%)</td>
<td>13 (36.1%)</td>
<td>24 (51.1%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.59 (1.2)</td>
<td>7.52 (0.83)</td>
</tr>
<tr>
<td>Min/max</td>
<td>5.7/9.5</td>
<td>6/9.4</td>
</tr>
<tr>
<td>Fructosamine (µmol/L) Mean (SD)</td>
<td>324.9 (65.2)</td>
<td>285.6 (51.6)</td>
</tr>
<tr>
<td>Min/max</td>
<td>213/465</td>
<td>209/406</td>
</tr>
<tr>
<td>type 2 diabetes number (%)</td>
<td>17 (47.2%)</td>
<td>35 (74.5%)</td>
</tr>
<tr>
<td>BMI (kg/m²) Mean (SD)</td>
<td>25.9 (2.3)</td>
<td>35.0 (4.9)</td>
</tr>
<tr>
<td>Min/max</td>
<td>21/29</td>
<td>30/49</td>
</tr>
<tr>
<td>Race – number (%)</td>
<td>White/Caucasian 29 (80.6%)</td>
<td>34 (72.3%)</td>
</tr>
<tr>
<td>Black/African American 4 (11.1%)</td>
<td>10 (21.3%)</td>
<td>3 (7.0%)</td>
</tr>
<tr>
<td>Asian/Hispanic/Latino/Other 3 (8.3%)</td>
<td>6 (12.3%)</td>
<td>3 (7.0%)</td>
</tr>
<tr>
<td>Height (cm) Mean (SD)</td>
<td>172.4 (8.5)</td>
<td>170.1 (13)</td>
</tr>
<tr>
<td>Min/max</td>
<td>147/188</td>
<td>137/200</td>
</tr>
<tr>
<td>Weight (kg) Mean (SD)</td>
<td>77.3 (10.5)</td>
<td>101.1 (19.3)</td>
</tr>
<tr>
<td>Min/max</td>
<td>56/101</td>
<td>68/151</td>
</tr>
<tr>
<td>Average daily dose (units) Mean (SD)</td>
<td>11.8 (6.3)</td>
<td>18 (9.3)</td>
</tr>
<tr>
<td>Min/max</td>
<td>3/26</td>
<td>5/40</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Worldwide, the 8 mm length continues to be the most commonly used length needle. The data from this analysis and the above studies do not support this practice. As long as insulin is delivered into the subcutaneous (SC) tissue, absorption is similar whether it is deposited deep or superficially. Shorter needles also reduce the risk for intramuscular (IM) injections, which have been shown to increase the speed and variability of insulin absorption that may result in unanticipated hypoglycemia. Based on ultrasound measurements of skin and SC fat thickness in diverse adults with diabetes, the risk of IM injections was estimated according to needle length, pooled across the four common body sites for insulin injection (abdomen, thigh, arm, and buttocks). The estimated risks (assuming 90° insertion without a raised skin fold) were 0.4% with the 4 mm PN, 1.8% 5 mm, 5.7% 6 mm, 15.3% 8 mm, and 45% 12.7 mm. With shorter needles and proper injection technique, e.g. raised skin fold or 45° insertion when appropriate, the risk of IM injections can be reduced.

Table 2. Relative pain with 150 mm VAS.

<table>
<thead>
<tr>
<th>Study group</th>
<th>BMI (kg/m²)</th>
<th>Mean (mm)</th>
<th>95% upper bound CI (mm)*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 vs 5 mm</td>
<td>BMI &lt; 30</td>
<td>-7.24</td>
<td>6.84</td>
<td>0.195</td>
</tr>
<tr>
<td></td>
<td>BMI ≥ 30</td>
<td>-13.82</td>
<td>-0.85</td>
<td>0.040</td>
</tr>
<tr>
<td>4 vs 8 mm</td>
<td>BMI &lt; 30</td>
<td>-18.86</td>
<td>-8.3</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>BMI ≥ 30</td>
<td>-29.09</td>
<td>-19.36</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*One-sided t-test.

Table 3. Reports of leakage from skin by needle type and BMI, in study completers.

