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ORIGINAL RESEARCH

Injection Technique Education in Patients with Diabetes Injecting Insulin into Areas of Lipohypertrophy: A Randomized Controlled Trial

Liming Chen · Qiuling Xing · Jing Li · Jianxin Zhou · Yi Yuan · Ying Wan · Brian K. Pflug · Kenneth W. Strauss · Laurence J. Hirsch

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ABSTRACT

Introduction: The aim of this randomized controlled trial was to assess the impact of providing intensive injection technique (IT) education to patients routinely injecting insulin into sites of lipohypertrophy (LH).

Methods: Between November 2016 and May 2018, insulin-injecting patients with LH treated at Tianjin Metabolism Hospital (a public tertiary medical institution), Tianjin, China, were included in a 6-month prospective randomized controlled trial and randomized into either the intervention (the IT-education group) or the control (control group) arm. The control and IT-education groups were seen by different groups of trained nurses on different clinic days. IT education emphasized moving injections to normal tissue sites, within-and between-site injection rotation, an initial reduction of insulin total daily dose (TDD), and stopping needle reuse. Needles were provided to the IT group, while controls acquired needles in their usual way. Differences in changes in glycated hemoglobin (HbA1c) and insulin TDD were the primary and main secondary endpoints, respectively.

Results: The control (n = 104) and IT-education (N = 106) groups had similar demographic parameters (97% with type 2 diabetes) and baseline IT behavior. HbA1c reduction was similar in the IT-education and control group in the intention-to-treat (ITT) analysis (6-month between-group difference 0.16% [1.7 mmol/mol], 95% confidence interval [CI] − 0.11, 0.43 [− 1.2, 4.7]; p = 0.239) but was significant by the per-protocol (PP) analysis (difference 0.31% [3.4 mmol/mol], 95% CI 0.02, 0.60 [0.2, 6.6]; p = 0.038). Changes in TDD insulin in the IT-education group were

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L. Chen (✉) · Q. Xing · J. Li · J. Zhou
NHC Key Laboratory of Hormone and Development, Tianjin Key Laboratory of Metabolic Diseases, Chu Hsien-I Memorial Hospital and Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin, China
e-mail: xfx22081@vip.163.com

Y. Yuan
Medical Affairs, Becton Dickinson and Company, Inc., Shanghai, China

Y. Wan · Brian K.Pflug
Diabetes Care, Becton Dickinson and Company, Inc., Franklin Lakes, NJ, USA

Kenneth W.Strauss
Former Global Medical Affairs, BD Diabetes Care, Becton Dickinson and Company, Inc., Erembodegem, Belgium

Laurence J.Hirsch
Former Global Medical Affairs, BD Diabetes Care, Becton Dickinson and Company, Inc., Franklin Lakes, NJ 07417, USA

approximately − 7 and − 8 IU by the ITT and PP analyses, respectively, versus − 1 IU (non-significant) in the controls (both between-group differences $p \leq 0.05$). Despite the study design, IT education "contamination" (unplanned adoption of IT-intervention behaviors) was documented in 63 control patients. By post hoc analyses, HbA1c in "contaminated" controls decreased by 0.70% (7.7 mmol/mol) vs. 0.20% (2.2 mmol/mol) in "non-contaminated' patients ($p = 0.019$) at 6 months.

Conclusions: Proper IT, including learning to not inject into sites of LH, proper within- and between site rotation, needle reuse reduction, and the use of 4-mm, 32-G needles in Chinese patients injecting into sites of LH enables a safe reduction of TDD insulin while maintaining overall glycemic control.

Trial Registration: Trial registration: ChiCTR-IOR-16009270 in the Chinese Clinical Trials Registry.

Keywords: Injection technique; Insulin; Lipohypertrophy

Key Summary Points

Why carry out this study?

Many patients (> 50% in China) with diabetes mellitus who inject insulin develop swelling, nodules or hardening of the fat tissue where insulin is injected under the skin. This is called lipohypertrophy (LH), and is often not noticed by the patients or their health care professionals.

Why is LH important?

Absorption of insulin injected into areas of LH is reduced and much more variable than that from normal tissue, putting patients at risk for unexplained variations in their blood glucose levels (both high and low). Patients with LH have higher average blood glucose levels (glycated hemoglobin [HbA1c]) despite using more insulin daily than those without LH. There is no medicine to treat or cure LH.

What causes LH?

LH develops primarily due to repeated injections at the same place—generally over months to years. Risk factors include duration of insulin therapy and number of injections daily, not rotating injections within a site or between sites, and reusing needles.

What was done?

We conducted a randomized controlled clinical trial to see whether providing intensive education in proper insulin injection technique (IT) would improve HbA1c as well as being able to reduce the total daily dosage of insulin (intervention group) compared to control subjects getting usual care.

What was learned from the study?

Proper IT, including learning to not inject into areas of LH, proper within- and between site injection rotation, stopping needle reuse, and injecting with 4-mm, 32-G needles (to give more places to inject), in Chinese patients injecting into sites of LH allows the safe reduction of total daily insulin dose while maintaining overall glycemic control.

