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ORIGINAL RESEARCH



Needle-free injection of basal insulin improves fasting glucose variability as assessed by continuous glucose monitoring in T2DM: a prospective randomized multicenter open-label crossover study

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ABSTRACT

Background: Fasting glucose variability (FGV) extensively promotes the onset and development of diabetic complications. This study aimed to evaluate the FGV in type 2 diabetes mellitus (T2DM) patients administered basal insulin using a needle-free insulin injector (NFII).

Research design and methods: This was a prospective randomized multicenter open-label crossover study. We randomly assigned 48 T2DM patients to receive basal insulin by NFII or conventional insulin pen (CIP) for 7–14 days and were then crossed over after washout. We conducted continuous glucose monitoring to investigate the FGV, our primary outcome was a composite parameter of the FGV with a fasting blood glucose target between 4.4 and 6.1 mmol/L.

Results: The coefficient of variation for sensor glucose at 6 a.m. with CIP was 11.67 (8.70,14.81)% vs. 9.48 (6.48,12.24)% with NFII ($p = 0.003$), and the coefficient of variation for mean sensor glucose at 5–6 a.m. with CIP was 12.70 (9.17,16.56)% vs. 9.23 (7.01,11.98)% with NFII ($p < 0.001$). The overall basal insulin dosage with CIP injection was 18.00 (16.00, 20.00) IU vs. 16.00 (12.00, 19.00) IU during NFII ($p < 0.003$).

Conclusion: Compared with CIP, the use of the NFII to inject basal insulin improved FGV in T2DM.

Clinical trial registration: <https://www.chictr.org.cn> Identifier is ChiCTR2000034674.

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basal insulin; continuous glucose monitoring; fasting glucose variability; needle-free insulin injection; type 2 diabetes mellitus

1. Introduction

Increasing evidence has, in fact, revealed that glucose variability (GV) significantly impacts the development of diabetic complications. We also readily acknowledge the information garnered from the ADVANCE [1], DEVOTE [2], ACCORD and VADT [3] diabetes trials, which demonstrated that long-term GV, in terms of fasting glucose variability (FGV) and/or HbA1c variability is correlated with an increased risk of both cardiovascular and microvascular complications in type 2 diabetes mellitus (T2DM). Additionally, other studies have indicated that FGV is related to augmented risk of hypoglycemia, peripheral artery disease, and diabetic macular edema in T2DM [4–6]. It is thus obvious that FGV extensively promotes the onset and development of complications in the course of diabetes.


Researchers previously suggested that an fasting blood glucose (FBG) level of 6.1 mmol/L not only improved HbA1c levels but also minimized the risk of hypoglycemia compared

with targets of 5.6 mmol/L and 7.0 mmol/L [7]. While another study revealed that an FBG level of 6.1 mmol/L constituted an insulin-titration target that provided significant improvements in GV and HbA1c in T2DM patients [8]. Strict control of FBG may also engender fasting blood glucose variability (FGV) by increasing the risk of hypoglycemia [9]. Hence, minimizing GV while achieving favorable FBG control is the overall goal of treatment. With the development of insulin injection technology, we herein evaluate whether the new injection modalities created to improve GV are of value.

Needle-free insulin injectors (NFII) deliver insulin at high velocity into subcutaneous tissue and distribute insulin over a larger area than using a syringe [10]. A recent study indicated that injection site did not affect the absorption of insulin in needle-free injections [11]. Furthermore, researchers have shown that NFII generate greater insulin absorption than a conventional insulin pen (CIP) in hyperinsulinemic-euglycemic-clamped healthy subjects [12]. As a result, early

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postprandial glucose levels and 24-h mean glucose levels were found to be improved in patients with diabetes [13–16]. Our group also found that NFII significantly lowered the dosage of insulin (3.11 units per day) needed relative to CIP [14]. However, the mechanisms underlying these findings remain unclear. We have observed insulin leakage from the needle tip or skin site after needle withdrawal, and this has been discussed in several investigations of needle insulin injection [17–19]. We hypothesized that NFII would enable more complete subcutaneous absorption of basal insulin, thereby reducing the FGV level. Our aim was to evaluate the effects of NFII and CIP on FGV in T2DM patients who were treated with basal insulin under good fasting glucose control.

