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Comparison of glucose variability in patients with type 2 diabetes administrated glargine with needle-free jet injector and conventional insulin pen

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Abstract

Background: The effects of insulin delivered by needle-free jet injector on glycemic variations (GV) in patients with type 2 diabetes (T2D) which remains largely unknown.

Research design and methods: We aimed to compare the glucose variability in Chinese T2D patients administrated glargine 100 U/mL (Gla-100) with needle-free jet injector and conventional insulin pen. This was a self-comparative, observational study of 26 patients who were subjected to a flash glucose monitoring system (FGM) for 14 consecutive days. During the study period, all subjects received Gla-100 daily before breakfast using a conventional insulin pen, with the exception of day 3 and day 7, when insulin was delivered by needle-free jet injection. We analyzed FGM data of day 3, day 5, day 7 and day 9 at the endpoint.

Results: There were no differences in the glycemic variability between the jet injector group and conventional pen group. However, patients with needle-free jet injection had a lower 24 hr mean glucose (MG) and lower incremental area under the curve (AUC) of 1 hr, 12 hr, and 24 hr, compared to the conventional pen group ($p=0.005$).

Conclusions: Gla-100 delivered by needle-free jet injection potentially lowered MG in patients with T2D in Chinese population.

Key words: flash glucose monitoring, Gla-100, glycemic variation, needle-free jet injection, type 2 diabetes

1. Introduction

It is estimated that the number of adults with diabetes worldwide has reached 285 million in 2010 and it is expected to rise to 439 million by 2030, and most patients are expected to have type 2 diabetes (T2D) [1]. China has the world's highest number of people with diabetes with over 98.4 million adults affected partially because of the aging pattern in the population and the rising obesity rates [2].

Insulin treatment is essential for patients with type 1 diabetes (T1D) and T2D for glucose variations control [3]. Nearly half of T2D patients in Chinese population are treated with insulin [4]. Currently, the commonly used insulin delivering methods include: subcutaneous injection, insulin pump, nasal inhalation, oral insulin and transdermal delivery of insulin [5]. Transdermal delivery of insulin through the skin barrier is a minimally invasive method of insulin delivery compared to the painful subcutaneous injection [6]. Recent advances in transdermal insulin delivery systems include chemical enhancers-promoted, electrically facilitated, mechanical force-triggered, and microneedle (MN)-assisted approaches, with needle-free jet injection being one of the mechanical force-triggered method [7].

Needle-free jet injection can be defined as a needle-free drug delivery method in which molecules are transported directly across the skin in the subcutaneous or intramuscular regions via a high velocity (>100 m/s), which not only reduces pain during drug delivery process, but also dispenses the drug over a larger area and more evenly than does injection by syringe [8]. Another point of importance is that, the study also found that needle-free jet injections is a preferred way to reduce anxiety in patients with needle phobia [9]. Using the clamp technique, researchers found this method has two times the rapid insulin absorption than those employing the conventional insulin pen method and lead to a decrease in postprandial hyperglycemia in patients with diabetes that may benefit patients who have difficulty in controlling postprandial glycemic excursions [10].

The flash glucose monitoring system (FGM) shows a potential for delivering blood glucose readings for 14 consecutive days in the diabetic patients, especially for improvement of glycemic variation control [11].

However, whether or not the insulin is delivered by needle-free jet injector improves the glycemic variation control in patients with T2D remained largely unknown. The aim of this study was to observe the effects of needle-free jet injector on glycemic variations in T2D patients using FGM .

