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ORIGINAL RESEARCH



Efficacy and safety of a needle-free injector in Chinese patients with type 2 diabetes mellitus treated with basal insulin: a multicentre, prospective, randomised, crossover study

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ABSTRACT

Objective: To evaluate the efficacy and safety of a needle-free injector in Chinese patients with type 2 diabetes mellitus treated with basal insulin.

Methods: 62 patients with type 2 diabetes were enrolled in a multicenter, randomised, prospective, open-label, crossover study. All patients received subcutaneous insulin glargine administered by a needle-free injector or a glargine pen for 7 ~ 14 days, and were then crossed over after wash out.

Results: Patients in the insulin needle-free injector (NFI) and glargine pen (GP) groups achieved similar fasting blood glucose control. However, the dosage of insulin required to achieve the target FBG level in the NFI group was lower than in the GP group (16.14 ± 5.13 U/day vs 19.25 ± 6.20 U/day, respectively; $p = 0.0046$). This difference was more significant in patients who received higher insulin dosages compared with those receiving lower dosages. Use of the needle-free injector was also associated with significantly less pain ($p < 0.001$) and less fear of injection ($p < 0.001$) than glargine pens.

Conclusion: The use of a needle-free injector can significantly lower the dosage of insulin required to achieve good glycemic control and reduce topical adverse reactions and the fear of injections as well, which help to improve patient compliance.

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Insulin; needle-free injector; glargine insulin pen; diabetes mellitus; type 2; efficacy; blood glucose control; safety; local adverse effects; patient compliance

1. Introduction

Since the advent of insulin in 1921, it has brought hope to countless people with diabetes mellitus. With the increase in the number of people with diabetes over the past few decades, especially type 2 diabetes, the number of patients who require insulin injection therapy has increased rapidly. Whereas patients with type 1 diabetes will begin to receive insulin once they have been diagnosed, in patients with type 2 diabetes, the function of islets will gradually decrease as the disease progresses. As well as these patients, insulin therapy is also required for patients with severely impaired liver and kidney function, those who can not tolerate oral treatment regimens, and patients with acute elevations of blood glucose [1,2].


Although insulin therapy is effective in lowering blood glucose levels, it also poses some problems for patients. For example, high-dose insulin injections may increase body weight [3], thereby increasing insulin resistance, and resulting in patients requiring more insulin to maintain control of blood glucose concentrations. In addition, the way in which insulin is

injected itself is painful. The pain caused by a single injection of more than one needle per day can result in fear of injections, anxiety, and even depression. Moreover, metal insulin needles can produce a foreign body reaction under the skin, cause an allergy, or an inflammatory reaction leading to subcutaneous bruising and redness [4]. The way insulin is infused subcutaneously through syringes is not perfect. High doses of insulin concentrating under the skin may not be conducive to the smooth release and absorption of insulin [5]. For these reasons, research into new insulin dosage forms that can be taken orally or absorbed through the skin and mucous membranes has continued, for example resulting in the development of oral, topical and nasal spray insulin preparations [5–7]. Thus far, however, these methods are still at a relatively early stage, both in terms of technology and their clinical validation in the diabetic population.

Needle-free jet injectors deliver insulin at high velocity into subcutaneous tissue and distribute insulin over a larger area than a syringe [8]. The QS-M needle-free injector (Beijing QS Medical Technology Co. Ltd, China) was approved for insulin injection by the China Food and Drug Administration in 2012.

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 Supplemental data for this article can be accessed [here](#)

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Previous studies showed regular insulin and rapid-acting insulin analogues administered by the QS-M needle-free injector resulted in earlier and higher insulin exposure than conventional insulin pens, resulting in a significant decrease in plasma glucose concentrations as compared with the conventional pen injections [9–12]. Currently, however, there are few studies on the application of needle-free injectors in patients treated with basal insulin. This study aimed to evaluate the efficacy and safety of the QS-M needle-free insulin injector in Chinese patients with type 2 diabetes mellitus being treated with basal insulin.

2. Methods

2.1. Patients and inclusion/exclusion criteria

This study was approved by the local institutional review boards of the participating centres. Written informed consent was obtained from all participants before beginning the trial, which has been registered with the ClinicalTrials.gov (NCT03420040). Sixty-five patients with type 2 diabetes who were being treated with insulin glargine were recruited for the study at 6 hospitals in China.

