

A Randomized Controlled Trial to Assess the Impact of Proper Insulin Injection Technique Training on Glycemic Control

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Received: August 10, 2017 / Published online: October 13, 2017
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ABSTRACT

Introduction: Improper injection technique can negatively affect glycemic control and treatment tolerability. We assessed the impact of structured insulin injection training on glycemic control.

Methods: We compared changes in glycated hemoglobin (A1C) and fasting plasma glucose following structured insulin injection training in a 6-month pilot study in patients with type 1 or 2 diabetes. Patients were recruited from mobile clinics in Moscow, Russia, and randomized into three groups. Groups 1 and 2 received structured injection training, and group 3 did not. Group 1 received 4-mm needles sufficient for each injection; groups 2 and 3

provided their own needle supply. Changes in insulin total daily dose (TDD), injection technique, needle reuse, and lipohypertrophy (LH) were assessed.

Results: Of 120 patients enrolled, 116 were included in all analyses (group 1, $n = 43$; group 2, $n = 35$; group 3, $n = 38$). At 6 months, mean [95% CI] reductions in A1C were significant in groups 1 and 2 (-1.00% [10.9 mmol/mol (-1.3 to -0.6)] and -1.00% [10.9 mmol/mol (-1.4 to -0.7)]), respectively; $P < 0.001$ for both), but not in group 3 (-0.02% [0.2 mmol/mol (-1.2 to 1.6)]). Increases in insulin TDD, however, were similar and significant across groups (approximately 6 IU; $P < 0.05$). Injection technique improved, and needle reuse and LH declined in groups 1 and 2, but not in group 3.

Conclusions: Little is known about the glycemic impact of insulin injection training. We found that structured training and the use of short pen needles can improve injection technique, leading to significant A1C reductions and decreased rates of LH.

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A related oral presentation was given at the American Diabetes Association 76th Scientific Sessions, June 10–14, 2016, New Orleans, LA, USA.

Electronic supplementary material The online version of this article (doi:[10.1007/s13300-017-0315-y](https://doi.org/10.1007/s13300-017-0315-y)) contains supplementary material, which is available to authorized users.

Keywords: Clinical trial; Glycemic control; Insulin therapy; Lipohypertrophy; Training

INTRODUCTION

Insulin therapy is an essential part of treatment for many patients with diabetes mellitus (DM). All patients with type 1 DM (T1DM) receive

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life-long insulin therapy, and those with type 2 DM (T2DM) often become insulin dependent as their disease progresses [1]. Although treatment options have improved with the advent of insulin analogues [2], not all patients with DM achieve adequate blood glucose control [3], increasing their risk for micro- and macrovascular complications [4].

Diabetes self-management education (DSME) is an integral part of diabetes management and has the potential to markedly improve glycemic control [1, 4–6]. Previous evaluations of self-management programs have not specifically assessed the glycemic impact of providing insulin injection training, although this is an essential aspect of DSME [5, 6]. International and national recommendations for proper insulin injection technique are widely available [7–9]; however, it is commonly recognized that a substantial proportion of patients receiving usual care receive minimal injection training [10] and do not inject insulin properly [11].

Evidence suggests that patients can experience a range of issues due to improper insulin injection techniques such as incorrect insulin dose delivery, increased pain, and lipohypertrophy (LH), which ultimately result in poor glycemic control [12, 13]. Reported rates of injection site LH are high, though rates vary considerably across studies in various countries (from 30% to 65%) [11, 13, 14]. The development of LH has been associated with non-rotation of injection sites (reported in 16% of survey respondents [11]) and needle reuse in patients using insulin pens (reported in 56% of patients [15]) [16]. Injection into these areas of altered tissue can result in poor insulin absorption [17, 18]. In addition, the use of longer needles (i.e., longer than 8 mm) is not recommended, to avoid inadvertent intramuscular (IM) injection [12], which can cause rapid insulin absorption and increase hypoglycemic risk [19]. Shorter needles (e.g., 4 mm) can reduce the risk of IM injection and have been further shown to reduce pain and patients' fear of injection [19, 20].