2. Patients and methods

2.1. Study design and participants

We recruited 48 patients with T2DM who were treated with insulin degludec, insulin glargine, or neutral protamine hagedorn (NPH) insulin for the present study from four hospitals in China. This study was approved by the local Institutional Review Boards of the participating centers and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Inclusion criteria were as follows: (1) patients aged between 18 and 70 years, with a body mass index (BMI) of 18–30 kg/m²; (2) a diagnosis of type 2 diabetes more than one-half year ago; (3) patients receiving a once-daily injection of insulin glargine, insulin NPH, or insulin degludec at a total daily dose of 12 to 50 IU, taking one to three types of oral antidiabetic drugs (excluding sulfonylureas and glinides), and using their present antidiabetic therapy for over one month; and (4) a fasting venous blood glucose between 5.0 and 9.0 mmol/L. Exclusion criteria were as follows: (1) laboratory examination results that showed (A) significant abnormal liver function or active liver disease (aspartate aminotransferase [AST] 3.0 times higher than the upper limit of normal or alanine aminotransferase [ALT] 3.0 times higher than the upper limit of normal), (B) a creatinine clearance rate of <60 ml/min; (C) anemia of any cause; and (D) positive pregnancy test results for women of childbearing age; (2) exudative dermatitis, impetigo, or suppurative infection or other skin diseases where the skin conditions were not suitable for insulin injection; (3) the use of injectable drugs other than insulin (including GLP-1 receptor agonists); (4) poor blood glucose control and the patient's inability to participate in this study – including recurrent hypoglycemia, diabetic ketoacidosis, or hypertonic coma; (5) serious cardiovascular events within the last six months; (6) the use of glucocorticoids or immunosuppressants, immune deficiency, or immunosuppression; (7) a history of acute pancreatitis or pancreatectomy; (8) a history of cancer; (9) pregnant or breast-feeding women; (10) recent definite infections such as urinary tract infection or pneumonia; (11) recent active bleeding of vital organs, including gastric bleeding or cerebral hemorrhage; (12) conflicts of interest with the study; and (13) any other conditions where the investigator considered that

the subject would potentially fail to complete the study or that the study would pose a significant risk to the subject.

The study was approved by the Ethics Committee of Tangdu Hospital, the Second Affiliated Hospital of Air Force Medical University (Ethical Approval Number, K202102-09).

2.2. Study design

This study was a prospective randomized multicenter open-label crossover study and registered at <https://www.chictr.org.cn>, registration number ChiCTR2000034674. We evaluated FGV under conditions of T2DM patients who achieved the FBG target (4.4–6.1 mmol/L) when basal insulin (glargine, NPH, or degludec) was injected with NFII or CIP. The QS-P jet injector (Beijing QS Medical Technology Co. Ltd, China) was adopted for the present study, as its effectiveness and safety were affirmed in a previous study [15].

We assessed 52 patients for eligibility. Four were excluded, two of whom did not meet the inclusion criteria, and two others declined to participate. Thus, 48 patients were originally recruited to this study. Our study design and patient management process are shown in [Figure 1](#).

Prior to the first phase of study, there was a run-in phase of insulin administration (7–14 days) during which the investigator instructed patients on mastering the injection techniques such that they became proficient with both the QS-P Needle-free insulin injector (Beijing QS Medical Technology Co. Ltd, China) and conventional insulin pen (Levemir, FlexPen; Novo, Nordisk, A/S; Lantus, SoloSTAR; Sanofi, Paris, France; Novolin N, FlexPen; Novo, Nordisk, A/S). Both the type and dosage of oral medication consumed by the patients before enrollment in the study remained unchanged, and a meter (Roche, ACCU-CHEK, GUIDE) was used to monitor blood glucose. Continuous glucose monitoring (CGM) (ipro-2, Medtronic, Minneapolis, MN, USA) was conducted with patients who manifested an FBG level between 4.4 and 6.1 mmol/L through self-monitoring of blood glucose (SMBG) and who self-administered a basal insulin dose \geq 12 IU for two consecutive days; CGM was conducted for six days.

Patients who achieved the target were then randomized to either the CIP injection or NFII injection for 7–14 days as their first phase of treatment, with the type and dosage of oral medication fixed throughout the study. Basal insulin titration was implemented to achieve a target FBG level between 4.4 and 6.1 mmol/L through SMBG and a basal insulin dose \geq 12 IU for two consecutive days, then CGM was conducted for six days. After this point, we considered the first phase to have ended. Next, all patients from both groups were injected with CIP for 7–14 days (washout period), and their venous FBG concentrations were measured on the last day of the washout period. Those individuals who attained the standard venous FBG level (4.4–6.1 mmol/L) then entered the second phase of the trial. The original NFII injection group was crossed over to CIP injection, and the original CIP injection group was crossed over to undergo NFII injection. Other procedures were similar to those in the first phase.

2.3. Continuous glucose monitoring

Patients who achieved the FBG control target (fasting 4.4–6.1 mmol/L) and who received a basal insulin dosage \geq 12 IU