Inclusion criteria were: age between 18 and 70 years; a diagnosis of type 2 diabetes more than half a year ago; body mass index (BMI) in the range 18 to 30 kg/m²; a daily dose of insulin glargine ≥ 12 U, but less than 50 U administered for ≥ 1 month. The patients were taking 1 to 3 oral antihyperglycaemic drugs (not including secretagogues) and had fasting venous blood glucose concentrations in the range 5.0–9.0 mmol/L. Exclusion criteria were (1) there is conflict of interest with this research; (2) blood glucose control is not good enough to participate in this study, such as repeated hypoglycemia, diabetic ketoacidosis or hyperosmolar coma; (3) serious diabetic complications such as diabetic foot, diabetic nephropathy and so on; (4) severe cardiovascular events occurred in the last 6 months; (5) the application of hormone or immunosuppressant, or low immunity defect; (6) the use of non steroidal anti-inflammatory drugs; (7) the use of sulfonylureas and insulin secreting agents; (8) a person with a history of cancer; (9)

a history of unstable or rapid progressive renal disease; (10) an unstable history of major mental illness; (11) the history of hemoglobin (such as sickle red cell anemia, thalassemia, iron granulocytic anemia); (12) women who are pregnant or are breastfeeding; (13) in the near future there is a clear infection, such as urinary tract infection and pneumonia; (14) recent important visceral hemorrhage, such as gastric hemorrhage and cerebral hemorrhage, etc; (15) skin diseases such as exfoliative dermatitis, pustular sore and infection of pyogenic bacteria; (16) the history of acute pancreatitis or pancreatectomy; (17) the researchers believe that it may lead to any situation in which the subject is unable to complete the study or may cause significant risk to the subject; (18) the results of the laboratory examination are as follows: A. AST > 3 times the upper limit of normal or ALT > 3 times the upper limit of normal; B. The creatinine clearance rate was <60 ml/min; C. anemia caused by any cause of the disease; D. The results of pregnancy test in women of childbearing age were positive.

The study was approved by the Xijing Hospital Ethics Committee, which is attached to the Fourth Military Medical University.

2.2. Study design

This was a multicenter, prospective, randomized, crossover study, to evaluate the efficacy and safety of the QS-M needle-free injector in Chinese patients with type 2 diabetes mellitus treated with basal insulin. The study design and the flow of patients in the trial is shown in Figure 1.

The first phase of the study was a run-in period of insulin administration (7 ~ 14 days) during which the investigator instructed patients on how to master the injection techniques, so that they were proficient with both the QS-M needle-free injector and glargine insulin pen injections (Lantus, SoloSTAR; Sanofi, Paris, France). Both the type and dosage of oral medication the patients were taking before enrollment in the study were unchanged. A blood glucose meter (Bayer Ascensia Breeze2) was used to monitor the blood glucose concentration 7 times daily on the first

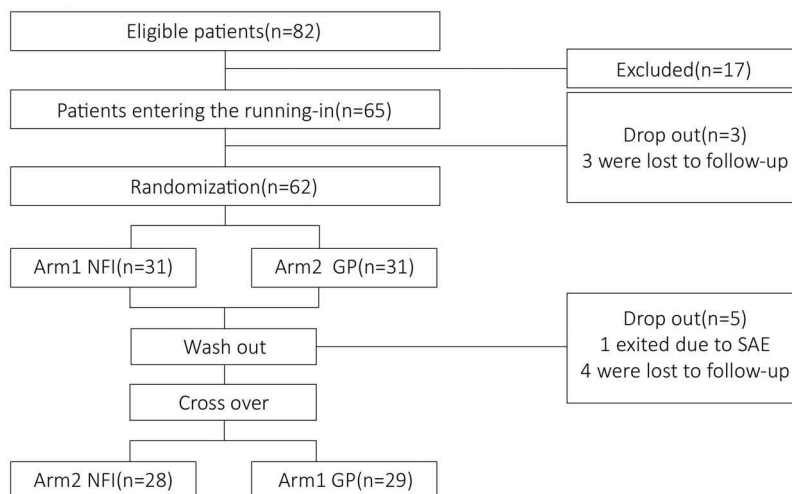


Figure 1. Study design and the flow of patients in the trial. NFI, needle-free injector; GP: glargine pen.