We conducted a 6-month randomized controlled trial (RCT) in patients with DM to assess change in glycemic impact, daily insulin dose, and needle reuse after structured insulin

injection training. Our hypothesis was that patients who received appropriate injection technique training and a supply of the required number of short insulin pen needles would achieve significantly greater glycemic control and improved tolerability compared with those who did not receive training or a supply of short insulin pen needles.

METHODS

Study Design and Population

This was a 6-month, open-label, comparative RCT pilot study in patients with DM (trial registry number ISRCTN12263696). Institutional review board approval was obtained before enrollment. Patients met inclusion criteria if they had been diagnosed with T1DM or T2DM, were aged 18–70 years, were currently on multiple dose injection therapy (three injections of prandial and one to two injections of basal insulin daily, prescribed as a pen injection and initiated at least 1 month before study entry), and were deemed ready to strictly adhere to the study protocol and scheduled physician visits. Patients with skin and soft tissue infections at the area of insulin injection were excluded, as were patients with a history of psychiatric disorders, mental deficiency, or language barrier that could adversely affect interactions with the treating physician in terms of achieving study objectives. Pregnant and breastfeeding women were also excluded. All participating patients provided signed informed consent before study entry.

Physicians were responsible for patient recruitment into the study. Recruitment was performed between July 1, 2013 and September 4, 2014 during “diamobile” visits (mobile clinic for diabetes management) in six different areas within Moscow, Russia. Patients were randomly assigned into three groups. Group 1 underwent appropriate injection technique training and were supplied with BD Micro-Fine 4-mm 32-gauge needles (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) for insulin injection pens for 6 months (one needle for each injection). Patients in group 2 underwent

appropriate injection technique training, but had to bring their own supply of needles during the study. The purpose of this group was to evaluate the effect of appropriate injection technique training in patients who do not also receive a supply of short insulin pen needles. Patients in group 3 served as a control and did not receive structured injection training and were also required to bring their own supply of needles during the study. Of note, at the time of the study, the smallest needle length size available in Russia was 5 mm. To avoid injection technique information exchange among groups, recruitment into each group was performed on different days. A given day's group allocation was randomly assigned by an individual at the study site who had no communication with the patients.

Interventions and Outcomes Assessed

A total of three clinical visits [baseline visit (days 1–5), month 3, and month 6] and four telephone follow-ups (month 1, 2, 4, and 5) were performed for each patient over the 6-month study period. At the baseline visit, patients in group 1 and group 2 received individual injection technique training through two 45-min training sessions conducted by one of two participating endocrinologists according to a preplanned structured program. During the first lesson, proper injection technique was explained and the following themes were discussed in detail: choosing and disinfecting the injection site, depth and angle of needle insertion, needle length, skinfold formation, needle retention time in the skin, injection site rotation, and insulin leakage prevention. In addition, patients were instructed on the necessity to change needles at every injection, prevent air bubbles in the pen cartridge, and mix prolonged/premixed insulins before the injection. Managing indurations at insulin injection sites, performing insulin injections in locations other than the home, and recommendations for used needle disposal and insulin storage were also explained. Patients were guided through appropriate injection technique after the first lesson was completed. The second lesson

occurred 2–5 days later, during which patient questions were answered and injection technique was assessed.

During each telephone follow-up, patients assigned to group 1 and group 2 received reinforcement on the importance of adhering to proper injection technique, changing needles, rotating injection sites, and injecting into a skinfold. The insulin treatment regimen was discussed at each visit with all patients, regardless of group. The points discussed during the telephone follow-ups are provided in the Supplementary Appendix.

