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Comparison of jet injector and insulin pen in controlling plasma glucose and insulin concentrations in type 2 diabetic patients

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Abstract

This study is conducted to investigate efficacy of an insulin jet injector and an insulin pen in treatment of type 2 diabetic patients. Sixty patients with type 2 diabetes were treated with rapid-acting insulin (regular insulin) and insulin analog (insulin aspart) using the jet injector and the pen in 4 successive test cycles. Postprandial glucose and insulin concentrations in blood were measured over time. Areas under curves of glucose and the insulin were calculated, and efficacy of 2 injection methods in treatment of the diabetes was compared. Regular insulin and insulin aspart administration by the jet injector showed significant decreases in plasma glucose levels as compared to the pen injection ($P<0.05$). Postprandial plasma glucose excursions at the time points of 0.5 to 3 hours were obviously lower in the jet-treated patients than the pen-treated ones ($P<0.05$). Postprandial plasma insulin levels were markedly higher in the jet-treated patients than the pen-treated ones ($P<0.05$). Area under the glucose curve in the pen-treated patients was significantly increased as compared to the jet-treated ones ($P<0.01$). Efficacy of the insulin jet injector in treatment of type 2 diabetic patients is obviously superior to the insulin pen in regulating plasma glucose and insulin levels.

Abbreviations: AUC_{glu} = area under the glucose curve, $AUC_{insulin}$ = area under the insulin curve, HbA1c = glycosylated hemoglobin.

Keywords: insulin pens, jet injectors, postprandial plasma glucose concentrations, type 2 diabetes

1. Introduction

Administration of exogenous insulin used for patients with type 2 diabetes is an important therapy in controlling occurrence of hyperglycemia with its complications. Subcutaneous insulin injection is a common approach to treatment of the diabetes. Approximately 88% and 95% of the diabetic patients in Europe and Japan selected insulin pens for their treatment. About 70% patients in the United States would like to take a needle syringe due to a lower cost as compared to the insulin pen.[1] Since treatment with insulin pens and needle syringes involved skin penetration, the treatment naturally caused a pain and a fear. For those people who have the needle phobia, subcutaneous injection of insulin would be a difficult approach to treatment of diabetes, since the people have a fear of needles which causes them to avoid the treatment. In addition, some patients could use one needle for many times with reasons including saving money, operating convenience, and forgetting replacing the needle. Repeated use of an insulin pen needle has become an increasing health issue due to severe pain occurred at the injection site and the possible contamination of macroscopic blood regurgitation into insulin cartridges in the pen-like injectors.[2]

A jet injector is a type of medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis. The injector disperses insulin into the subcutaneous adipose tissue compartments with efficiency over 90%.[2] In comparison with a needle syringe and an insulin pen, the jet may produce a high pressure of injection and a tiny hole on the surface of skin.[3–5] The medication travels through the hole in the jet device that is about 1/3 to 1/4—the diameters of the pens and the needle syringes, respectively.[6–8] Therefore, the skin injury by the jet is negligible in treatment of diabetes. In previous studies, short-acting insulin and rapid-acting insulin analogs administration by jet injectors showed a peak insulin level achieved within a relatively shorter time as compared to the insulin pens.[9,10] Pharmacokinetics (PK) of insulin administration by the injectors are more close to the PK of endogenous insulin secretion after a meal as compared to the pens.[11] However, contradistinction of treatment effectiveness between these 2 medical devices has not been reported in Chinese type 2 diabetic patients.

In this study, treatment efficacy of insulin and insulin aspart delivered by a jet injector (QS-M, QS Medical Technology; Beijing, China) and an insulin pen (NovoPen 5, Novo Nordisk, Copenhagen, Denmark) was compared in the cohort of type 2 diabetic patients. Our findings provided information regarding benefits of the jet injector in treatment of the patients.

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LG and XX have contributed equally to the article.

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2. Materials and methods

2.1. Patients and inclusion criteria

We randomly recruited 64 patients with type 2 diabetes requiring for insulin treatment in the period from August 2014 to March 2015. Major inclusion criteria for the patients were: clinical diagnosis as Type 2 diabetes according to the 1999 WHO criteria; age ≥18 years and adequate contraceptive measures in women; glycosylated hemoglobin (HbA1c) ≤9.0% and insulin dosage of 20 to 150 IU daily for 8 weeks; no hypoglycemia, ketoacidosis hyperosmolar hyperglycemic state and other serious diseases of heart, brain, liver, and kidney within 6 months before this study; no treatments of anticoagulants, hormones, immunosuppressants, oral antidiabetics except metformin, acarbose, and nateglinide; no pregnant women and women who are breast-feeding; and no contraindication of nateglinide.