We also found that roughly two thirds of the control subjects unexpectedly adopted several of the IT practices that were taught to the experimental group, with subsequent improvement in their HbA1c as well.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13636739.

INTRODUCTION

Many patients with diabetes mellitus who use insulin develop swelling, nodules, or induration of subcutaneous adipose tissue at the injection sites. These lesions, termed lipohypertrophy (LH), are often not noticed by the patients or their health care professionals (HCPs) [1], despite several studies reporting prevalence rates of approximately 30–50% or more [2–5]. A recent cross-sectional study in four Chinese cities revealed an LH prevalence of 53.1% among insulin pen users [6].

In a randomized crossover trial using a euglycemic clamp, injections into areas of LH showed blunted insulin absorption and significantly increased pharmacokinetic variability compared with injections into normal tissue; a mixed meal tolerance test confirmed the decreased insulin uptake and exacerbated glycemic excursions [7]. As a result of this decreased insulin absorption in lipohypertrophic sites, patients with LH generally use higher total daily doses (TDD) of insulin while displaying worse blood glucose control and higher glycated hemoglobin (HbA1c) levels [1, 2, 6]. Thus, LH may raise the risk of adverse clinical outcomes and increase healthcare costs, both in the short and long term. Recommendations to address LH have been published [8].

Observational studies show an association of LH with the length of time on insulin, elevated number of daily injections, frequent reuse of pen needles, and especially inappropriate rotation of injections, both between- and within injection sites [1, 2, 5, 6, 9, 10]. On the other hand, the association of LH with sex and body mass index (BMI) is less clear [1, 2, 5, 6, 9, 10]. An early study indicated needle length related to the development of LH, but the study only evaluated 8- and 12.7-mm needles [11]. In the FITTER ITQ survey analyses [8], needle length was associated with LH prevalence in univariable analyses, but not when the duration of insulin therapy and/or proper site rotation were included in the multivariable regression analysis. The China LH prevalence study found that 95% of participants reused their pen needles, with a median frequency of 10 times [6]. Insulin needles, usually prescribed by physicians to patients in China, are reimbursed in some cities and provinces (e.g., Tianjin, Shanghai, Jiangsu, Zhejiang, Guangdong, Fujian, Hainan), but not in others. Patients and caregivers, therefore, can also purchase insulin needles with self-payment methods from a retail pharmacy. Multiple injections in the same location, especially with reused needles, are modifiable risk factors associated with LH. These practices likely relate to a lack of understanding and errors in insulin self-administration and cost avoidance [1, 12–14].

Interventional trials have been conducted to evaluate the effects of intensive injection technique (IT) education on insulin dosing, glycemic control, glycemic variability, and patient injection behaviors, with favorable results [15–18]. Nevertheless, several of these trials have been small, non-controlled, and/or pilot trials involving patients both with and without LH. One prospective randomized controlled trial (RCT) in French patients with LH was undertaken but did not enroll the planned number of subjects; they also encountered 'contamination' or wash-in of the control group's injection behaviors [17].

Similar trials in China have not been conducted. Therefore, we performed a prospective 6-month RCT at a major Chinese teaching center to assess the impact of intensive IT education on clinical, metabolic, and IT-related behavioral parameters in adults who routinely inject insulin into clinically detected sites of LH.

METHODS

Patients

This trial was conducted between November 2016 and May 2018 in Tianjin Metabolism Hospital, Tianjin, China. The Tianjin Metabolism Hospital is a public hospital providing tertiary care which also sees patients in private physician practices. Patients eligible for medical insurance in Tianjin are reimbursed for 95% of their treatment costs, including pen needles. The inclusion criteria were: (1) 18–75 years of age, (2) type 1 or 2 diabetes, (3) HbA1c of 7%

(53 mmol/mol) to 11% (97 mmol/mol), inclusively, measured within the preceding 3 weeks, (4) treatment with self-administered insulin delivered by a pen for at least 1 year, at least once daily ± oral medications, (5) clinically visible and/or palpable LH confirmed by the appropriate examinations, (6) insulin injections primarily at LH sites, (7) no education on LH within the preceding 6 months, and (8) willing to perform self-monitored blood glucose (SMBG) per protocol with study-provided glucometers and strips.

The main exclusion criteria were (1) pregnancy or planned pregnancy within 3 months, (2) participation in other clinical trials within 3 months, (3) other significant medical diseases, 4) other medical conditions or therapy that may lead to lipodystrophy or affect study outcomes (e.g., anti-retroviral or corticosteroid therapy), or (5) current patient not suitable for this study as per investigators' judgment.

The study was approved by the Ethics Committee of Tianjin University Hospital (registration: DXBYYhMEC2016-13-3) and conducted in accordance with Chinese laws and the original Declaration of Helsinki with its subsequent amendments. All subjects were informed of the study purpose, requirements, and expectations and signed the informed consent form. At the end of the trial, control group patients were offered the same education, tools, and devices as those in the IT-education group, including a 6-month supply of BD 4-mm, 32G pen needles. The trial was registered as ChiCTR-IOR-16009270 in the Chinese Clinical Trials Registry.