and second days, and the insulin dose was adjusted to achieve the target blood glucose concentration (fasting blood glucose, 4.4–6.0 mmol/L). Patients who achieved the target were then randomised to either the glargine insulin pen or QS-M needle-free injector groups for 7 ~ 14 days as first phase of treatment. The type and dose of oral medication were remained the same as which were taken during the run-in phase. Insulin titration was then performed according to the attending physician's instruction to achieve the target fasting blood glucose level (4.4–6.0 mmol/L) by SMBG, and then the blood glucose level was monitored 7 times a day by SMBG for 2 consecutive days before the washout period. Venous fasting blood glucose concentrations were also measured at the last day of first phase. Patients who still met the inclusion criteria then entered the second trial period. After a washout period, during which all patients from both arms were injected with glargine pen for 7 ~ 14 days. The original QS-M needle-free injector group was crossed over to receive glargine pen injections, and the original glargine pen group was crossed over to receive QS-M needle-free injections. And other procedures were similar to the first treatment phase.

2.3. Endpoints

The main efficacy parameter was the amount of insulin used to achieve the same blood glucose level with the use of the QS-M needle-free injector or glargine pen. The primary outcome is a composite of the change in fasting blood glucose at the final visit relative to baseline of each phase, and insulin dosage to maintain this glucose level. The secondary outcome are the rate of side effects of injection and the pain score in each group.

2.4. Safety and tolerance assessment

After finishing all treatment phases, a questionnaire survey form was provided for each patient to assess their acceptance and tolerance in use of the QS-M injector and the Lantus pen. The form included a few short-answer questions for the aspects of operation convenience, a fear of injection, acceptance, and skin injuries (bleeding, bruise, red and swollen). An injection-associated pain score was rated from 0 – no pain to 10 – pain as bad as you can imagine.

2.5. Evaluation of the glycaemic variability

According to the Experts Consensus on Management of Glycaemic Variability of Chinese Society of Endocrinology (CSE), standard deviation of blood glucose (SDBG), postprandial blood glucose excursions (PPGE), and the largest amplitude of glycaemic excursions (LAGE) was calculated respectively [13]. In brief, finger tip glucose level of fasting, before and 2 h postprandial of each meal and before bedtime were obtained through SMBG using a glucometer (Bayer Ascensia Breeze2) given by researcher. SDBG, LAGE and PPGE were calculated by reported equation after finishing all phases, and target standards of each GV parameters recommended by CSE are SDBG < 2.0 mmol/L, PPGE < 2.2 mmol/L and LAGE < 4.4 mmol/L [14–17].

2.6. Sample size and statistical analysis

The study compared the amount of insulin used to achieve the same blood glucose level administered by QS-M needle-free injector or glargine pen. In the sample size estimation process, $\alpha = 0.025$, $Z_{1-\alpha} = 1.96$ (one-tailed u-test), $\beta = 0.1$, $Z_{1-\beta} = 1.282$ (one-tailed u-test); $n = 6.000$ (according to results of pre-trial and equal standard deviations in two groups). It is considered that 3 IU reduction of insulin is meaningful. According to PASS 11.0 (NCSS, LLC), a sample size of 22 for needle-free and glargine pen groups. Assuming a drop-out rate 20% (which is not expected to be exceeded), the sample size will be adjusted to 27 subjects per treatment group. Considering the convenience of grouping subjects to the six centers, the sample size is enlarged to 30 cases per group, 10 cases per center, so the total sample size for this study is 60. The computer generates random number table. Then using the random number table, the test group and control group were assigned according to the order of enrollment. Data were analysed for the full analysis set (FAS), which included all patients who were randomised to receive insulin by at least one injection method and had a baseline efficacy evaluation, and for the per-protocol set (PPS) which 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) had insulin dosage data available at baseline and the end of the study. The safety analysis set (SS), included all patients who received at least one treatment after randomisation. Demographic data and baseline characteristics were summarised for each patient using frequency distribution and summary statistics, and baseline comparisons were performed. Analysis of the primary outcome included insulin dosage to achieve the same fasting blood glucose level after insulin injection via a needle-free injector or a glargine pen. Consistent with a normal distribution, a *t*-test was used to compare changes in the amount of insulin used with the 2 injection methods. Consistent with skewed data, nonparametric tests were also used to compare changes in insulin levels between the 2 different injection methods. Point estimates and two-sided 95% confidence intervals were calculated for mean changes between the groups.