<table>
<thead>
<tr>
<th>Needle type</th>
<th>Number of events¹</th>
<th>BMI &lt; 30 kg/m²</th>
<th>BMI ≥ 30 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>N=82</td>
<td>N=86</td>
</tr>
<tr>
<td>4 mm (72)</td>
<td>650</td>
<td>272 (41.8%)</td>
<td>378 (58.2%)</td>
</tr>
<tr>
<td>5 mm (39)</td>
<td>481</td>
<td>190 (39.5%)</td>
<td>291 (60.5%)</td>
</tr>
<tr>
<td>8 mm (45)</td>
<td>357</td>
<td>148 (41.5%)</td>
<td>209 (58.5%)</td>
</tr>
<tr>
<td>Total (106)</td>
<td>1488</td>
<td>610 (41.0%)</td>
<td>878 (59.0%)</td>
</tr>
</tbody>
</table>

*Subjects reporting leakage with both needles (4 mm and either 5 mm or 8 mm) are only counted once in the total.

¹Event calculations do not include injections without reported leakage.

Figure 2. Box-plot of percentage change in fructosamine for BMI groups ≥30 kg/m² and <30 kg/m² within each study pen needle group, 4 vs 5 mm and 4 vs 8 mm pen needles.
thus eliminating another variability factor for insulin uptake and improving the predictability of insulin action. The introduction of insulin pens increased the concern of medication leakage from the injection site due to the need to hold the PN under the skin for up to 10 seconds after depressing the injection button, and especially with shorter needles. In this analysis, fewer leakage events were reported with the 4 mm needle length for both BMI groups. However, it appears that some obese subjects may leak more often – regardless of needle length. Of the >1400 reported injections with reports of leakage, 59% were reported by subjects in the ≥30 kg/m² BMI group, who comprised 51% of study subjects, vs 41% in those with BMI <30 kg/m². There were similar increases in the relative number of leakage reports among obese subjects for all three PN lengths in this study (Table 3). These differences in reported skin leakage did not impact glycemic control as measured by fructosamine. The actual amount of leakage following injections with insulin pens also appears to be very small. In this study, the droplet size of the reported leakage events was most commonly estimated to be ≤0.1 unit of insulin⁴. A more objective quantitative analysis with different needles as short as 4.5 mm confirmed that actual leakage volume is small – less than 1% of the total dosage, and the amount increased with greater dosage in absolute terms but decreased as a percentage of the total administered dose¹⁴.

All subject groups reported less pain when using the 4 mm × 32 G PN, with the differences significant except for the non-obese subjects in the 4/5 mm comparison group. The mean VAS pain scores were approximately 19 mm (p = 0.002) and 29 mm lower (p < 0.001) for the 4 mm PN vs the 8 mm needle, in the BMI groups <30 and ≥30 kg/m², respectively, and nearly 14 mm less for the 4 mm PN vs the 5 mm needle in the ≥30 kg/m² BMI group. Other studies¹⁵,¹⁶ and our prior investigations suggest that a 10 mm difference is clinically meaningful. Clearly, a limitation of this report is its post hoc nature. As a consequence of comparing the two BMI subgroups in this analysis, the sample sizes became smaller. However, the subgroup findings are very consistent with the overall study findings, which showed no apparent relationship between BMI and Δ Fru (Fig 5 in Reference 4). These findings should be confirmed in a prospective randomized controlled study in obese subjects.

Conclusion

Needles used for subcutaneous injections have progressively become shorter and thinner. While all published studies report that shorter needles are as effective as longer needles (and nearly always preferred by patients), many clinicians remain hesitant to recommend these needles, especially in obese patients. This analysis strongly supports the conclusion that the 4 mm × 32 G pen needle provides equivalent glycemic control in both obese and non-obese patients and should be considered by both prescribers and educators as a beneficial option for their patients.

Transparency

Declaration of funding

Becton, Dickinson & Company Inc. provided funding for this study.

Declaration of financial/other relationships

L.J.H., M.A.G., LL., and J.B. have disclosed that they are employees of Becton, Dickinson & Company. L.J.H. has disclosed that he owns stock in Becton, Dickinson & Company and Merck. M.A.G., LL., and J.B. have disclosed that they own stock in Becton, Dickinson & Company. L.J.H. and M.A.G. conceived of the analysis; J.B. and LL. performed the statistical analyses; L.J.H., M.A.G., J.B., and LL. contributed to the drafting of the manuscript and revisions for substantive content. All authors approved the final manuscript for publication, and all authors vouch for the integrity of the data.

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References