Randomization

The participants were randomized by a central randomization system and blinded by the envelope method into the intervention arm (IT-education group) and the control arm (control group).

Nurse Training

Participating nurses were trained on the protocol, randomization schedules, and case report forms for data collection and randomly allocated into two groups, with one group responsible for the intervention group and the other responsible for the standard treatment group (control group). All nurses were certified to be experts in detection, grading, and measurement of LH, including visualization and palpation of adipose tissue, as described by Gentile et al. [9]. Emphasis was placed on the need for oblique lighting to aid the visual detection of LH lesions, a warm examination room, and that the patient lie supine with their knees drawn up to relax abdominal muscles for palpation of that site. Further training was given to nurses in the intervention arm, including mastery of education tools specific to that study arm. Once the participants were randomized, they received training and follow-up separately and only by the appropriate group of nurses. The controls were not permitted to attend training for the IT-intervention arm. The two groups had return visits on different days of the week. The objective was to avoid contamination bias where a nurse provided more or less training than the arm required per the protocol. Nurses were asked not to consult with colleagues on training techniques until the end of the study.

Intervention Group

After randomization to the IT-education group, the participants completed intensive nurse-to-patient education at visit 1 within 2 weeks. Two weeks after visit 1, participants received follow-up over the telephone or by returning to the hospital. The participants returned to the hospital for a follow-up visit at the fourth week, with subsequent monthly follow-ups. During each visit, the nurses provided additional guidance and education if they grasped the proper IT.

The participants in the IT-education group were taught to recognize where they had LH and to stop injecting there. They were instructed to use the provided 4-mm, 32-G pen needles for improved site access, to avoid possible intramuscular injections, and to stop needle reuse, i.e., to use a fresh needle for each injection. Finally, the patients were taught the proper

rotation technique, i.e., to space injections within a site at least 1 cm apart, to avoid reinjecting at a previous site for 2–4 weeks, and to use each of the four main injection locations, and not only the abdomen. An array of educational tools (brochures, grids, and a Lipobox™ [BD, Franklin Lakes, NJ, USA] which simulated the look and feeling of LH lesions) was used in this training.

To avoid potential hypoglycemia due to improved insulin absorption [7], the protocol specified that the IT-intervention group also had their insulin TDD immediately reduced by 10–20% depending on current blood glucose levels compared to their individual goal and the frequency of hypoglycemia. Subjects were then followed within 1 week to ensure that the glucose levels were not increased compared to insulin TDD reduction levels or after hypoglycemia or its symptoms. Insulin was then titrated every 2–4 weeks by 2–4 IU (not to exceed 6 IU) to reach target blood glucose levels.

Control Group

Participants in the control group received standard care without IT education. The participants had one routine follow-up visit per month conducted face-to-face or by phone. At 3 and 6 months, a hospital clinic visit was required, including sampling for HbA1c. Control participants became aware of their LH during the physical exam at study entry but were not given any specific information regarding its significance or possible treatment approach. These participants obtained their pen needles as they normally did throughout the trial. Additionally, at their regularly scheduled return clinic visits (3 and 6 months), control participants were asked if they had changed their IT habits (e.g., stopped injecting into sites of LH, improved rotation habits, and/or stopped reusing their needles) since the study start. Those who had done so (i.e., had been "contaminated") at either return visit were post hoc analyzed separately.

Data Collection and Endpoints

Baseline demographic and clinical data, including insulin injection behavior, were collected. The participants were asked to perform glucose monitoring at least seven times per day at least 1 day per week for the study's duration using the provided meters and test strips. The training was provided to the participants on how to use the provided glucometer. The patients were required to bring their glucometers to the study nurses during hospital visits. The study nurses downloaded the data from the glucometers to a computer.

The primary endpoint of the study was the between-group difference in HbA1c change at 6 months from baseline. The main secondary endpoint was a change of insulin TDD. The location and size of LH were confirmed by physical examination by two independent nurses (one nurse conducted the examination, and the other conducted a review and confirmation) [9, 13]. LH presence (but not size) was confirmed by ultrasound examination as well. At 6 months, the change from baseline of LH length along the longest diameter measured by manual palpation was determined. IT behavioral changes and changes in glycemic variability and unexpected hypoglycemia at 6 months, as defined previously [17], were also study outcomes. Adverse events (AEs) were recorded at each follow-up visit.

Statistical Analysis

In a previous non-controlled interventional trial, HbA1c decreased by 0.58% (6.3 mmol/mol) from baseline at 3 months, and the standard deviation (SD) was 1.3% [15]. We set the significance level at $\alpha = 0.05$ (two-sided) and the power at 80%; therefore, the minimum sample size for each group was 80 participants. Allowing for a dropout rate of 10–15%, the sample size was increased to 90 participants per group.