All procedures in this study have been reviewed and approved by the Ethics Committee of Beijing Hospital, China (approval number, 2014BJYYEC-039-02). All subjects signed written informed consent forms for this study.

2.2. Insulin administration

Insulin administration by jet injectors was accomplished by the same specialist for all patients, and the site of injection was selected on abdomen. Experiments were carried out via 4 successive test cycles including regular insulin (cycles 1 and 3) and insulin aspart (cycles 2 and 4) administration by jet injectors and pens (Fig. 1). Overall, each cycle comprised original insulin treatment of a 3-day, a washout period of a 3-day, and testing performance of these 2 treatment devices in the final day of the experiments. The study procedures in each cycle were designed as in original treatment, the patients stayed in the previous treatment of regular insulin and insulin aspart at the doses of 20 to 150 IU daily on days 1 to 3; in the washout period, the patients received nateglinide (120–180 mg) 3 times a day on days 4 to 6. The blood glucose levels were continuously monitored for adjusting the dose of nateglinide. The blood samples were collected in the morning of the sixth day after the patients fasted overnight (>8 hours); on the test day, the adjusting amounts of insulin and insulin aspart were prepared with a reduction of 10% based on their own routine doses to avoid occurrence of hypoglycemia. The patients started to eat a 400-calorie meal (50 g egg, 50 g sugar-free bread, and 250 mL milk) after the drugs were injected into the skin of the abdomen using the jet injectors and the pens. The blood samples were collected at the time points (hour) of 0.5, 1.0, 2.0, and 3.0, and then the plasma glucose and insulin concentrations were determined at the indicated times.

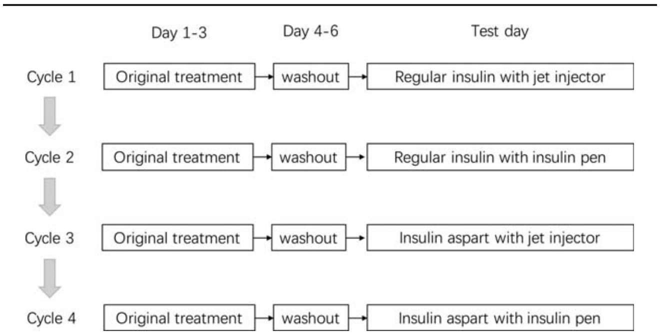

Figure 1. Schematic representation of study research designs. All patients were treated with insulin and aspart by using insulin jet injectors (cycles 1 and 3) or insulin pens (cycles 2 and 4), respectively. Postprandial blood glucose and insulin concentrations were measured on the test day of each cycle.

2.3. Measurement of glycosylated hemoglobin

To identify and select the study cohort that has a lower risk of developing complications related to the diabetes, a test for the HbA1c level was carried out using the affinity chromatography (Ultra 2, PRIMUS, Trinity Biotech Plc., Wicklow, Ireland). Plasma glucose levels were determined via the glucose oxidase method. Area under the glucose curve (AUC_{glu}) and area under the insulin curve ($AUC_{insulin}$) were calculated during a time period of 0 to 3.0 hours after a meal. The insulin and C-peptide levels were measured by competitive inhibition radioimmunoassay (IMMULITE 2000, Siemens Healthineers Global, Erlangen, Germany).

2.4. Assessment of tolerance

After finishing all treatment cycles, a questionnaire survey form was provided for each patient to assess their acceptance and tolerance in use of the jet injectors and the pens. The form included a few short-answer questions for the aspects of satisfaction, ease of use, a fear to the injection, acceptance, and skin injuries (blooding, bruise, and swelling). An injection-associated pain score was rated from 0—no pain to 10—pain as bad as you can imagine.

2.5. Statistical analysis

Data from normal distribution were expressed as mean ± standard deviation on some of the results and were compared using the paired *t* test. Data from skewed distribution were shown as a sample median (quartiles 1 and 3) of an interquartile range on some of the results and were compared using the paired Wilcoxon rank-sum test. All statistical analyses were performed using the SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered significant.