The primary outcomes measured included change from baseline in A1C and fasting plasma glucose (FPG) at 6 months. Glycemic outcomes were also evaluated at 3 months. In addition, the proportion of patients with A1C greater than 9% (poor glycemic control [21]) at baseline and 6 months was also assessed. A1C measurement was performed using a DCA Vantage Analyzer (Siemens Healthcare Diagnostics Inc., Malvern, PA, USA), and FPG was measured using a HemoCue[®] Glucose 201⁺ point-of-care glucometer (HemoCue AB, Angelholm, Sweden). Changes in insulin total daily dose (TDD), the frequency of needle reuse, and length of needle used were also evaluated before and after training. In addition, patients were monitored for injection-related adverse events at each clinic visit. Visual examination and palpation of insulin injection sites to reveal LH and/or bruising was performed at baseline and the final study visit; patients were also questioned on the frequency of injection-related pain and bruising during these visits. Events of hypoglycemia were also evaluated, although frequency analysis of symptomatic cases was not performed.

Additionally, patients were asked to demonstrate their insulin injection technique to the study clinician at the baseline and final visit. This included visual inspection of the pen (opened and checked for the presence of a needle) by the study clinician, and patient demonstration of proper skinfold formation and angle of needle insertion. The appropriateness of insulin dose was also evaluated and, if needed, recommendations on insulin dose adjustment were given, with appropriate follow-up according to community-based routine

practice. Blood glucose-guided insulin dose adjustments were managed by the participating endocrinologist. In addition, all patients completed the Insulin Injection Technique Questionnaire at baseline and end of study, which helped gain insight into patients' perception of the injection process and variations in technique [22].

Statistical Analysis

Data were summarized using descriptive statistics with mean and median values presented along with SD and 95% CI. Chi-square test was used for the primary analysis, which compared the change from baseline in A1C values at month 6 for each group. Secondary outcomes were similarly analyzed. Statistical comparisons were not made between the groups. Though a power calculation was not performed, a sample size not less than 105 was planned, with 35 patients in each group. Statistical significance was determined using an alpha level set at 0.05. Standard SPSS 16 software (IBM, Armonk, NY, USA) was used for all statistical analyses.

Compliance with Ethics Guidelines

The local ethics committee of the Moscow Regional Research and Clinical Institute approved the protocol on 13/06/2013 (protocol No 3). 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, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

Patients

A total of 120 patients were enrolled and randomized (group 1 [structured training/supplied short 4-mm needles], $n = 43$; group 2 [structured training/no supplied needles], $n = 38$; group 3 [no structured training/no supplied

needles], $n = 39$), four of whom withdrew consent because of scheduling ($n = 3$ in group 2 and $n = 1$ in group 3) and were therefore not included in the final analysis (Supplementary Appendix). The final follow-up visit was on March 3, 2015. Groups appeared similar in age, DM duration, duration of insulin use, insulin daily dose, and BMI at baseline (Table 1). All patients were Caucasian. No patients were receiving any glucose-lowering medications other than insulin. FPG levels were consistent across groups, although most patients had unsatisfactory glycemic parameters at baseline (i.e., A1C greater than 7% and FPG greater than 7.2 mmol/L) [1, 4], including more than 30% in each group with A1C above 9%.

The majority of patients across groups used only the abdominal area for injections at baseline. Insulin was most commonly injected using 8-mm needles (at least 75% of patients in each group), though some patients used shorter (5 mm [14% in group 1]) or longer needles (12.7 mm [13% in group 3]). Regardless of group, all patients reported reusing needles at baseline, with the majority reusing needles 2–5 times (49% in group 1) or 6–10 times (37% in group 2; 50% in group 3). At baseline, lipodystrophy was observed in more than 20% of patients overall, and painful injections were reported by 21% of patients. Bruising at the injection site was observed in 26% of patients, of whom 22% reported bruising several times per month and 3.5% reported bruising several times per week (Table 1).