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NY, USA). Distributions of intra-group differences among baseline, 3 months, and 6 months were

assessed, as well as inter-group differences. Values are presented as mean ± SD, median and interquartile range, or percentage. A mixed-effect model with repeated measures was used where the participants were a random effect.

Data were analyzed by two different approaches. The intention-to-treat (ITT) analysis included data from all participants who signed the informed consent form and were randomized. Some participants dropped out or were excluded from the study or specific analyses for reasons such as not attending follow-up visits or significant protocol deviations. Per-protocol (PP) analyses were also performed. Post hoc analyses of "contaminated" control participants' IT behaviors were reported only at the $\alpha = 0.05$ level.

RESULTS

Enrollment

Early in the study, sponsor site monitors communicated to the sponsor that the TDD insulin of the first 15 participants randomized to the IT-education group had not been reduced by the study staff per protocol due to concerns that the participants' HbA1c levels were > 8.0% (64 mmol/mol). After prompt consultation with the principal investigator and staff, the protocol was amended to increase the sample size by 30, in anticipation that an additional 15 participants would be assigned to both the IT-education and control arms of the trial. The TDD dose was subsequently reduced in these first 15 IT participants, included only in the ITT dataset, not in the PP analyses. A total of 238 subjects were screened, of whom seven had type 1 diabetes; 210 subjects were enrolled and randomized to the two groups for the ITT analyses. The study flowchart, significant protocol deviations, and/or loss to follow-up are shown in Electronic Supplementary Material (ESM) Fig. 1 . There were 104 patients in the control group with 92 in the PP cohort, and 106 in the IT-education group with 86 in the PP cohort.

Baseline Features

Overall, the control and IT-education groups had similar baseline characteristics (Table 1), with average HbA1c at 8.4 ± 1.1% (68.0 ± 12.0 mmol/mol) versus 8.6 ± 1.0% (71.0 ± 10.9 mmol/mol), and TDD insulin at 45.3 ± 21.8 versus 47.1 ± 20.6 IU, respectively. Nearly all patients (208 of 210) in both groups injected insulin into the abdomen, and over 40% used twice-daily pre-mixed insulin. More than 95% of patients reused needles, with approximately 45% using a single needle ≥ 6 times (Table 1). Duration of diabetes was slightly longer in controls (16.8 ± 7.6 vs. 14.4 ± 5.8 years; $p = 0.010$), but years injecting insulin (7.1 ± 5.4 vs. 6.9 ± 4.7 years) were similar between the two groups. A significantly greater percentage of patients randomized to the control group reported rotating injections between sites compared to those in the IT-intervention group (23.1 vs. 5.7%; $p < 0.001$).

Primary Endpoint

By ITT analysis, HbA1c declined by 0.71% (7.8 mmol/mol) (95% [confidence interval] CI − 0.91, − 0.52 [− 9.9, − 5.7]) and 0.55% (6.0 mmol/mol) (95% CI − 0.74, − 0.36 [− 8.1, − 3.9]), respectively, at 6 months in the IT-education and control groups (each $p < 0.001$ vs. baseline; between-group difference of 0.16% [1.7 mmol/mol], 95% CI − 0.11, 0.43 [− 1.2, 4.7]); $p = 0.239$). In the PP dataset, HbA1c decreased by 0.82% (9.0 mmol/mol) (95% CI − 1.03, − 0.61 [− 11.3, − 6.7]) and 0.51% (5.6 mmol/mol) (95% CI − 0.71, − 0.30 [− 7.8, − 3.3]), respectively, in the IT-education and control groups at 6 months (each $p < 0.001$ vs. baseline; between-group difference of 0.31% [3.4 mmol/mol], 95% CI 0.02, 0.60 [0.2, 6.6]; $p = 0.038$). These changes are shown in Fig. 1a, b.

Secondary Endpoints

By both ITT and PP analyses, TDD insulin was significantly reduced from baseline by approximately 15% (7 and 8 IU, respectively) in IT-