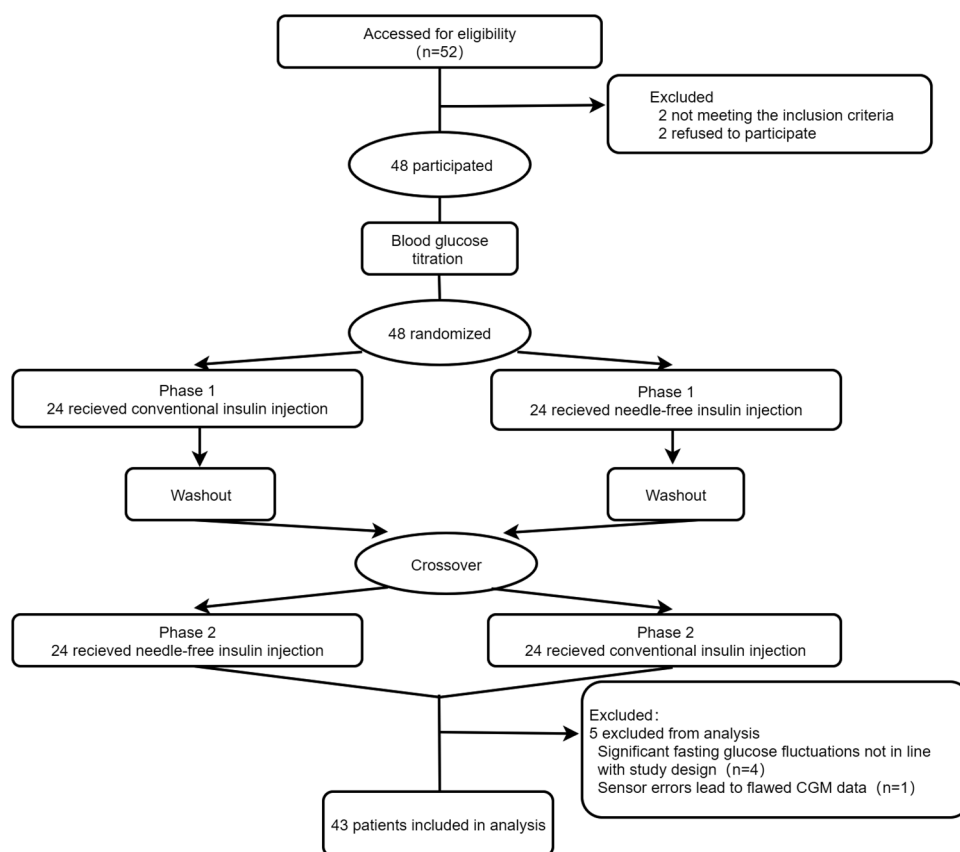


Figure 1. Study design and the flow of patients in the trial.

for two consecutive days underwent CGM for six days (except for the washout period) in this phase of the study. The following parameters were then calculated from the CGM data.

- (1) Mean sensor glucose (MSG) was defined as the 24-hour average sensor glucose (SG) during six days of CGM and reflected overall glucose control.
- (2) MSG at 5–6 a.m. (MSG5-6a.m.) was defined as the average SG between 5:00 a.m. and 6:00 a.m. during six days of CGM and reflected fasting glucose control.
- (3) SG at 6 a.m. (SG6a.m.) was defined as the SG at 6:00 a.m. during six days of CGM and reflected fasting glucose control.
- (4) The coefficient of variation (CV) for SG at 6 a.m. (CV-SG6a.m.) was defined as the CV of SG at 6:00 a.m. during six days of CGM and reflected the fasting glucose variability.
- (5) The CV for MSG at 5–6 a.m. (CV-MSG5-6a.m.) was defined as the average CV for MSG at 5–6 a.m. during six days of CGM and reflected fasting glucose variability.

2.4. Self-monitoring of blood glucose

Before CGM was instituted, SMBG was executed seven times per day on days 1 and 2 of each study stage, followed by daily fasting and monitoring of two-hour postprandial blood glucose (every other day) and bedtime blood glucose (every other day).

On day 1 of CGM, blood sugar was determined at one hour and three hours after wearing the monitor, before dinner, and before bedtime; on days 2–3 of CGM, blood glucose was determined before each of the patient's three meals, after each meal, and before going to bed; on days 4–6 of CGM, patients entered the test period after fasting, before lunch, before dinner, and before bedtime.

The CV of FBG (CV-FBG) was defined as the CV for peripheral FBG during the six days of CGM and reflected variability of FBG as assessed by SMBG.

2.5. Endpoints

Our primary study outcome was a composite parameter that comprised the FGV (CV-FBG, CV-SG6a.m., and CV-MSG5-6a.m.) when using different injection methods; the secondary outcome was the change in basal insulin dosage with the various injection methods. The exploratory endpoint, then, was the difference in CV-FBG, CV-SG6a.m., and CV-MSG5-6a.m. when using different basal insulins.

2.6. Clinical and laboratory examinations

We collected the following information from each patient: major chronic medical history, diabetes history, and medication status; comprehensive physical examination that included vital signs, height, weight, waist circumference, hip circumference, waist-to-hip ratio, and BMI; and a laboratory examination that encompassed FBG, routine blood tests, liver function,

kidney function, blood lipids, routine urine testing, and electrocardiographic data.