3. Results

3.1. Basic characteristics of patients

Of the 65 patients originally recruited for the study, 3 patients subsequently dropped out. The remaining 62 patients included 47 males and 15 females with a mean age of 52.71 ± 12.14 years. The baseline characteristics of the 62 randomised patients are shown in Table 1.

3.2. Fasting blood glucose levels

62 patients received both the needle-free injector and glargine pen insulin injections sequentially. At the end of the study, fasting blood glucose obtained by SMBG during the last 7 days in each treatment period showed a trend of lower

Table 1. Baseline characteristics of the patients ($n = 62$).

Characteristic	Value
Sex, n (%):	
Male	47 (75.8)
Female	15 (24.2)
Age, years	52.71 \pm 12.14
Duration of diabetes, years	9.69 \pm 5.75
Blood pressure, mmHg:	
Systolic	126.19 \pm 14.40
Diastolic	78.52 \pm 8.12
Height, cm	169.73 \pm 7.07
Weight, kg	71.53 \pm 7.97
BMI, kg/m ²	24.81 \pm 2.17
Resting heart rate, beats/min	76.84 \pm 8.32
Diabetic complications, n (%):	
Diabetic retinopathy	1 (1.6)
Diabetic neuropathy	1 (1.6)
Coexisting conditions, n (%):	
Hypertension	20 (32.3)
CVD	2 (3.2)
Hyperlipidemia	10 (16.1)
Fatty liver	1 (1.6)
Oral antihyperglycemic agents, n (%):	
Metformin	50 (80.6)
Acarbose	43 (69.4)
Saxagliptin	1 (1.6)
Linagliptin	1 (1.6)
Other drugs, n (%):	
Statins	8 (12.9)
CCBs	10 (16.1)
ARBs	6 (9.7)
ACEIs	2 (3.2)

Data are means \pm SD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease.

fasting glucose when patients using needle-free injector comparing to the insulin pen (Figure 2).

3.3. Insulin dosage changes

At the end of the study, the dose of insulin required to achieve the target fasting blood glucose level was significantly lower in the needle-free injector group than in the glargine pen group (16.14 \pm 5.13 U/day vs 19.25 \pm 6.20 U/day, respectively; $p = 0.0046$). Overall, the same patients who received both injections had mean insulin doses that were 3.11 U/person lower when they were treated with the needle-free injector

compared with the glargine pen injections (Figure 3(a,b)). More interestingly, when different dosages of insulin were taken into account and patients were divided evenly into 3 separate groups according to whether they received a high insulin dose, a middle insulin dose, or a low insulin dose with Glargine pen, the difference gap of the insulin dose required to achieve the target fasting blood glucose level between the needle-free injector and glargine pen groups increased proportionally with the increase of total insulin dose (Figure 3(c)).

3.4. Effects of the injection devices on blood glucose variability

Blood glucose variability is one of the important indicators for evaluating blood glucose control. Diabetic patients with similar fasting blood glucose control may have different risk of complications due to different levels of blood glucose variability. In this study, the 3 indicators of blood glucose variability that were assessed, via self-monitoring of blood glucose (SMBG), were the standard deviation of blood glucose (SDBG), postprandial blood glucose excursions (PPGE), and the largest amplitude of glycaemic excursions (LAGE). The means of these 3 indicators were similar between the needle-free injector and glargine pen groups. Although higher trends of PPGE and SDBG in needle-free group, proportions of patients reached target standards of each GV parameters did not differ significantly between the two treatment groups (Supplemental Fig 1A, B, C).