Glycemic Control

Significant improvements in glycemic outcomes in patients who received structured injection technique training were evident as early as month 3, as demonstrated by A1C reductions of -0.75% (8.2 mmol/mol [95% CI, -0.4 to -0.9]) in group 1 and -0.70% (7.7 mmol/mol [95% CI, -0.3 to -0.8]) in group 2 ($P < 0.05$ for each comparison). Decreases in A1C from baseline to 3 months in patients without structured training were not significant (group 3: -0.09% [1.0 mmol/mol (95% CI, -0.17 to 0.16)]); $P > 0.05$). At the

Table 1 Patient characteristics at baseline by group

Parameter	Group 1 (<i>n</i> = 43)	Group 2 (<i>n</i> = 35)	Group 3 (<i>n</i> = 38)
T2DM, <i>n</i> (%)	31 (72.1%)	26 (74.3%)	31 (81.6%)
Age, years	53.1 ± 13.3	53.4 ± 12.6	54.3 ± 12.1
Diabetes duration, years	9.8 ± 7.0	8.8 ± 7.0	8.3 ± 5.4
Duration of insulin use, years	5.9 ± 3.8	5.1 ± 3.4	4.8 ± 3.0
A1C, % (mmol/mol)	8.7 ± 1.4 (72)	8.5 ± 1.7 (69)	8.8 ± 1.9 (73)
A1C > 9%, <i>n</i> (%)	17 (39.3)	12 (34.2)	15 (39.4)
FPG, mmol/L	9.5 ± 3.9	10.2 ± 3.8	9.6 ± 3.9
BMI, kg/m ²	31.9 ± 8.4	32.9 ± 10.2	32.4 ± 8
Injection regions, <i>n</i> (%)			
Abdomen	29 (67.4)	30 (86.2)	32 (84.0)
Abdomen/thigh	5 (12.6)	1 (2.8)	2 (5.7)
Abdomen/thigh/buttock	0	0	1 (2.6)
Abdomen/thigh/shoulder	5 (11.0)	0	3 (7.7)
Needle length, <i>n</i> (%)			
12.7 mm	4 (9.0)	4 (10.0)	5 (12.9)
8 mm	32 (75.0)	29 (82.0)	29 (76.9)
6 mm	1 (2.3)	1 (4.0)	2 (5.1)
5 mm	16 (37.7)	1 (4.0)	2 (5.1)
Needle reuse, <i>n</i> (%)			
2–5 times	21 (48.8)	12 (34.3)	12 (31.5)
6–10 times	12 (27.9)	13 (37.1)	19 (50.0)
> 10 times	10 (23.3)	10 (28.6)	7 (18.4)
Injection site errors, <i>n</i> (%)			
Needle insertion < 5 s	13 (30.0)	10 (28.6)	16 (28.9)
Rotation	14 (32.0)	7 (20.0)	11 (28.9)
Insulin leakage after injection	6 (13.9)	2 (5.7)	5 (13.1)
Injection site pain, <i>n</i> (%)	12 (27.9)	4 (11.4)	8 (21.1)
Injection site bruising, <i>n</i> (%)	13 (30.2)	10 (28.6)	7 (18.4)
Lipodystrophy, <i>n</i> (%)	13 (30.0)	3 (8.5)	11 (28.9)

Numbers are mean ± SD, unless otherwise noted

A1C glycated hemoglobin, BMI body mass index, FPG fasting plasma glucose, T2DM type 2 diabetes mellitus

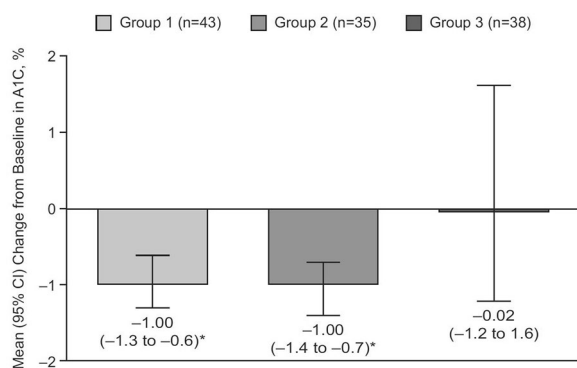


Fig. 1 Mean change from baseline A1C at 6 months. A1C glycated hemoglobin. * $P < 0.001$ vs baseline

