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ORIGINAL ARTICLE

Safety and Efficacy of Insulin Therapy Delivered via a 4mm Pen Needle in Obese Patients With Diabetes

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Abstract

Objective: To determine whether insulin delivered via a 4-mm × 32-gauge pen needle (PN) provides equivalent glycemic control as 8-mm × 31-gauge and 12.7-mm × 29-gauge PNs in obese (body mass index ≥30) patients with diabetes.

Patients and Methods: This prospective, multicenter, randomized, open-label, 2-period, crossover, equivalence, home-based study was conducted from October 26, 2010, through May 31, 2012. After a 3-week wash-in period, eligible patients aged 18 to 80 years with a hemoglobin A_{1c} (HbA_{1c}) level of 5.5% to 9.5% (37-80 mmol/mol) were randomized to compare either 4- vs 8-mm PNs or 4- vs 12.7-mm PNs, using each of the 2 assigned PNs for 12 weeks in random order. The primary outcome was change in HbA_{1c} level, with equivalence limits of ±0.4%.

Results: The 274 patients randomized (mean ± SD age, 56.7±11.0 years) had a mean ± SD body mass index of 37.0±6.1 (range, 29.1-59.9) and took up to 350 U of insulin daily; 226 patients were included in the modified intention-to-treat analysis. Mean (95% CI) changes in HbA_{1c} levels with the 4-mm PN were −0.08% (−0.21 to 0.06) and −0.10% (−0.19 to 0.00) vs the 8- and 12.7-mm PNs, respectively, within equivalence margins. The 4-mm PN was less painful than the larger PNs ($P<.05$), with similar leakage rates reported (4.1%-4.3%). Patients preferred the 4-mm PN over the 12.7-mm PN ($P<.05$) but not significantly vs the 8-mm PN. There were no differences between PNs in insulin doses and hypoglycemic or hyperglycemic adverse event rates.

Conclusion: The 4-mm × 32-gauge PN provides equivalent glycemic control as 8- and 12.7-mm PNs in obese patients with diabetes, with less pain and no increase in leakage. Shorter PNs should be considered in all insulin-requiring patients with diabetes, including those who are obese.

Trial Registration: clinicaltrials.gov Identifier: NCT01231984

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Diabetes mellitus, in particular type 2 (T2DM), has become a global epidemic, driven largely by the increased prevalence of overweight and obese individuals.[1-5] Most frequently, T2DM develops in middle-aged adults; in one study of adults aged 45 to 64 years without diabetes at baseline, odds ratios to develop diabetes for men who were obese were more than 7-fold greater than those in the normal-weight group.[5] The National Health and Nutrition Examination Survey 1999-2002 found that approximately 55% of patients with diagnosed T2DM are obese and 85% are overweight or obese.[6] The rates today are likely even greater worldwide.[7] Individuals with Type 1 diabetes mellitus (T1DM) are also increasingly becoming overweight and obese. In a study of nearly 600 patients with childhood-onset T1DM followed for 18 years, the prevalence of overweight and obesity increased by 47% and 7-fold, respectively.[8] The most recent US diabetes statistics indicate that as of 2011, of adults 18 years and older with diagnosed diabetes, 17.8% take insulin alone and 13.0% take insulin and oral medications.[9] With the strong correlations among diabetes, obesity, and insulin therapy, it is important to evaluate factors that may affect the performance of insulin injection therapy.

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Health care providers often question the effect of smaller needle dimensions on glycemic control, safety, and tolerability, as well as on patient-reported outcomes, such as insulin leakage and pain, in obese insulin-requiring patients. Historically, most patients with diabetes have used longer PNs (8-12.7 mm)[10]; obese patients traditionally are advised to use such needles.[11] However, a recent study[12] found that diabetic patients (including those with obesity) maintained stable glycemic control with less pain and no change in skin leakage using 4-mm PNs compared with 5- and 8-mm PNs over 3 weeks. In addition, 5- and 6-mm PNs gave similar results vs 8- and 12.7-mm needles, respectively, in earlier, longer trials that assessed hemoglobin A_{1c} (HbA_{1c}) levels in obese patients.[13,14] Although the previous 4-mm PN comparative study included patients with a body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) up to 49 (who responded similarly as nonobese individuals[15]), its generalizability to the insulin-requiring obese population is limited because single insulin doses were restricted to 40 U or less, fructosamine was used to assess glycemia, and the obese subgroup analyses were post hoc.[12,15]

To date, no controlled studies have prospectively evaluated the influence of a 4-mm PN on HbA_{1c} levels in obese patients. This study determined whether insulin delivered via a 4-mm PN provides equivalent glucose control, as measured by HbA_{1c} levels, as do 8- and 12.7-mm PNs in obese patients. Secondary objectives compared a variety of patient-reported outcomes, skin leakage, and the safety of 4-mm vs 8- and 12.7-mm PNs.

RESEARCH DESIGN AND METHODS

Study Design

This was a prospective, multicenter, randomized, open-label, 2-period, crossover, equivalence, home-based study. It began with a 3-week wash-in phase in which patients followed their usual insulin regimen using each of 3 PNs—4-mm × 32-gauge, 8-mm × 31-gaugue, and 12.7-mm × 29-gauge PNs (BD)—for 1 week in random order. This was done to minimize dropouts during the subsequent study by ensuring that patients were comfortable with larger PNs and found them acceptable. After the wash-in, eligible patients were randomized to either the 4- vs 8-mm PN group or the 4- vs 12.7-mm PN group, and they used one study PN for 12 weeks (period 1). Patients then crossed over to use the second study PN for 12 weeks (period 2); the order of PN use was controlled.

Patients followed their usual insulin regimen without dose limitations. They were instructed to insert the 4-mm PN straight in with no pinch-up and to pinch up when inserting the 8-mm PN into the abdomen or thigh. Patients were instructed to insert the 12.7-mm PN at 45° or to pinch up and inject at a 90° angle.

Patients

Adult patients with T1DM and T2DM aged 18 to 80 years with a BMI of 30 or greater and an HbA_{1c} level of 5.5% to 9.5% (37-80 mmol/mol) were eligible. Patients were recruited from investigator practices and via local advertising. They were required to be following a stable insulin regimen (no recent changes in dosing algorithms or basal insulin levels), taking insulin injections for 2 months or longer using only pens, and willing to self-monitor blood glucose levels at least twice daily. Patients were excluded if they used an insulin pump or syringe, changed other diabetes-related medications, had a history of intravenous drug abuse, participated in a previous clinical trial sponsored by BD, or were pregnant.

Assessments

The primary outcome was HbA_{1c} level after each 12-week study period, with a prespecified equivalence criterion for HbA_{1c} of ±0.4%. Secondary outcomes included relative injection pain, PN preference, ease of use, ease of insertion, injection anxiety, and safety. Tertiary analysis included self-reported insulin leakage from skin.

Relative injection pain was assessed via a 150-mm visual analog scale, which compared injection pain perceived by the patients at the end of the second 12-week period with that in the previous period. Visual analog scale scores ranged from −75 mm ("much less painful") to +75 mm ("much more painful"), with 0 mm (scale midpoint) meaning "as painful as the previous needle." Scores were corrected for order of PN use.

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