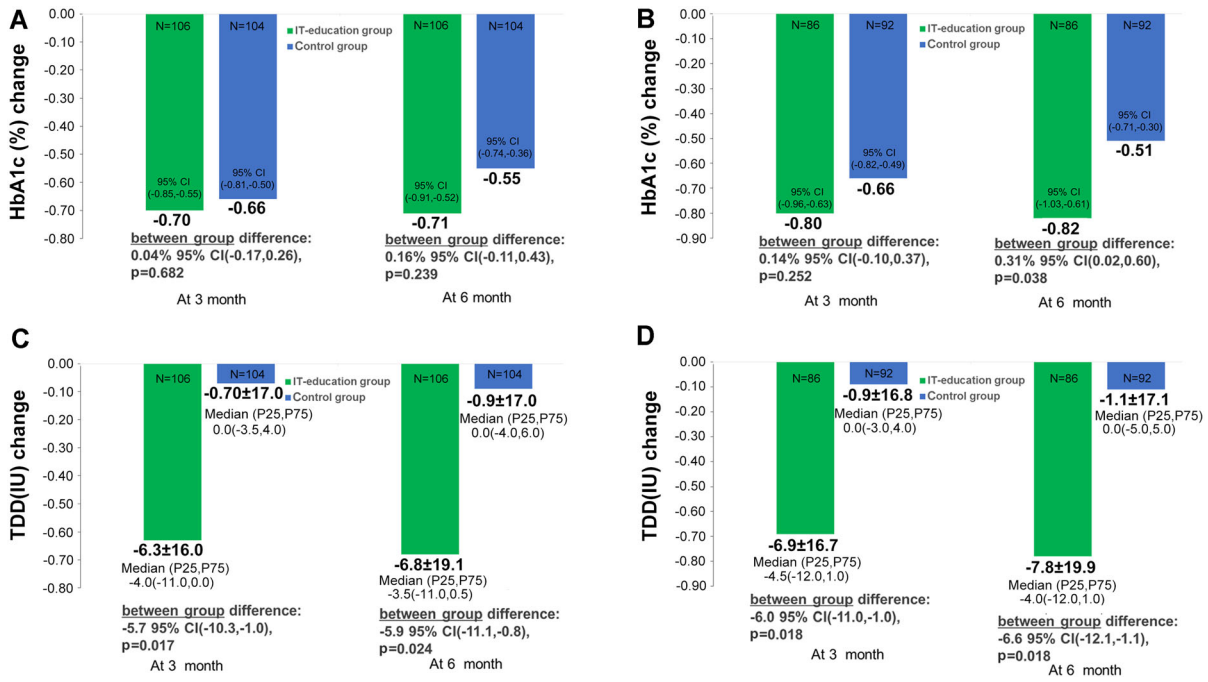

Fig. 1 Changes in study endpoints from baseline to 3 and 6 months. **a** Change in glycated hemoglobin (*HbA1c*) from baseline to 3 and 6 months, overall (ITT). **b** HbA1c change from baseline to 3 and 6 months, overall (PP). **c** Change in total daily dose (*TDD*) from baseline to 3 and 6 months (ITT). **d** Change in TDD from baseline to 3 and 6 months (PP). *CI* Confidence interval, *ITT* intention to treat, *PP* per protocol

education participants (both $p < 0.001$), and by approximately 1 IU in controls (nonsignificant, NS), respectively (Fig. 1c, d). Between-group differences at 6 months were also significant in both ITT (95% CI − 11.1, − 0.8; $p = 0.024$) and PP analysis (95% CI − 12.1, − 1.1; $p = 0.018$).

Significant IT behavioral changes were seen in nearly all participants in the IT-education group, and also in approximately two-thirds of controls (both ITT and PP analyses). Specifically, at baseline, all enrolled participants had LH and injected into lesions. By 3 and 6 month visits, 98% of IT-education subjects had stopped doing so, as did 71–72% of controls, indicating significant changes from baseline ($p < 0.05$). Between-group differences in IT behavior changes at 6 months were also significant ($p < 0.05$) (Table 2).

Rotating within injection sites was being practiced at 6 months by 98% of the patientsin the IT-education group, compared to 68% in the control group (both changes from baseline $p < 0.05$; between-group changes were also significant $p < 0.05$). Rotating injections between body sites and stopping injections into sites of LH were also adopted by patients in the control group, as shown in Table 2. Reuse of pen needles persisted in the control group (84%) but ceased in all but one participant in the IT-education group ($p < 0.001$ between groups). Roughly two thirds of controls changed their IT practice during the study (most within the first 3 months), and these changes appeared to have been sustained for at least until 6 months.

To assess the control group's changes in IT practices and the relationship between these changes ando clinical trial outcomes, we evaluated three aspects of proper IT in a post hoc analysis. We developed IT practice rankings from I to IV, with the former being a lack of proper IT behavior, and the latter reflecting proper or optimal practice. Controls with a ranking of III or IV at either 3 or 6 months were considered to be "contaminated" (Table 3).

Table 1 Demographic data at baseline of randomized patients ($N = 210$)