3.5. Safety and tolerability

All 62 patients completed a treatment acceptability questionnaire at the end of the study. Local adverse reactions such as redness and swelling at the injection site (5.6% in NFI vs 13% in GP) and bruising (5.6% in NFI vs 29.6% in GP) were significantly less frequent in the needle-free injector group than in the glargine pen group (Figure 4(a,b)). Patients felt more comfortable with the needle-free injector and similar workability to operate and acceptability comparing to the Glargine pen. Moreover, needle-free injector significantly reduced their injection fears (9.3% in NFI vs 66.1% in GP) (Figure 4(c,d)). Injection pain scores were also significantly reduced in the

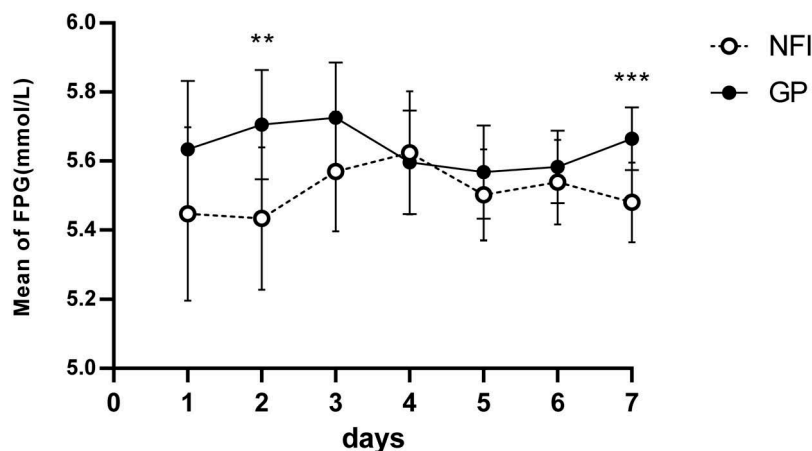


Figure 2. SMBG of fasting glucose of 7 days before the end of each treatment period. Data are shown as mean \pm SEM. ** $p = 0.0376$, *** $p = 0.0151$.