2. Patients and methods

2.1 Study patients

Participants were recruited from the outpatient diabetic clinic in the Nanjing First Hospital, Nanjing Medical University, China. The criteria for recruiting patients were as follows: diagnosis of T2D as defined by published Criteria of World Health Organization in 1999; age ≥ 18 years of age and had a body mass index (BMI) between 18 and 30 kg/m²; HbA1c $\leq 9\%$; and patients receiving a stable insulin dose (total insulin dose ≥ 20 IU but < 150 IU per day) for at least 8 weeks. The exclusion criteria were as follows: fasting blood glucose ≤ 3.9 mmol/L or >11.1 mmol/L; history of a major cardiovascular disease event (e.g., stroke, symptomatic peripheral artery disease, myocardial infarction, percutaneous coronary or peripheral artery angioplasty or coronary artery bypass surgery) in the previous 6 months; liver dysfunction (aspartate aminotransferase or an alanine aminotransferase level of more than two times the upper limit of normal range) or renal dysfunction (creatinine >150 $\mu\text{mol/L}$ or $\text{GFR} < 60$ $\text{ml}\cdot\text{min}^{-1}\cdot 1.73$ m^2); severe anemia and hemoglobin disorders (Hb < 60 g/L); and infection at an injection site or the presence of coagulation disorders. Pregnant patients were also excluded. This study was approved by the ethics committee of the Nanjing First Hospital (NCT03785301). The methods were carried out in accordance with the Declaration of Helsinki guidelines, including any relevant details. Informed consent was obtained from participants with insulin-treated T2D.

2.2 Research design

This was a self-comparative, observational and single-center study. Patients who met the criteria were subjected to FGM for 14 days (day 0 at 8:00 am - day 14 at 8:00

am). During the FGM monitoring period, all patients were provided with a standardized diet, which was designed to ensure a total daily energy intake of 105 KJ/kg/day. They were also required to refrain from both structured and recreational physical activity. All subjects were administered Gla-100 (Basalin, CN) daily by trained nurses before breakfast using a reusable conventional insulin pen, except on day 3 and day 7, when insulin was delivered by needle-free jet injection. We analyzed the FGM data of day 3 and day 5 together with that of day 7 and day 9 at the endpoint (Fig.1).

2.3 FGM

The FGM data was analyzed from day 3, day 5, day 7 and day 9 (from 8 a.m. the day to 8 a.m. the next day). The following parameters were calculated from the FGM data:

1. 24 hr MG was defined as the average glucose of 96 measurements equally spaced in time.
2. The parameters of glycemic variability included the mean amplitude of glycemic excursion (MAGE) and the standard deviation of MG (SDBG). MAGE was obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs; only excursions >1 SD was considered. For SDBG determination, the standard deviations of a total of 96 values collected during a 24 hr FGM period for each study subject. The incremental area under the curve (AUC) of the glucose level > 10.0 mmol/L and the AUC of a glucose level <3.9 mmol/L were also calculated using the trapezoid rule.
3. The parameters of postprandial glucose fluctuation included the peaks of postprandial glucose (PPG), and postprandial glucose excursions (PPGEs). PPG peaks were defined as the highest glucose value within a 3-hr window from the start of the meal. PPGE was calculated as the peak glucose value after meals minus the glucose level at the beginning of each meal.
4. The parameters of 15 minutes predprandial glucose is the glucose value before the meal.

5. After insulin was administered with the needle-free jet injector or the conventional insulin pen, AUC for 1 hr, 2 hr, 3 hr, 6 hr, 12 hr, and 24 hr were calculated respectively.
6. The frequency of nocturnal and diurnal hypoglycemic episodes during the period.

2.4 Data analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL). The continuous variables were presented as a mean \pm standard deviation (SD), Student's paired t-test was used to compare the parameters that conform to the normal distribution. A two-way ANOVA used for repeated data analyzes. The parameters that do not conform to the normal distribution are expressed as the median (interquartile range), and calculated using the non-parametric tests. P value was two-tailed with a significant level of 5%.

3. Results

Table 1 summarizes the baseline characteristics of the participants, including age, ratio of M/F, BMI, HbA1c, duration of diabetes, daily dose of insulin, systolic blood pressure (SBP), diastolic blood pressure (DBP) and oral glucose-lowering agents. All 26 subjects completed the study. During the research period, there was no sensor shedding, no change of the original treatment, no symptomatic hypoglycemia, no redness, irritation or infection at the injection site were observed.

The 24 hr FGM glucose profile of patients after administration of Gla-100 with needle-free jet injector or conventional insulin pen is shown in Fig. 2. The 24 hr MG was lower in the jet injector group than those in the conventional pen group (8.3 ± 1.5 vs. 8.8 ± 1.5 , $p=0.005$). Difference was seen in the AUC of blood glucose below 3.9 mmol/L between the two groups (0.00 (0.00 , 0.00) vs. 0.00 (0.00 , 0.00), $p=0.047$). There were no differences in the parameters of glycemic variability between the jet injector group and the conventional pen group (Table 2).