3. Results

3.1. Baseline characteristics of patients

A total of 64 patients were involved in this study. Four of the patients were removed from the first cycle due to pain and bruise on blood collection sites. The rest included 33 males and 27 females with a mean age of 62.5 ± 6.9 years (Table 1). All of the patients successfully finished the tests of a 4-cycle involving treatments with regular insulin and insulin aspart using the jets and the pens.

Table 1

The basic characteristics of patients.

Characteristics	Value
Sex, n (male, female)	(33, 27)
Age, y	62.5 ± 6.9
Diabetic duration, y	13.6 ± 7.8
Systolic blood pressure	130.7 ± 14.1
Diastolic blood pressure	76.1 ± 9.8
Body mass index, kg/m^2	25.2 ± 2.7
Waist–hip ratio	0.9 ± 0.1
Low-density lipoprotein cholesterol, mmol/L	2.6 ± 0.8
Insulin, μIU/mL	28.3 ± 35.2
C-peptide, ng/mL	456.2 ± 243.4
HbA1c, %	7.1 ± 0.8
Insulin-u, median (quartile 1, quartile 3)	6 (4, 10)

HbA1c = glycosylated hemoglobin.

3.2. Effects of injection devices on controlling postprandial plasma glucose levels

Postprandial plasma glucose concentrations during a time period of 0.5 to 3.0 hours were examined in the patients who received regular insulin administration using the jet or the pen. The results are shown in Fig. 2A. In contrast to the pen, treatment with the insulin jet resulted in significant decreases in the glucose levels at 0.5, 1.0, and 2.0 hours after administration (all $P<0.01$). Average values (mmol/L) for the glucose levels at the indicated times were 9.0 ± 2.6 and 9.7 ± 2.9, 10.7 ± 3.0 and 11.5 ± 3.1, and 10.6 ± 3.2 and 11.4 ± 3.5 in the jet- and the pen-treated patients, respectively. Effects of insulin aspart delivered by the 2 dosing devices on controlling postprandial plasma glucose levels were examined, and the results are shown in Fig. 2B. Treatment with the jet significantly decreased the glucose level at the time point of 0.5 hours as compared to the pen ($P<0.05$). An average value for the glucose at the given times was 9.2 ± 2.2 and 9.3 ± 2.3 in the jet- and the pen-treated patients, respectively.

Glucose excursion is a change in glucose concentration from before to after a meal. The change in glucose concentration was examined during a time period of 0.5 to 3.0 hours after the patients received insulin treatment with the jet and the pen. The results are shown in Fig. 3A. Treatment with the jet significantly reduced glucose excursions at the indicated times as compared to the pen (all $P<0.05$). In terms of insulin aspart, excursions in plasma glucose were examined with treatments of the jet and the pen. The results are shown in Fig. 3B. The insulin aspart injection using the jet significantly reduced the plasma glucose excursion at 0.5 hours after administration ($P<0.01$). However, there were no statistical differences in the glucose excursions at other time points between these 2 treatment devices.

3.3. Effects of injection devices on postprandial plasma insulin concentrations

Postprandial plasma insulin concentrations during a time period of 0.5 to 3.0 hours were examined in the jet- or the pen-treated patients. The data for the regular insulin injection are shown in Fig. 4A. Treatment with the insulin jet resulted in significant increases in the plasma insulin levels at the time points of 0.5 and 1.0 hour as compared to the pen (both $P<0.05$). An average concentration (μIU/mL) for the insulin level at the indicated times was shown as 66.7 ± 40.6 and 53.3 ± 33.5; 73.1 ± 47.2 and 66.7 ± 43.6 in the jet- and the pen-treated patients, respectively. In further analysis, there were no differences detected in the