2.7. Sample size and statistical analysis

We assumed for our primary endpoint that the glucose variability in the NFII group was smaller than that in the CIP group. Based on a literature review and previous studies, insulin reductions were estimated at 3–6 IU. Based upon an $\alpha = 0.05$ (bidirectional) and a loss rate of 10%, we expected that a 1:1 ratio for 50 patients would detect a difference of 3 IU between the two groups with 85% confidence. Analysis of the primary outcome included CV-SG6a.m., CV-MSG5-6a.m., and CV-FBG. The per-protocol set (PPS) included patients in the full-analysis set who were compliant with the treatment protocol and who (1) completed each treatment regimen, (2) did not violate the inclusion/exclusion criteria, and (3) provided at least three days of glucose data between 5:00 a.m. and 6:00 a.m. so as to achieve the control target according to the GCM data. Normally distributed continuous variables are expressed as mean (SD), with medians (interquartile ranges [IQRs]) used for non-normally distributed continuous variables. For parameters conforming to a normal distribution, we employed paired Student's *t* tests and used the non-parametric Wilcoxon's test for data that did not follow a normal distribution. Sensitivity analyses were also performed to examine the robustness of the treatment effect observed in the primary analysis. We adjusted the hierarchical logistic model for sex, age, duration of treatment, BMI, educational level, and insulin type and derived the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) from the hierarchical logistic model. Statistical analyses were implemented with SPSS software (Statistical Package for the Social Sciences, version 25.0; IBM Corporation, Armonk, NY), and R-software version 4.1.2 was used to generate the forest plot. We considered $p < 0.05$ to be statistically significant.

3. Results

3.1. Baseline characteristics

In Table 1, we summarize the baseline characteristics of our study participants. Of the 48 patients originally recruited to this study, five were subsequently excluded from analysis as their glucose levels were beyond the preset-FBG target or they showed incomplete sensor glucose data from CGM. The remaining 43 participants included 31 males and 12 females, with a mean age of 56.0 (48.0, 61.0) years.

3.2. Evaluation of glucose control using different injection methods

MSG values throughout the day were 7.39 (0.99) mmol/L with CIP injection and 7.54 (1.13) mmol/L with NFII injection (Figure 2A); MSG5-6a.m. was 5.73 (0.76) mmol/L with CIP injection and 5.71 (0.80) mmol/L with NFII injection (Figure 2C); and SG6a.m. values were 5.79 (0.61) mmol/L with CIP injection and 5.78 (0.70) mmol/L with NFII injection (Figure 2E). FBG values were 5.82 (0.47) mmol/L with CIP injection and 5.63 (0.53) mmol/L with NFII injection (Figure 2G). No significant difference in MSG, MSG5-6a.m., SG6a.m., or FBG between the two injection methods (p values are shown in Figure 2). Glucose control for seven days between different insulin injection periods also showed no significant difference except for attenuated FBG with NFII injection relative to that with CIP injection on day 5 (Figure 2H).

3.3. FGVs and basal insulin dosage using different insulin injection methods

CV-SG6a.m. with CIP injection was 11.67(8.70, 14.81)% vs. 9.48 (6.48, 12.24)% with NFII injection ($p = 0.003$) (Figure 3A); CV-MSG5-6a.m. with CIP injection was 12.70(9.17, 16.56)% vs. 9.23 (7.01, 11.98) % with NFII injection ($p < 0.001$) (Figure 3C); CV-SG6a.m. and CV-MSG5-6a.m. were significantly reduced with

Table 1. Baseline characteristics.

	ALL (n = 43)	Deglutec (n = 9)	Glargine (n = 28)	NPH (n = 6)
Sex (Male, n/%)	31/72.1	5/55.6	22/78.6	4/66.7
Age (years)	56.00 (48.0–61.0)	56.00 (12.35)	53.62 (8.78)	55.50 (10.19)
Duration (years)	12.0 (6.0–19.0)	15.56 (11.51)	11.57 (7.33)	13.33 (7.66)
BMI (kg/m ²)	24.20 (2.13)	24.01 (1.42)	24.21 (2.28)	24.39 (2.45)
Waist (cm)	88.78 (7.21)	90.21 (5.63)	88.41 (7.85)	88.83 (6.46)
SBP (mm Hg)	121.37 (12.30)	125.50 (7.54)	118.62 (13.24)	129.17 (8.01)
DBP (mm Hg)	76.14 (7.46)	78.88 (5.77)	74.24 (7.85)	81.67 (2.58)
FBG (mmol/L)	6.73 (1.07)	7.30 (0.97)	6.54 (1.11)	7.04 (0.56)
Oral antidiabetics (n/%)				
Metformin	36/83.7	7/77.8	26/92.9	3/50.0
SGLT2i	18/41.9	2/22.2	13/46.4	3/50.0
DPPIV	13/30.2	2/22.2	9/32.1	2/33.3
Glucosidase inhibitor	11/25.6	1/11.1	8/28.6	2/33.3
Education (n/%)				
Elementary education	9/20.9	1/11.1	8/28.6	0
Secondary education	24/55.8	5/55.6	16/57.1	3/50.0
Higher education	10/23.3	2/22.2	5/17.9	3/50.0

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; SGLT2i, sodium-glucose co-transporter 2 inhibitor; DPPIV, dipeptidyl peptidase IV inhibitor; NPH, neutral protamine Hagedorn.