Difference was found between 15 minutes preprandial glucose of lunch and dinner ($p<0.05$), the PPG of lunch was lower in the jet injector group than in the

conventional pen group (9.9 ± 3.0 vs. 11.9 ± 2.8 , $p<0.001$), but no other difference was found among the values at various postprandial time points ($p>0.05$) (Table 3).

After Gla-100 was administered with the needle-free jet injector, the AUC of 1 hr, 12 hr, and 24 hr were significantly reduced when compared to those using conventional pen method ($p<0.005$) (Table 4).

The frequency and duration of hypoglycemia (defined as blood glucose <3.9 mmol/L) were less in the jet injector group than in the conventional pen group ($p<0.05$). After the injection of Gla-100, 11 patients developed asymptomatic hypoglycemia for a total of 32 times in the needle-free jet injection group, and 8 patients in the conventional pen group developed asymptomatic hypoglycemia for a total of 16 times (0.64% vs. 0.32%, $p=0.021$). Remarkably, there was no difference in the frequency and duration of nocturnal hypoglycemia episodes between the two groups.

4. Discussion

In this study, we observed that insulin delivered by needle-free jet injector on blood glucose profiles had a potential for improvement in lowering 24 hr MG. There were no differences in glycemic variability between the jet injector group and the conventional pen group.

Although the subcutaneous insulin injection is the standard route for insulin delivery, it may be associated with pain, needle phobia, reduced compliance, and risk of infection. Injection-related discomfort continues to have a significant response as insulin injection-related anxiety and non-adherence. Research has shown that up to 94 percent of insulin users experience anxiety, pain, or fear similar to injection injury phobia [12]. Injection pain and embarrassment are risk factors for injection omission in patients with T2D [13]. Therefore, transdermal insulin delivery has been extensively studied as an alternative in recent years [7]. Jet injection is a needle-free drug delivery method that employs a high-speed stream of fluid that impacts the skin and delivers drugs subcutaneously [14-16]. Needle-free jet injection is associated with high delivery efficiency, with delivery rates over 90%, similar to subcutaneous

injection [17].

In this study, our data indicate that the administration of insulin Gla-100 with a needle-free jet injector can reduce the 24 h MG of patients monitored by FGM and an increase of hypoglycemia. The BMI of all the subjects in this study was around 25 kg/m², which was in line with the definition of overweight in the Chinese population. Needle-free jet injection could quickly correct marked hyperglycemia in overweight and obese patients with diabetes [18].

We also observed that AUC 1 hr, AUC 12 hr, and AUC 24 hr after injection were lower than that of the conventional pen group. The underlying mechanisms may be the following: firstly, the needle-free jet injection distributed insulin over a larger area and more evenly in the skin tissue than that of conventional insulin pen. Secondly, the pharmacokinetics of this delivery pathway are more similar to the endogenous insulin secretion of the pancreas [19], and increases plasma insulin level faster [20].

Fewer studies have focused on the effects of long-acting insulin injected by jet injector on the glucose profiles in patients with T2D. Gla-100 prepared by using recombinant DNA technology, is a long-acting insulin analog that is able to simulate basal insulin secretion [21]. It has been reported that Gla-100 has a long duration of action, low variability, higher predictability and lower incidence of hypoglycemia [22]. However, in this study, we observed that the postprandial level mainly before lunch and dinner was lower, and the frequency and time of asymptomatic hypoglycemia increased, without an increase in nocturnal hypoglycemia compared to those of conventional group. The underlying mechanism may be that the application of needle-free jet injector lead to insulin to disperse quickly under the skin and an increase in the surface-to-volume ratio of insulin stored under the skin promotes faster absorption of insulin into the bloodstream [23]. It's more logical to hypothesize that the use of long-acting insulin with needle-free jet injector may reduce the amount of basal insulin in patients with T2D, thereby reducing the financial burden on patients. However, future studies that focused on these effects are required.

Despite these advantages, there are several problems that limit in the current

use of needle-free jet injector. High pressure sprays can cause adverse reactions, including bruises, bleeding and pain [24, 25]. Needle-free jet injectors actually cause no less pain than subcutaneous administration and are used in more sophisticated ways than the conventional insulin pens [26].