Characteristics	Control group ($n = 104$)	IT-education group ($n = 106$)	p
Age (years)	60 ± 9.0	59 ± 7.0	0.173
Median (IQR)	61 (55, 67)	59 (54, 64)	
Male	49 (47.1)	49 (46.2)	0.897
BMI (kg/m^2)	26.3 ± 3.5	26.5 ± 3.6	0.638
Median (IQR)	26.0 (23.9, 28.3)	25.9 (23.8, 28.0)	
Duration of diabetes (years)	16.8 ± 7.6	14.4 ± 5.8	0.010
Median (IQR)	16.2 (11.9, 21.4)	13.9 (10.0, 18.8)	
Years injecting insulin	7.1 ± 5.4	6.9 ± 4.7	0.957
Median (IQR)	6.0 (3.0, 10.0)	6.0 (3.0, 10.0)	
HbA1c, % (mmol/mol)	8.4 ± 1.1 (68 ± 12.0)	8.6 ± 1.0 (71 ± 10.9)	0.221
%, median (IQR)	8.2 (7.7, 9.1)	8.7 (7.8, 9.3)	
Number of injections daily			0.924
1	19 (18.3)	23 (21.7)	
2	49 (47.1)	46 (43.4)	
3	9 (8.7)	9 (8.5)	
4	27 (26.0)	28 (26.4)	
Rotation between injection sites	24 (23.1)	6 (5.7)	< 0.001
Rotation within one injection site	30 (28.8)	38 (35.8)	0.278
Correct rotation 1 site (move ≥ 1 cm)	4 (3.8)	2 (1.9)	0.443
Needle reuse	99 (95.2)	102 (96.2)	0.747
Number of uses of one needle			0.568
2 times	19 (19.0)	27 (26.5)	
3–5 times	37 (37.0)	32 (31.4)	
6–10 times	16 (16.0)	18 (17.6)	
> 10 times	28 (28.0)	25 (24.5)	
Injection sites			0.328
Abdomen	102 (98.1)	106 (100)	
Thigh	18 (17.3)	9 (8.5)	
Arm	19 (18.3)	11 (10.4)	
Buttock	5 (4.8)	2 (1.9)	
Current insulin therapy			0.059

Table 1 continued

Characteristics	Control group (n = 104)	IT-education group (n = 106)	p
Prandial only	10 (9.6)	4 (3.8)	
Basal only	17 (16.3)	33 (31.1)	
Basal + prandial	28 (26.9)	22 (20.8)	
Pre-mixed	41 (39.4)	42 (39.6)	
Other	8 (7.7)	5 (4.7)	
Bleeding or bruising at injection sites	79 (76.0)	76 (70.8)	0.394
Baseline insulin TDD (units)	45.3 (21.8)	47.1 (20.6)	0.547
Median (IQR)	43.0 (32.0, 57.5)	47.5 (32.0, 56.0)	
Number of severe hypoglycemic episodes in the last 3 months which required assistance			0.015
None	88 (84.6)	102 (96.2)	
1–2 times	9 (8.7)	1 (0.9)	
3–5 times	3 (2.9)	1 (0.9)	
> 5 times	4 (3.8)	2 (1.9)	

Values in table are presented as the mean ± SD, or as a number with the percentage in parentheses, unless indicated otherwise

BMI Body mass index, *HbA1c* glycated hemoglobin, *IQR* interquartile range, *IT* injection technique, *SD* standard deviation, *TDD* total daily dose

Table 2 Changes in injection technique practices at 6 months compared to baseline in per-protocol and intention-to-treat analyses

Changes	PP		ITT	
	Control group (n = 92)	IT-education group (n = 86)	Control (n = 104)	IT-education group (n = 106)
Subjects with improved LH lesions[a]	3.3%	9.3%	4.3%	9.0%
Stopped LH injections	72%*	98%*†	71%*	98%*†
Rotated between sites	61%*	90%*†	62%*	91%*†
Rotated within sites	67%*	98%*†	68%*	98%*†
SMBG tests per month	–	–	23	27†

PP per protocol, *ITT* intention to treat, *LH* lipohypertrophy, *SMBG* self-monitoring of blood glucose

*$p < 0.05$ change from baseline, †$p < 0.05$ difference between groups at 6 months

[a] Percentage of subjects with fewer lesions at 6 months vs. baseline

Table 3 Change in injection technique practice in the control group by the intention-to-treat analysis ($N = 104$)

IT skill level[a]	Baseline	3 months	6 months
I	86 (82.7)	26 (25.0)	31 (29.8)
II	16 (15.4)	34 (32.7)	35 (33.7)
III	2 (1.9)	23 (22.1)	18 (17.3)
IV	0	21 (20.2)	20 (19.2)

Values in table are presented as the number of patients with the percentage in parentheses

[a] Ranking of 3 skills (rotating between injection sites, rotating within sites [spacing injections 1 cm apart], no longer injecting into LH). I = no skills practiced, II = one of three skills practiced, III = two or three skills practiced, IV = all three skills practiced

When the 63 "contaminated" control patients were analyzed separately from the "non-contaminated" ones, the former showed significant HbA1c improvement versus baseline (− 0.70% [− 7.7 mmol/mol], $p < 0.05$); this improvement was much greater than in the "non-contaminated" patients in the control-group (− 0.20% [− 2.2 mmol/mol], nonsignificant); the between-subgroup difference was significant ($p = 0.019$). Reductions in HbA1c in the "contaminated" control subjects did not differ statistically from those in the IT-education group by the ITT analysis (Fig. 2). Overall, the "contaminated "control patients showed minimal, nonsignificant changes in TDD insulin.

LH lesions were not present at 6 months in 15 (14.2%) participants in the IT-education group and 14 (13.5%) controls ($p = 0.885$). Of the lesions that remained, both control and IT-education participants showed decreased lesion size at 3 and 6 months. The difference between the two groups was nonsignificant (ESM Fig. 2). The mean number of LH lesions per subject was 2.0 at baseline and did not change at 6 months in either group.

Performance of SMBG by participants using the meters and strips provided as part of the protocol was minimal in both study arms. The number of tests done each month was less than 30 in each group.