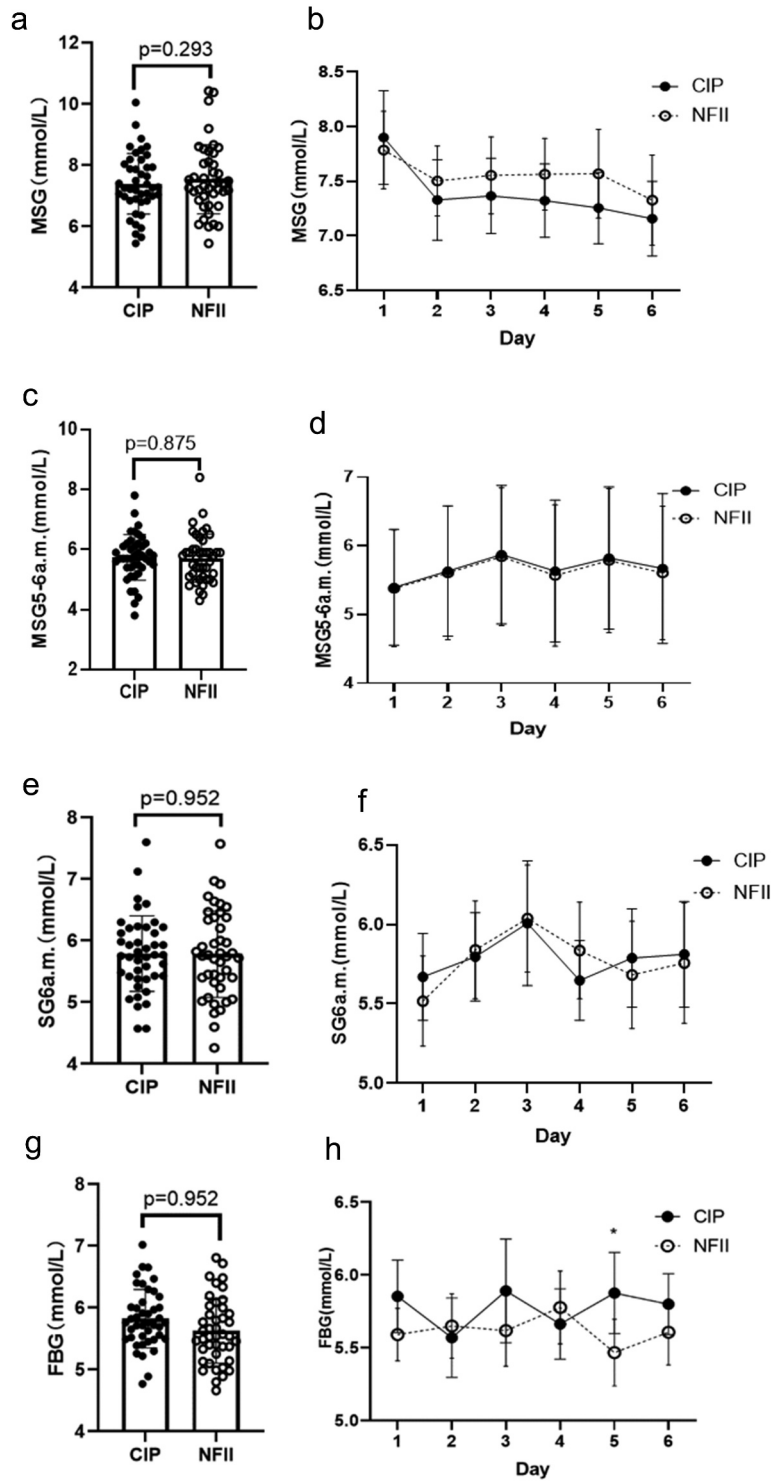


Figure 2. Glucose control during different injection methods. (A) Mean sensor glucose (MSG) during different injection methods. Filled circles refer to the conventional insulin pen (CIP) and empty circles refer to the needle-free insulin injector (NFII). (B) MSG of 7 days before the end of each injection method. (C) Mean sensor glucose in 5–6 a.m. (MSG5-6a.m.) during the two injection methods. (D) MSG5-6a.m. of 7 days before the end of each injection method. (E) Sensor glucose at 6 a.m. (SG6a.m.) during the two injection methods. (F) SG6a.m. of 7 days before the end of each injection method. (G) Fasting blood glucose (FBG) during the two injection methods. (H) FBG of 7 days before the end of each injection method.* $p = 0.02$.

NFII relative to CIP when using degludec and glargine, no significant effect for the NPH group (Figure 3B, D). CV-FBG did not differ between the two injection periods (8.92[4.73, 12.46]% with CIP and 8.10[5.84, 13.29]% with NFII, $p = 0.923$) (Figure 3E, F). And basal insulin dosage with CIP injection was

18.00 (16.00, 20.00)IU vs. 16.00 (12.00, 19.00)IU with NFII injection ($p < 0.003$) (Figure 3G). In addition, the basal insulin dosage significantly declined with the use of NFII compared to CIP when using glargine, and no significant difference was observed in the degludec and NPH groups (Figure 3H).