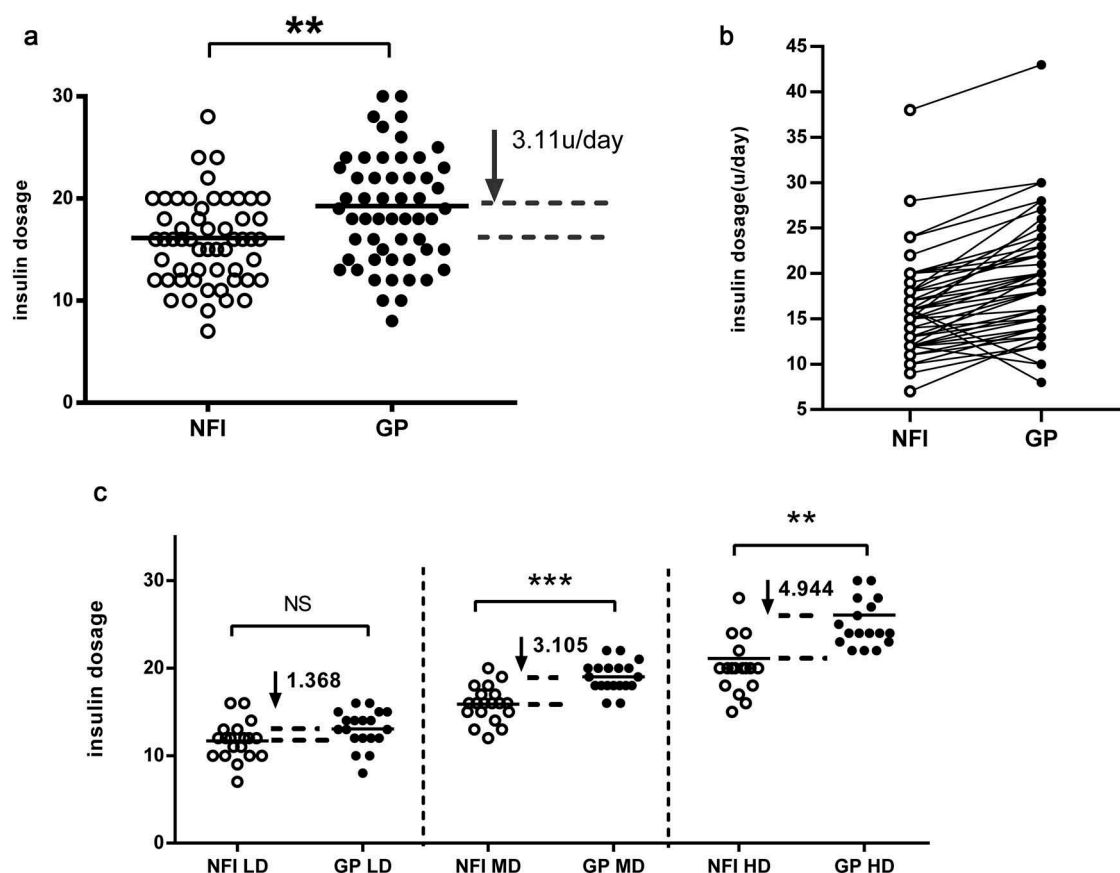


Figure 3. (a) Mean and individual doses of insulin required in the two treatment groups. Filled circles refer to the glargine pen (GP) and empty circle refer to the needle-free injector (NFI). Horizontal bars represent the corresponding mean values for all participants in each group, and the arrow shows the difference between the two groups. $**p = 0.0046$. (b) The two data points of FBG for a particular individual connected by a line. (c) When different dosages of insulin were taken into account and patients were divided evenly into 3 separate groups (according to whether they received a high insulin dose, a middle insulin dose, or a low insulin dose with glargine pen), the differences in the insulin dose required to achieve the target FBG level between the NFI and GP groups for each dose level are shown. NS, not significant; $**p = 0.0062$; $***p < 0.0001$.

needle-free injector group comparing to the glargine pen group (mean scores, 2.61 ± 1.680 vs 4.8 ± 1.430) (Figure 5 (a)). The pain level was scored on a scale of 0–10 where 0 is freedom from pain, 1–3 is mild pain, 4–6 is moderate pain, and 7–10 is severe pain. Almost 80% patients in the needle-free injector group had mild pain scores (i.e. scores of 0–3), however, the pain scores increased to the moderate level when patients shift in the glargine pen group (Figure 5(b)).

4. Discussion

Despite the use of effective combinations of oral medications, the American Association of Clinical Endocrinologists (AACE) guidelines and the consensus guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) state that insulin is invariably the most important treatment to maintain blood glucose stability for diabetic patients with severe complications and patients who are intolerant of oral medications [1]. As insulin analogues and new premix formulations continue to become available for clinical use, the flexibility of insulin application remains a priority. However, the way insulin is injected has stagnated for a very long time compared with changing insulin preparations [18]. To reduce the adverse effects associated

with injections, research into alternative methods of delivery of insulin has continued [6–8,11,12]. Currently, needle-free injectors seem to be the most feasible, convenient, stable and economical method. Needle-free injectors, also known as jet injections, are based on the principle of pressure jets, pushing the liquid from micropores to form a very thin liquid column, which instantly penetrates through the skin to the subcutaneous tissue with a spray-like diffusion, resulting in faster absorption and a more rapid effect [9–12]. As the injected depth with the needle-free injection is limited, nerve endings are stimulated only slightly, and the sting is not as obvious as with needle injections [19,20].

Compared with needle syringes and insulin pens, the injection micropores produced by the jet through the high pressure on the skin surface are only one-quarter and one-third the diameter of insulin pens and the syringes, respectively [20]. Consequently, when treating diabetes, the skin damage caused by the spray is negligible. A cross-sectional survey of the use of the insulin pens also showed that 35.26% of type 2 diabetic patients had lipohypertrophy, and 58.68% had symptoms of bleeding and bruising at the injection site [21]. The QS-M needle-free injector used in this study has been proven to be an effective alternative injection device to insulin pens in previous studies [9,10]. Previous research has shown that the