Adverse Events

There was no evidence of an increased risk of hypoglycemia in the IT-education group, and AE incidence was very low in both groups. The most common AEs were infections, which were not thought to be related to the study intervention. No participants discontinued the study due to an AE or serious AE.

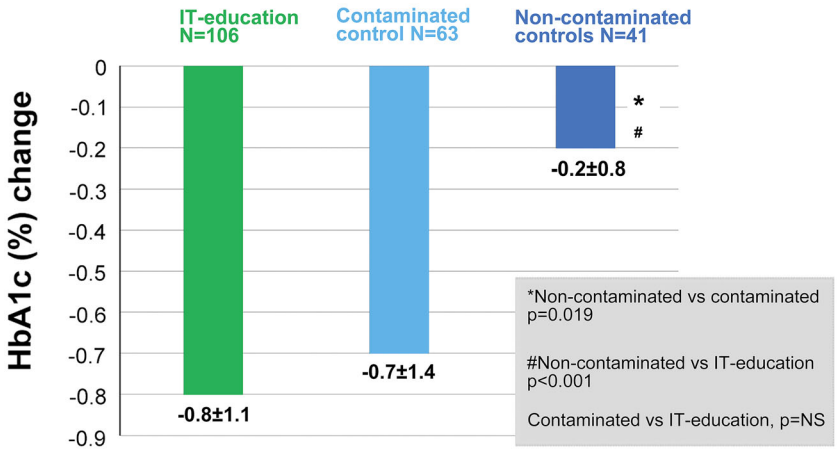

Fig. 2 Change in HbA1c from baseline to 6 months in the intervention arm vs. "contaminated" and "non-contaminated" control subgroups (ITT)

DISCUSSION

The results of this RCT suggest that teaching proper IT, coupled with stopping needle reuse and starting the use of 4-mm, 32-G needles in patients injecting into sites of LH, allows safe TDD insulin reduction while maintaining overall glycemic control (ITT analysis) or even improving it (PP analysis). Nearly all participants in the IT-education group and approximately two-thirds of controls made significant changes in IT behavior, including no longer injecting into LH areas, rotating within and between injection sites, and (for IT-education subjects) stopping needle reuse. These behavior changes were sustained for 6 months. The IT intervention was effective, but unintended spillover to control subjects ("contamination") lessened the between-group differences in HbA1c change and LH lesion size and number. Due to the minimal performance of SMBG, we were unable to assess the impact of the intervention on glycemic variability. Reports of hypoglycemia were rare.

Prior IT intervention trials have been reported. Two of these included patients with and without LH [15, 16] and provided similar IT education as our study, including the provision of 4-mm, 32-G pen needles. Each of these studies found reductions in HbA1c and TDD insulin over 3–6 months, but both were uncontrolled, and there was a 25% loss to follow-up in one study [15].

Misnikova et al. [18] conducted a prospective pilot RCT involving 120 insulin-using participants attending clinics in Moscow, Russia, of whom > 20% had LH. One group received usual care; two intervention groups received IT training, of which one group also received free BD 4-mm pen needles. Significant reductions in HbA1c of 1.0% (10.9 mmol/mol) (baseline 8.6% [71 mmol/mol]) were observed after 6 months in both intervention groups, with no change in the controls. However, daily doses of both prandial and basal insulin increased in all groups, most likely owing to the efforts of the clinicians to lower the high baseline HbA1c levels and the low prevalence of LH in the study population. Campinos et al. [17] undertook a properly powered multi-center RCT near Paris, France, in patients with LH, but only recruited two-thirds of the target number of patients; they also had extensive wash-in of proper IT practices in the usual care group. The IT intervention led to significant reductions in TDD insulin and HbA1c, but with smaller effects in the control arm, with the result that the 6-month between-group differences in change from baseline were nonsignificant. Although these previous studies have limitations, they support this study's view that IT education works by safely improving glycemic control in insulin-injecting patients with diabetes with or without LH.

In China, the cost of excess insulin consumption related to LH (approximately 11 IU daily) has been estimated to be around 2 billion China Yuan (CNY) (US$297 million) annually [6]. Decreased TDD in the IT-education group of this study suggests that IT-education may also be cost-effective. Using a net mean reduction in TDD insulin of 6.8 IU, we conservatively estimated the decrease in annual insulin-related costs for Chinese diabetes patients receiving this type of IT education, with the unit cost of insulin during the study being 0.25 CNY/IU. There are roughly 9 million insulin-injecting patients in China, with 42% insulin therapy adherence [6]. The discount rate was set at 3%. Therefore, the estimated annual cost decrease for insulin in patients with LH related to IT training is approximately 1.37 billion CNY (around US$207.0 million).