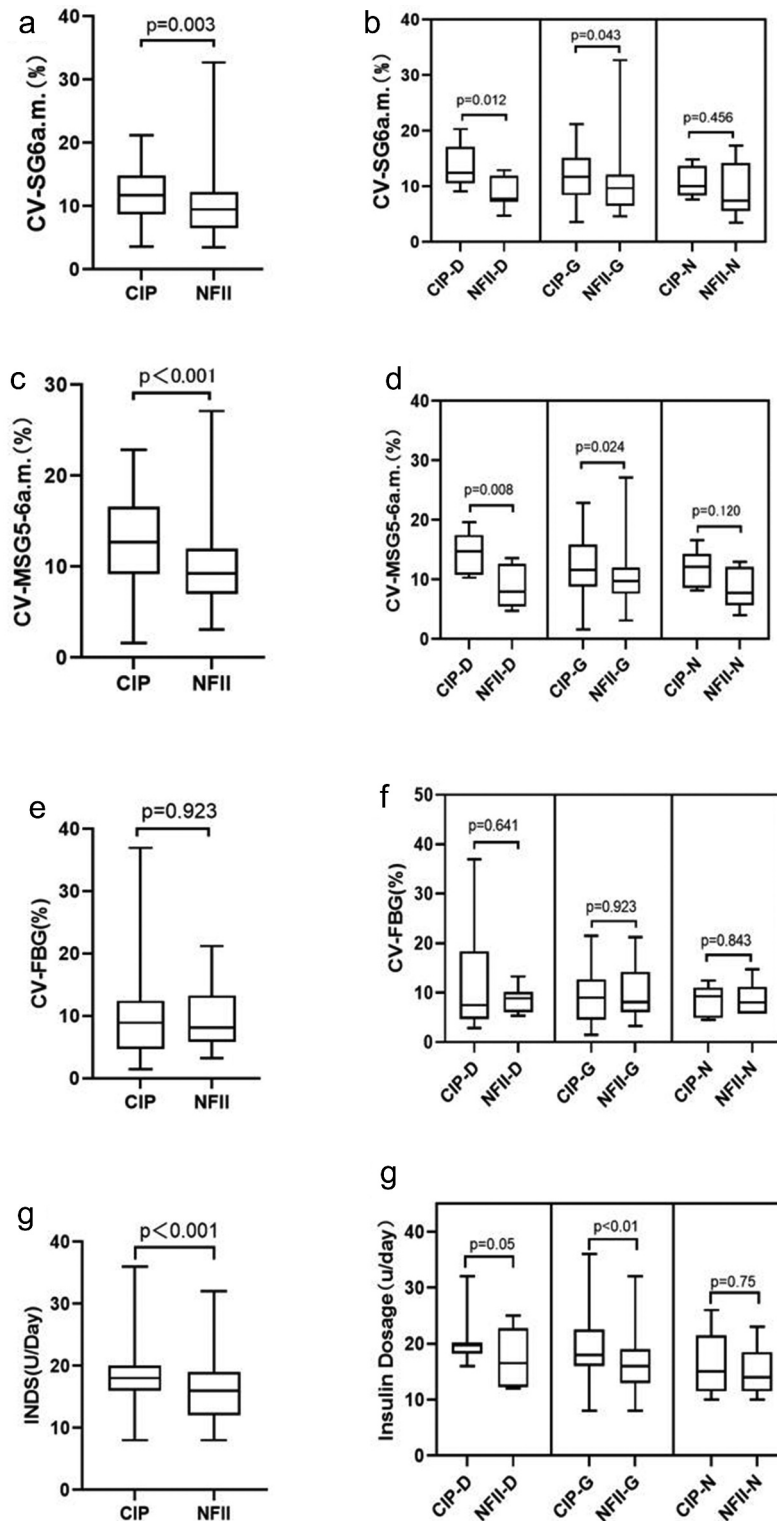


Figure 3. FGV and basal insulin dosage during different insulin injection methods. (A) Coefficient of variation of sensor glucose at 6 a.m. (CV-SG6a.m.) during the two injection methods. Filled circles refer to the conventional insulin pen (CIP) and empty circles refer to the needle-free insulin injector (NFII). (B) CV-SG6a.m. during different insulin injection methods using different basal insulin. (C) Coefficient of variation of mean sensor glucose between 5 and 6 a.m. (CV-MSG5-6a.m.) during different insulin injection methods. (D) CV-MSG5-6a.m. during different insulin injection methods using different basal insulin. (E) Coefficient of variation of fasting blood glucose (CV-FBG). (F) CV-FBG during different insulin injection methods using different basal insulin. (G) Overall basal insulin dosage during different insulin injection methods. (H) Different basal insulin dosage during different insulin injection methods using different basal insulins.