6-month follow-up visit, clinically meaningful (i.e., 1% reduction [23–25]) and statistically significant improvements from baseline A1C were noted in group 1 and group 2 ($P < 0.001$ for each comparison; Fig. 1), though not in group 3 ($P = 0.7$). Reductions from baseline in FPG at 6 months were also observed in group 1 (mean 9.5 mmol/L at baseline to 7.67 mmol/L at month 6) and group 2 (mean 10.2 mmol/L at baseline to 7.81 mmol/L at month 6), whereas an increase in FPG was observed in group 3 (mean 9.6 mmol/L at baseline to 10.09 mmol/L at month 6, Tables 1 and 2).

Of the patients with poor glycemic control at study entry, the proportion with A1C greater than 9% decreased from 39.3% to 9.3% from baseline to 6 months in group 1, respectively, and from 34.2% to 8.6% from baseline to 6 months in group 2, respectively. However, the proportion of patients with A1C greater than 9% in group 3 remained unchanged from baseline to 6 months (37.1%).

Insulin Dose and Injection Technique

Significant increases from baseline in insulin TDD were deemed necessary in all three study groups by month 6, regardless of whether injection technique training was provided (Fig. 2). Both basal and prandial insulin doses significantly increased across all groups ($P < 0.05$, Table 2).

At the end of study, all patients in group 1 (100%) reported using the 4-mm needles provided (Table 2). The use of short needles

increased in group 2, with the majority of patients (66%) using 5-mm needles. However, the length of needle used at the end of study in group 3 remained unchanged to that observed at baseline (77% using 8-mm and 13% using 12-mm needles). Importantly, groups who received insulin injection technique training at baseline had substantially less needle reuse at the end of the study. Group 1, which was supplied with 4-mm needles in addition to training, reported no reuse of needles for the duration of the study (Table 2). A marked decrease in needle reuse was also observed in group 2 from baseline, with 17% reporting reusing needles two to five times (vs 34% at baseline) before changing to a new needle (because of insufficient supply of needles), and no patients reused needles at least six times (vs 66% at baseline). However, the frequency of needle reuse observed at the final visit for patients in group 3 was similar to that at baseline, with the majority reusing the same needle for 6–10 injections (53% vs. 50% at baseline; $P > 0.05$).

There were no events of injection site tenderness or bruising in group 1 at 6 months. Similarly, fewer patients in group 2 were observed to have injection site tenderness and bruising at the final visit compared with baseline. In group 3, the number of patients with tenderness or bruising at 6 months remained generally unchanged from baseline (Table 2). No new LH foci in group 1 or group 2 were observed at the final study visit; however, in group 3, all previous LH foci persisted and new foci emerged in one patient. No events of severe hypoglycemia occurred in any patient.

CONCLUSIONS

This study supports the clinical benefit of proper insulin injection training to improve glycemic outcomes in patients with DM. Patients who received structured injection training demonstrated improved injection technique and had clinically significant reductions from baseline in A1C at 3 (–0.70% to –0.75%) and 6 months (–1.0%) and in FPG at 6 months, whereas those who did not receive