Some limitations in this study must be addressed. First, we did not collect data of patients' satisfaction with the needle-free jet injector. Second, we did not investigate the pharmacology of Gla-100 administrated with needle-free jet injector versus conventional pen.

5. Conclusion

In conclusion, Gla-100 delivered by needle-free jet injector lead to a potential improvement of lowering MG and 15 minutes preprandial glucose levels in patients with T2D in the Chinese population. Our data indicate that the use of long-acting insulin injection with needle-free jet injector may reduce the doses of basal insulin in patients with T2D and thus reduce the economic burden on diabetic patients.

1. A total of 26 patients were recruited and all of them completed the study.
2. The 24 hr MG was lower in the jet injector group than those in the conventional pen group.
3. The 15 minutes preprandial glucose of lunch and dinner, and the postprandial glucose of lunch was lower in the needle-free jet injector group compared with insulin pen group.
4. After Gla-100 was administrated with needle-free jet injector, the incremental areas under the curve (AUC) at 1 hr, 12 hr, and 24 hr were significantly reduced compared to those of receiving conventional pen.
5. The frequency and duration of hypoglycemia (blood glucose < 3.9 mmol/L) in patients receiving insulin delivered by needle-free jet injector were decreased compared to those in the conventional pen group.
6. Differences in glycemic variations regarded as standard deviation (SD) of mean glucose and the mean amplitude of glycemic excursion (MAGE) has not been

observed.

Author Contributions

JH Ma and XF Su contributed to the conception and design of the study. YX Sun, J Wang, HQ Li, and XJ Su contributed to the conduct/data collection. J Wang, YX Sun, and HQ Li contributed to data analysis. YX Sun contributed to manuscript writing. XF Su and JH Ma performed the final approval of the manuscript.

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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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Legends

Figure 1 Flow chart.

Figure 2 24 hr MG after injection.

Table 1 Clinical characteristics of the patients.

Table 2 Glucose fluctuations parameters for insulin administration with the jet injector and the conventional insulin pen.

Table 3 Glycemic variations after meals between groups.

Table 4 The incremental area under curve after insulin injection between two groups.

List of abbreviations

FGM: Flash glucose monitoring system, MAGE: the mean amplitude of glycemic excursion, SDBG: the standard deviation of MG: AUC: the incremental area under the curve, PPG: the peaks of postprandial glucose, PPGEs: the postprandial glucose excursions

Table 1 Clinical characteristics of the participants.

	Whole group (26 patients)
Male-to-female ratio	19/7
Age (years)	59.23±8.36
BMI (kg/m ²)	25.65±2.68
HbA1c (%)	7.52±0.92
Duration of diabetes (years)	11.23±4.52
Daily of insulin dose (units)	19.77±4.92
SBP (mmHg)	131.77±15.46
DBP (mmHg)	77.19±8.17
Hypertension	13
Use of metformin	15

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

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Table 2 Glucose fluctuations parameters for insulin administration with the jet injector and the conventional insulin pen

Parameters	Jet injection	Conventional Pen	p value
24 hr MG (mmol/L)	8.13 ± 1.51	8.62 ± 1.64	0.001
MAGE (mmol/L)	6.18 ± 1.93	6.79 ± 2.39	0.103
SDBG (mmol/L)	2.47 ± 0.74	2.41 ± 0.65	0.473
Max BG (mmol/L)	14.00 ± 2.36	14.20 ± 2.33	0.455
Min BG (mmol/L)	4.38 ± 1.33	5.06 ± 1.49	0.001
AUC > 10 mmol/L	38.57 (12.74, 85.27)	49.97 (16.79, 99.50)	0.103
AUC < 3.9 mmol/L	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.047

MAGE: the mean amplitude of glycemic excursion; SDBG: the standard deviation of MG; AUC > 10 mmol/L: the incremental area under the curve (AUC) of a glucose level > 10.0 mmol/l; AUC < 3.9 mmol/L: the incremental area under the curve (AUC) of a glucose level < 3.9 mmol/l

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Table 3 Glycemic variations after meals between groups