3.4. Subgroup analysis of the effects of different injection methods on FGV

We used a logistic regression model to analyze FGV in subgroups upon administration of NFII and CIP. The mean dichotomized CV-MSG5-6a.m. value was adopted as the dependent variable, and sex, age, duration of administration, BMI, educational level, and insulin type were adopted as independent variables. Figure 4 depicts the forest plot illustrating the evaluation of subgroups with respect to treatment effects. We thus detected no significant interactions between different insulin injection methods or in the aforementioned baseline characteristics or insulin type.

4. Discussion

In the present study, we evaluated day-to-day FGV and basal insulin dosage with NFII or CIP injection using a fasting glucose target between 4.4 and 6.1 mmol/L and with the receipt of different basal insulin treatments. SMBG and CGM were both executed throughout the trial, and the CV-SG 6a.m., CV-MSG 5-6a.m., and CV-FBG were adopted as indicators of FGV. We uncovered significant reductions in CV-SG6a.m. and CV-MSG 5-6a.m. levels and basal insulin dosage when basal insulin analogs were administered using NFII.

It is worth noting that there are several metrics for assessing glucose variability: Glucose standard deviation (SD), glucose coefficient of variation, and the mean amplitude of

glycemic excursions (MAGE) (which are derived from CGM or flash glucose monitoring data) are commonly used to reflect GV throughout the day [20-22]. Some authors have thus far investigated GV throughout the day in T2DM patients when using NFII. For example, in a prospective clinical trial of T2DM, Jianhua et al. reported no differences in day-to-day MAGE and SD between NFII and CIP groups when using insulin glargine [16]. Another prospective study by Ma indicated no difference in MAGE, CV, or SD between NFII and CIP groups with respect to T2DM [15]. However, we know of no study of FGV that encompasses the application of NFII. In the Verona Diabetes Study, T2DM patients who demonstrated increased CV-FPG over three years showed an increased risk of total, cardiovascular, and cancer mortality over the subsequent 10 years [23]. Furthermore, an abundance of evidence has revealed an association between diabetic complications or even mortality and FGV [4-6,24]. We consider CV-FBG to also be an indicator of concern, especially in patients using basal insulin.

We first adopted CV-SG 6a.m., and CV-MSG 5-6a.m. as indicators of FGV and as the primary endpoint. A previous study revealed a robust correlation between MSG and FBG in T2DM patients [25]. SG at 6 a.m. and MSG at 5-6 a.m. reflected the actual FBG level in fasting and resting states since the effect of physical activities and diet on FBG could be ruled out. However, unlike CV-SG at 6 a.m., and CV-MSG at 5-6 a.m., no significant difference was observed in CV-FBG between the two different insulin injection modalities. Indeed, we subsequently analyzed the data and ascertained that a substantial

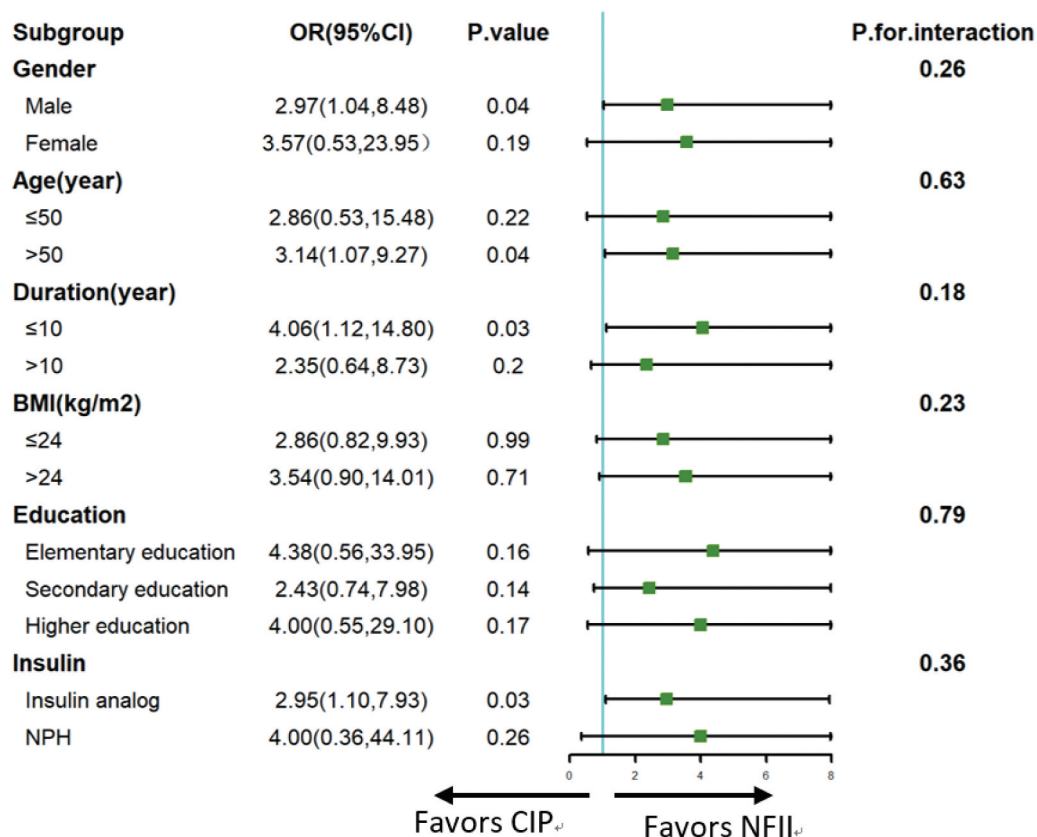


Figure 4. Subgroup analysis depicted as a forest plot of the effects of different injection methods on fasting glucose variability.