Table 2 Glycemic outcomes and injection-related assessments at 6 months

Parameter	Group 1 (<i>n</i> = 43)	Group 2 (<i>n</i> = 35)	Group 3 (<i>n</i> = 38)
A1C, % (mmol/mol)	7.7 ± 1.2 (61)*	7.4 ± 1.1 (57)*	8.71 ± 1.71 (72)
FPG, mmol/L	7.67 ± 1.18*	7.81 ± 2.03*	10.09 ± 3.28
Insulin change from baseline, units ^a			
Basal daily dose	2.5 (0.6–1.3)*	3.4 (1.9–4.8)*	2.8 (0.8–4.5)*
Prandial daily dose	3.3 (1.0–5.6)*	3.0 (1.4–4.5)*	3.6 (0.7–5.1)*
Needle length, <i>n</i> (%)			
12.7 mm	0	2 (5.7)	5 (12.9)
8 mm	0	10 (28.5)	29 (76.9)
6 mm	0	0	2 (5.1)
5 mm	0	23 (65.7)	2 (5.1)
4 mm	43 (100)	0	0
Needle use, <i>n</i> (%)			
1 time	43 (100)	29 (82.9)	0
2–5 times	0	6 (17.1)	13 (34.2)
6–10 times	0	0	20 (52.6)
> 10 times	0	0	5 (13.1)
Injection site errors, <i>n</i> (%)			
Needle insertion < 5 s	3 (6.9)	2 (5.7)	16 (28.9)
Rotation	0	0	11 (28.9)
Insulin leakage after injection	6 (13.9)	2 (5.7)	5 (13.1)
Injection site pain, <i>n</i> (%)	0	3 (8.5)	5 (13.1)
Injection site bruising, <i>n</i> (%)	0	0	7 (18.4)
Lipodystrophy, <i>n</i> (%)	7 (16.2)	2 (5.7)	12 (31.5)

Numbers are mean ± SD, unless otherwise noted

A1C glycated hemoglobin, FPG fasting plasma glucose

* $P < 0.05$ compared with baseline value

^a Mean (95% CI)

training continued to use poor injection technique and had no significant improvement in glycemic outcomes. These findings are consistent with previous study outcomes showing significant reductions from baseline in mean A1C (−0.58%) and FPG (−14.2 mg/dL [0.79 mmol/L]; $P < 0.05$ for all assessments) in patients with DM [10].

Achievement of stable glycemic control in patients with DM receiving insulin treatment is often a difficult task requiring collaboration between the healthcare provider and patient [4]. DSME is an essential component in this process [1, 4] and should include proper insulin injection technique training. Grassi et al. reported a decrease of 2.0 IU in TDD of insulin

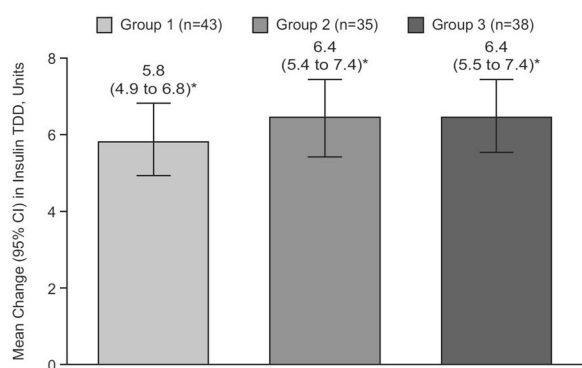


Fig. 2 Mean change from baseline insulin dose. TDD total daily dose. * $P < 0.05$ vs baseline

in patients who received structured injection training [10]. In our study, daily doses of both prandial and basal insulin increased in all groups, most likely owing to mean A1C levels that were high at baseline (greater than 7% across groups) and a corresponding increased insulin dosage requirement. The mean increase in TDD was approximately 6 IU across groups. However, these relatively small mean dose increases in conjunction with improved injection technique allowed patients in group 1 and group 2 to achieve significant decreases in A1C. In contrast, similar increases in insulin dosage did not result in significantly reduced A1C in group 3.

In the majority of cases, LH is discovered by visual examination and palpation of injection sites. We assessed for LH by visual inspection, and the rate observed at baseline was relatively low across groups (approximately 22% overall). However, we found that patients with LH routinely injected exactly into these areas of altered tissue because it was less painful. This may have led to unpredictable changes in insulin absorption and contributed to poor glycemic outcomes in group 3.