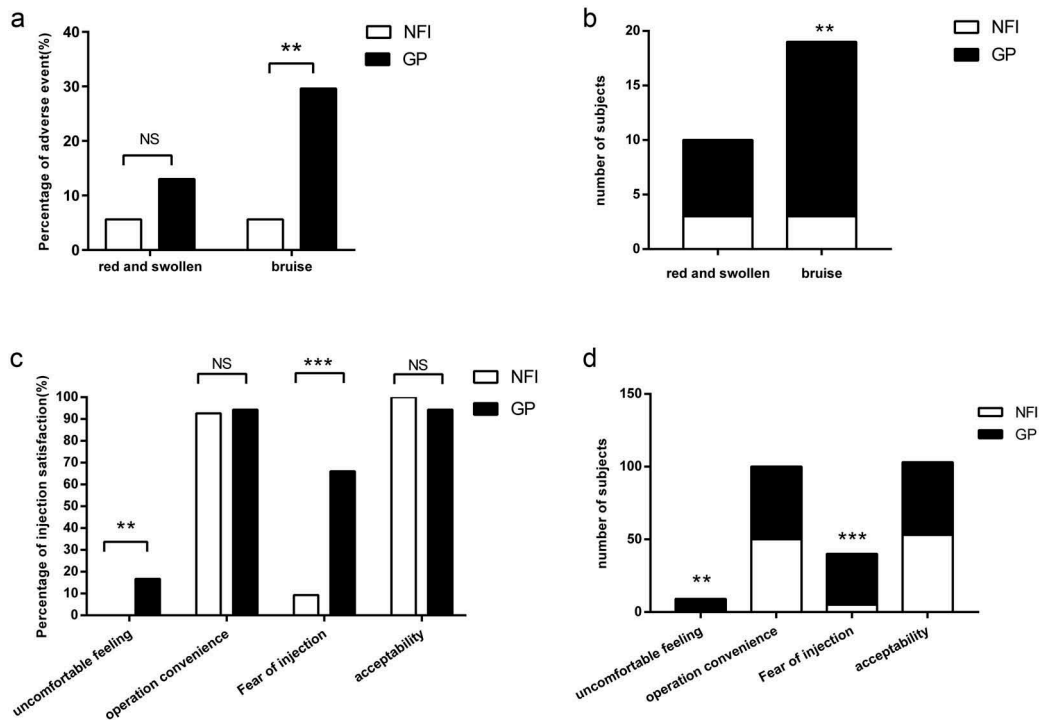


Figure 4. Adverse effects such as redness and swelling at the injection site and bruising were calculated in (a) Percentage of events in needle-free injector (NFI) and glargine pen (GP) treatment, NS, not significant. ** $p = 0.001$. Number of subjects with adverse effects are shown in (b) Percentage of injection satisfaction such as fear of injection are shown in (c) NS, not significant. ** $p = 0.006$, *** $p < 0.001$. (d) Number of subjects in each item of satisfaction questionnaire.

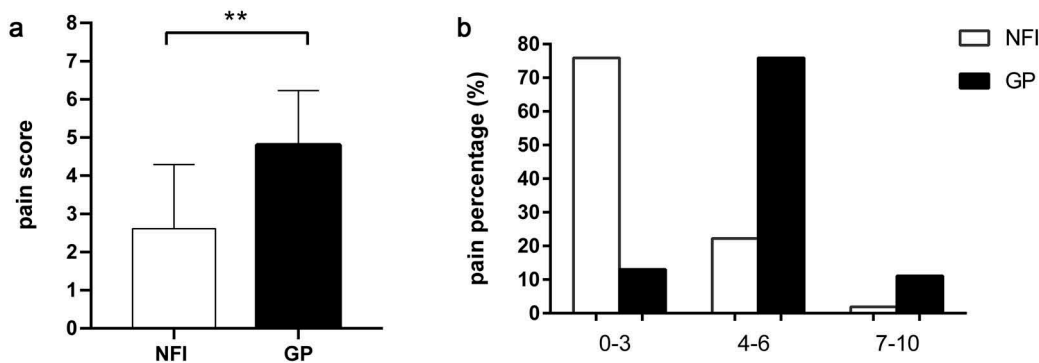


Figure 5. Injection pain scores for both needle-free injector (NFI) and glargine pen (GP) treatment from the questionnaire of patients by the end of the study are shown in (a) With mean ± SEM. ** $p < 0.001$. (b) Pain score level was stratified into three sections, and patients percentage in each pain score section for NFI and GP treatment are shown.