Parameters	Jet injection	Conventional Pen	p value
Pre-B BG (mmol/L)	7.19 ± 1.51	6.99 ± 1.52	0.185
PPG of B (mmol/L)	13.26 ± 2.45	13.28 ± 2.83	0.946
PPGE of B (mmol/L)	6.06 ± 2.12	6.29 ± 2.42	0.415
Pre-L BG (mmol/L)	6.10 ± 2.53	7.64 ± 2.62	0.002
PPG of L (mmol/L)	9.92 ± 3.01	11.93 ± 2.83	0.000
PPGE of L (mmol/L)	3.82 ± 3.15	4.29 ± 2.57	0.391
Pre-D BG (mmol/L)	6.19 ± 2.11	7.02 ± 2.14	0.039
PPG of D (mmol/L)	10.90 ± 3.07	11.27 ± 2.52	0.376
PPGE of D (mmol/L)	4.71 ± 2.94	4.25 ± 2.47	0.368

Pre-B BG: the glucose of 15 minutes predprandial of breakfast; PPG of B: the peak postprandial of breakfast; PPGE of B: postprandial of breakfast glucose excursions; Pre-L BG: the glucose of 15 minutes predprandial of lunch; PPG of L: the peak postprandial of lunch; PPGE of L: postprandial of lunch glucose excursions; Pre-D BG: the glucose of 15 minutes predprandial of dinner; PPG of D: the peak postprandial of dinner; PPGE of D: postprandial of dinner glucose excursions

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Table 4 The incremental area under curve after insulin injection between two groups

Parameters	Jet injection	Conventional Pen	p value
AUC 1 h	25.46 ± 4.96	31.51 ± 9.97	0.000
AUC 2 h	72.50 ± 13.55	74.10 ± 20.00	0.540
AUC 6 h	220.82 ± 40.93	227.24 ± 48.28	0.322
AUC 12 h	412.80 ± 78.29	447.60 ± 88.20	0.001
AUC 24 h	772.17 ± 143.52	817.24 ± 155.88	0.002

AUC 1 h: the incremental area under the curve (AUC) of 1 hour after injection; AUC 2 h: the incremental area under the curve (AUC) of 2 hour after injection; AUC 6 h: the incremental area under the curve (AUC) of 6 hour after injection; AUC 12 h: the incremental area under the curve (AUC) of 12 hour after injection; AUC 24 h: the incremental area under the curve (AUC) of 24 hour after injection

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Figure 1

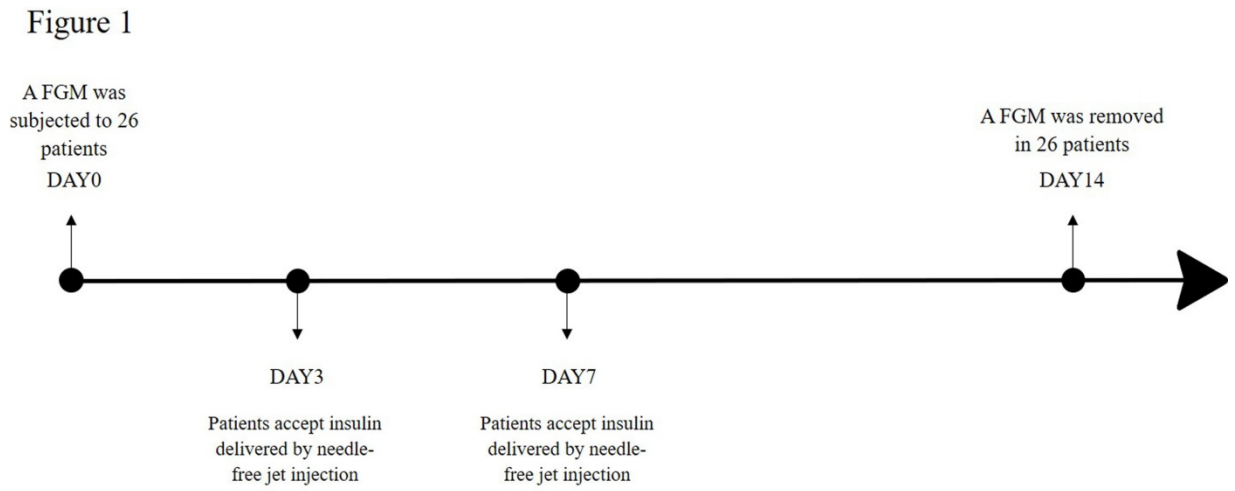


Figure 2