Although the majority of patients enrolled in this study were found to be reusing needles and participating in improper injection techniques at baseline, groups who received structured training had notably reduced rates of needle reuse at the end of study (none in group 1 and only 17% in group 2), as well as reduced rates of LH and adverse injection site reactions, such as pain and bruising. This is of particular interest

for patients in group 2, who received structured training but were not supplied with needles, indicating that training was well received and understood, and patients increased their personal supply of needles accordingly. In comparison, in patients in group 3 who received no training, the continued use of poor injection technique and needle reuse likely contributed to ongoing LH and persistent adverse reactions [13]. It may be of interest for future research to include a group of patients who are provided with a supply of needles, but not provided with structured training, to determine the effect needle supply alone has on needle reuse and other outcomes.

The use of longer needles (longer than 8 mm) increases the risk of IM injections [12]. However, if a patient using these longer needles makes a skinfold correctly, the risk of IM injection may potentially decrease. In this study, only a small proportion of patients at baseline used longer needles (12.7 mm; range 9.0–12.9% across groups) and, of these patients, small proportions did not make the correct skinfold (6.3%) and were observed inserting the needle at a 90° angle (17.9%). The use of 4-mm needles combined with proper injection technique (group 1) and, to a lesser extent, training on proper injection technique alone (group 2) decreased the incidence of painful injections. This possibly increased treatment adherence, thus contributing to improved glycemic outcomes in groups 1 and 2.

Some limitations to this study should be noted. Because we did not perform a power calculation, it is unclear whether the sample size was sufficient to provide appropriate power. We also did not perform statistical analyses to compare outcomes between the three groups. Thus, findings from this study may be considered preliminary. Furthermore, the conclusion that injecting into a skinfold is not necessary with shorter needles may not apply to all patient populations. For example, children have comparatively thin layers of subcutaneous fat, thus necessitating the use of a skinfold to avoid IM injection. Similarly, although the mean BMI of patients enrolled in this study was greater than 30 kg/m², lean adults are at greater risk for IM injection [19]; therefore, use of a skinfold is

crucial in these patients. Several outcomes in this study were assessed through observation by the investigator, which may have resulted in some degree of bias. For example, ultrasound is the only objective method to assess for LH. Because LH assessments in this study were performed by visual inspection, the rates observed may have been underestimated. Likewise, subjective responses on questionnaires may be a source of bias, though attempts were made in this study to administer the Insulin Injection Technique Questionnaire consistently across all groups.

Results from this pilot study suggest a crucial role for proper injection training when initiating insulin in patients with diabetes. Findings concur with previous reports that the majority of DM patients have significant issues with insulin injection, including reusing needles, removing the needle from the skin too quickly after injection, and incorrect injection site rotation. Injection technique improved in patients who received structured training, likely resulting in the observed improvements in glycemic outcomes, LH, and adverse injection site reactions. Although the small numbers of patients included in this study preclude comparison of glycemic outcomes between interventions, we observed significant reductions in A1C in the two intervention groups that received injection training and no significant improvements in the group that received no training. Finally, results demonstrated that 4-mm needles helped reduce injection pain, which could possibly encourage better insulin therapy adherence. Findings, therefore, support the routine practice of providing proper insulin injection technique training and encouraging the use of shorter needles for all patients with DM who receive insulin treatment.

ACKNOWLEDGEMENTS

Becton–Dickinson provided funding for article processing charges, and provided resources for the study, but did not otherwise fund the study. Editorial support was provided by Sheri Arndt, PharmD, and Meg Shurak, MS, of C4 MedSolutions, LLC (Yardley, PA) a CHC Group

company, with funding from Becton–Dickinson. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Inna V. Misnikova, Valeria A. Gubkina, Tatyana S. Lakeeva, and Alexander V. Dreval have nothing to disclose.

Compliance with Ethics Guidelines. The local ethics committee of the Moscow Regional Research and Clinical Institute approved the protocol on 13/06/2013 (protocol No 3). 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, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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