use of the needle-free injector can increase the absorption rate of insulin resulting in a faster onset of action time that mimics physiological insulin secretion patterns [9–11,22]. The present study showed that patients in the needle-free injector group exhibited better acceptability, and had less uncomfortable feelings, fear of injections and pain than patients in the glargine pen group. While the needle-free injector and the glargine pen injections showed similar levels of patient convenience for operation, incidence of topical adverse reactions such as bruising were significantly lower in the needle-free injector group. Use of the needle-free injector was also associated with significantly less pain than glargine pen injections. It is known that a large number of people with diabetes who receive insulin therapy have poor compliance, and the rejection of injections is an important reason for this. By reducing

the anxiety, tension and fear associated with injections, we believe that patients' compliance with treatment will be greatly improved [23,24].

In this study, the most interesting finding was that the use of a needle-free injector significantly reduced the insulin dosage required for glycaemic control, and the degree of the reduction was positively correlated with the insulin dose used. Our results showed that in the group receiving the higher insulin dose, the average insulin dose reduced almost 5U/day (Figure 3(c)) when the needle-free injector was used, which is equivalent to a reduction of about 150 U per month of insulin injection. Patients who are receiving high-dose insulin therapy also have increased risks of weight gain, edema, and antibody production. Such patients can reduce these risks by simply changing the injection method without changing

the insulin form. And from the perspective of health economics, the use of insulin in the long run will not only change the risks and prognosis for type 2 diabetic patients, but also save social medical resources. The treatment used in this study was insulin glargine, which is currently one of the most widely used insulin in the world. Moreover, as basal insulin is the one of the first-line insulin recommended by most guidelines in the world, we believe that our findings will benefit the vast majority of patients using basal insulin.

In the last 10 years, with the good performance of glucagon-like peptide-1 (GLP-1) receptor agonists in clinical studies of cardiovascular outcomes and the efficacy of these agents in reducing blood glucose and producing weight loss, they have been recommended for diabetic patients as a second-line combination treatment option in addition to metformin by more and more international guidelines. For example, in the latest consensus recommendations of the ADA and EASD, it has been clearly pointed out that GLP-1 receptor agonists are one of the first choices for use in combination with metformin in patients with type 2 diabetes who have a history of atherosclerotic heart disease [2]. However, we shouldn't ignore the fact that the way of treatment with injections has become the biggest obstacle to GLP-1 for its clinical application and compliance. As well as for treatment of diabetes, the needle-free injector has good prospects for clinical application of other drugs such as GLP-1 receptor agonists by changing the mode of administration. Moreover, a large number of clinical studies have been conducted on the use of needle-free injectors for growth hormone treatment [25–27]. We believe that this type of injection represents a trend in the future of injection therapy.

The current study has some limitations. First, this trial was an open-label study. We could not exclude possible biases induced by recognition of the insulin injection way. Moreover, the treatment phases were relatively short, and we still do not know if the needle-free injection can remain its advantage on side effects for a long term. Finally, the insulin we use are basal insulin, whether needle-free injector also lower the quick-acting insulin dose for same glycemic control is also worth study in the future.

5. Conclusion

The use of a needle-free injector can lower the dosage of insulin required to achieve good glycaemic control in patients with type 2 diabetes. The results of this study indicate that the benefits of a needle-free injector in the treatment of the type 2 diabetes may be superior to those of glargine pen injections, not only by reducing the adverse effects associated with high insulin dosages, but also by reducing topical adverse reactions and the fear of injections, which should help to improve patient compliance with insulin treatment.

Author contributions

Y Xing and X Xiaomin contributed equally to the study. Y Xing, X Xiaomin and Q Ji conceived and designed the study. X Xiaomin, J Xu, J Liu, Q He, W Yang, J Zhou, B Gao, J Ming, X Liu, J Lai, T Liu and M Sshi contributed to the collection of data. N Zhang, X Liu, L Wang, J Fu and Y Xing analysed and interpreted the data. Y Xing and X Xiaomin wrote the paper. J Ming contributed to the writing of the manuscript. All authors contributed to

discussion, reviewed the manuscript critically for important intellectual content and approved the final version to be published. Q Ji is responsible for the integrity of the work as a whole.

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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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