number of patients had already been active for one to two hours between waking and self FBG monitoring, which may not have reflected the actual resting and fasting states.

Our study suggested that using NFII reduced the FGV in degludec and glargine groups but not in the NPH group. Panwei et al. conducted a study to compare the CV of FBG between insulin glargine and insulin NPH in T2DM by oral antidiabetic drugs and demonstrated that insulin glargine was more potent in improving glycemic control than NPH with respect to a stable FBG [26]. Ling et al. reported that glargine-300 was associated with attenuated nocturnal GV using CGM over a 24-week study period compared with NPH insulin [27]. Compared with NPH insulin, basal insulin analogs (e.g. insulin glargine and insulin degludec) also provided pharmacokinetic and pharmacodynamic profiles that more closely emulated the normal physiologic patterns of basal insulin secretion [28,29]. In addition, the findings from glucose clamp studies in T1DM indicated that NPH showed higher within-subject variability (CV% of AUC-GIR) (detemir < glargine < NPH), which may have translated into large deviations from mean insulin activity, increasing the risk of both hyper- and hypoglycemia [30]. We posit that the glycemic variability that was determined by the pharmacokinetic and pharmacodynamic profiles of NPH may not have been sufficiently improved by NFII. However, the sample size of participants using NPH in the present study was small, and a larger-sample study is thus still needed to confirm our data.

Backflow or leakage of insulin to the skin surface can sometimes occur after subcutaneous injection. According to one clinical trial, 44%–56% of patients reported insulin leakage [31], and the amount of leakage increased commensurately with increasing insulin dosage [17]. It is thus desirable to minimize any leakage to the skin surface to ensure that the full dose of the drug is delivered to the subcutaneous space. A previous study illustrated a reduction in insulin leakage with the use of a thinner needle [32], as a thinner needle with a narrower wall improves insulin flow and results in less insulin leakage [33]. The needle-free jet injector we adopted in the present study delivers insulin with no needle across the skin through spray-like diffusion at high velocity (typically >100 m/s) and dispenses it over a larger subcutaneous area than injection with a needle [34]. We therefore hypothesized that leakage from a needle-free injector was lower than that from needle alternatives. To prove this additional hypothesis, we conducted a prospective clinical study in healthy subjects (Fig. S1) and verified that the use of NFII reduced the leakage area by 51.8%–64.7% compared to CIP, and this phenomenon became more significant with increasing dose (Fig. S2). We believe that this effect resulted in the lower dosage requirement and the reduction in FGV that we observed with NFII relative to CIP in the current study under similar conditions of glucose control.

This was the first-ever study in which the effect of the needle-free injection of basal insulin on FGV was evaluated. The strengths of our study were the combination of SMBG and CGM to assess blood glucose and the use of multiple indicators to reflect FGV and thus increase the reliability of the study. There were, however, also limitations to the present investigation. First, this study reflected relatively small

and heterogeneous samples for each insulin type in the three basal insulin groups; a larger-sample study therefore needs to be conducted. Second, this was an open-label analysis due to the difference in injection modalities, and although the cross-over design may have reduced the bias associated with the open-label status, bias was still present. Third, five (12%) of the patients who completed the trial provided incomplete CGM data, and while they were excluded from the analysis, we could not dismiss their potential influence.

5. Conclusions

We herein provided clinical evidence for a significant advantage of NFII over a CIP in improving FGV in type 2 diabetes patients using basal insulin analogs, as we demonstrated that the NFII reduced CV-SG6a.m., CV-MSG5-6a.m., and dosage of basal insulin analogs. Furthermore, we suggested that less fluid leakage may have accounted for these effects. We posit that our collective results shed new insights into the significant advantage of NFII in glucose control in T2DM.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions

JZ and QHJ contributed to the study design, data interpretation, and critical review of the manuscript; FS contributed to the literature search, data analysis, data interpretation, and writing of the manuscript; BG contributed to the study design, data interpretation, and editing of the manuscript; LT, ALY, LJR, YX and KYM managed relationships with the individual study centers, recruited patients, and conducted the study; SML and CNH conducted the study; HL provided technical support for the determination of insulin leakage area in this study; and JZ and QHJ were the guarantors of this work, and as such, had full access to all of the data in the study and took overall responsibility for the integrity of the data and the accuracy of the data analysis.

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