A prior prevalence study in Spain found patients with LH used a mean of 15 IU insulin more per day than those without LH [2]. The additional annual insulin cost was estimated to be over 120 million euros in that country. From the IT intervention study in France, estimated cost-savings for insulin were of the order of 25 million euros per year [17]. Safe reduction of insulin consumption by a low-intensity intervention such as IT education can be cost-effective, almost immediately. Nevertheless, further details are needed about providing such IT education at scale, including duration of effect, to calculate whether it would be net cost-saving. These considerations do not include longer-term potential cost reductions due to effects on

diabetes-related complications that would be associated with lowering the higher HbA1c levels seen in several LH trials and surveys [1, 6, 15–17]. Additionally, these estimates do not account for the potential reductions in hypoglycemia that have been reported both in a case report as well as in a short-term but uncontrolled IT-intervention protocol in patients with type 1 diabetes with LH [19, 20].

There are a number of major limitations to this study, providing important lessons of future trial design and execution. One was the initial reluctance by the study staff to reduce the TDD insulin by 10–20% for the participants enrolled in the IT-education (intervention) group (to prevent hypoglycemia). At baseline, the mean HbA1c was 8.5% (69 mmol/mol), so insulin dose reduction was not considered usual practice and was not implemented for the first 15 subjects randomized to that study arm. This led to the previously described changes in the protocol and enrollment, emphasizing the need to adhere to the clinical trial design—as approved by the relevant Ethics Committee. A second challenge involved infrequent SMBG performance (< once daily) by patients in both study arms, which prevented analysis of changes in glycemic profiles or variability. Lastly, nearly two-thirds of the control group received or adopted portions of the IT education reserved for those patient in the intervention arm (i.e., were "contaminated" or washed-in). This may have occurred when participants queried the study HCPs at the initial examination about the nature, cause, and treatment of their LH; the HCPs were advised to only state that the study was a scientific experiment evaluating one potential approach to treating LH. Participants might also have obtained information independently, including by internet search—but these are speculations. Despite a strong protocol design to minimize such effects, we believe this knowledge led to unusually high changes in IT behavior (i.e., "contamination") among control participants—as supported by the post hoc analyses. Very similar outcomes were seen in the previous trial in France that served as the model for this study [17].

Demographic factors in China significantly limited patient selection. The estimated incidence of type 1 diabetes per 100,000 person-years is 1.93 for the population aged 0–14 years and 1.01 for all ages [19]. From a previous observational study of LH in insulin-using adults in four cities in China [6], a prevalence of 93% was found for type 2 diabetes mellitus (T2DM). Not surprisingly, nearly all patients in the current study had T2DM. As shown in Table 1, premixed insulin taken twice daily was the most commonly prescribed regimen in study participants (nearly 40%); again, similar to the findings by Ji et al.[6] The combination basal + prandial insulin was used by roughly another 25%. Thus, most patients were injecting ≥ 2 times per day. There might be little overall metabolic improvement in patients with a single insulin injection per day, but these patients only accounted for one-fifth of the full analysis set. Future studies may target on patients with ≥ 3 injections per day, with the aim to verify whether the intervention can lead to more benefits in metabolic parameters. Some patients were overweight, although not significantly obese. In the study by Ji et al. [6], higher BMI was associated with LH occurrence, though to a much lesser extent than poor IT and needle reuse.

Several solutions seem plausible for these issues. Questions and other tools should be built into study questionnaires to assess the presence and extent of "contamination", to facilitate planned analysis of "contaminated" versus "non-contaminated" control participants, avoiding the need for post hoc assessment. This process may impact sample size calculations, possibly increasing target numbers and the cost of trials. Other approaches may use cluster randomization by center rather than within centers while maintaining a clear geographic and communication firewall between centers. We acknowledge, however, that control subjects in such studies still have opportunities to educate themselves.

CONCLUSION

Our results support the effectiveness of intensive IT education to safely reduce TDD of insulin while maintaining overall glycemic control

in participants injecting into sites of LH. Our experience also confirms the challenges of performing this type of RCT. Indeed, the American Diabetes Association added proper injection techniques into its Standards of Care guidelines for insulin therapy in 2019 for the first time [20]. In insulin-using patients with LH, proper injection site rotation, use of short pen needles to increase site access, decreasing needle reuse, and avoiding injecting into sites of LH can safely reduce insulin TDD with favorable effects on HbA1c. This should then cascade to a cost reduction to the entire health care system, both in the short and long terms.

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Disclosures. Kenneth W. Strauss and Laurence J. Hirsch are former employees of BD and are retired. Yi Yuan, Ying Wan, Brian K. Pflug, and Teresa Oliver are present employees of BD. Other authors (Liming Chen, Qiuling Xing, Jing Li, and Jianxin Zhou) have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the Ethics Committee of Tianjin University Hospital (DXBYYhMEC2016-13–3) and conducted in accordance with Chinese laws and the original Declaration of Helsinki with its subsequent amendments. All subjects were informed of the study purpose, requirements, and expectations and signed informed consent. At the end of the trial, control group patients were offered the same education, tools, and devices as those in the IT-education group, including 6 months' supply of BD 4 mm, 32G pen needles. The trial was registered as ChiCTR-IOR-16009270 in the Chinese Clinical Trials Registry.

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

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