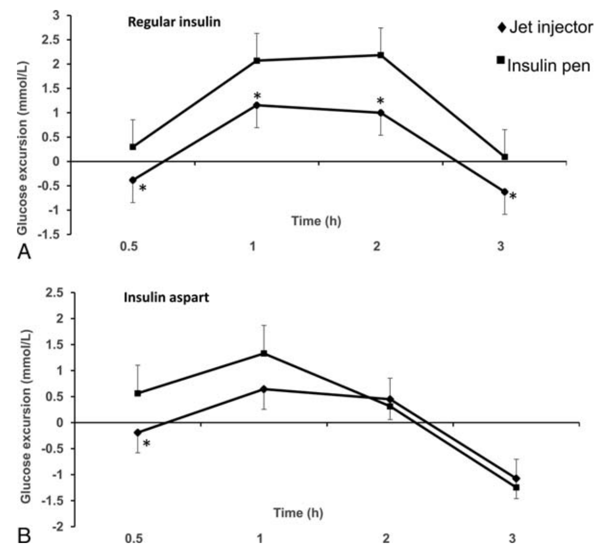

Figure 3. Glucose excursions were examined during a time period of 0.5 to 3.0 hours after the patients received regular insulin (A) or insulin aspart (B) administration by using the jet injectors or the insulin pens. The results were expressed as a sample median of an interquartile range (quartiles 1 and 3). $^{*}P<0.05$ versus insulin pen (n=60).

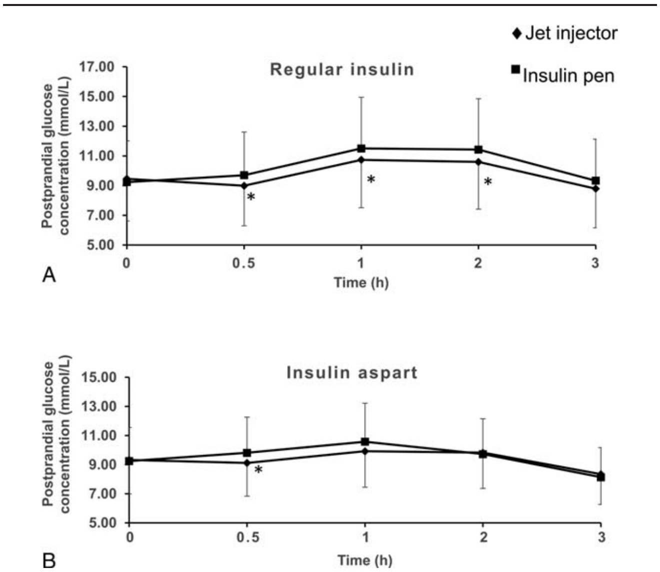

Figure 2. Changes in postprandial plasma glucose concentrations in the patients received regular insulin (A) or insulin aspart (B) administration by using jet injectors or the insulin pens. The results were expressed as a sample median of an interquartile range (quartiles 1 and 3). $^{*}P<0.05$ versus insulin pen (n=60).

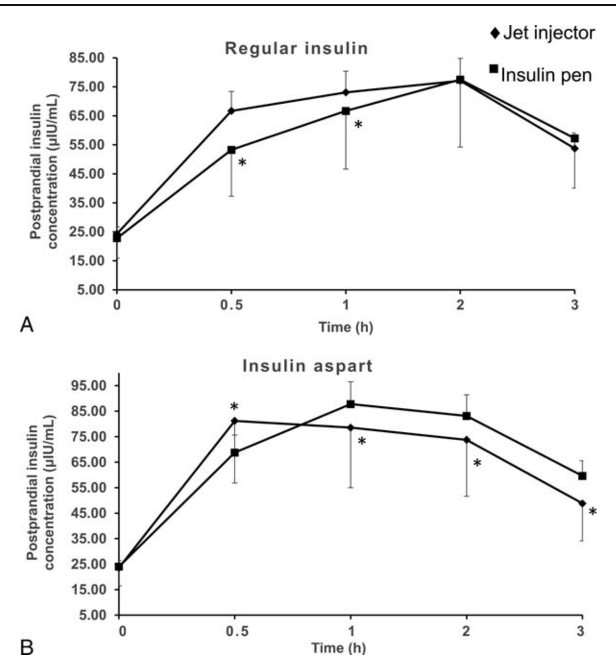

Figure 4. Postprandial insulin concentrations after administration of regular insulin (A) or insulin aspart (B) were examined in the jet- or the pen-treated patients. The results were expressed as a sample median of an interquartile range (quartiles 1 and 3). $^{*}P<0.05$ versus insulin pen (n=60).

Table 2

Effects of injection devices on AUC_{glu} and $AUC_{insulin}$ (n=60).

	Jet injector	Insulin pen	P
AUC_{glu} of regular insulin	1775.5±504.7	1898.8±521.9	0.008
AUC_{glu} of insulin aspart	1686.8±507.1	1722.0±454.5	0.573
$AUC_{insulin}$ of regular insulin	10,070.6±6024.5	11,303.9±6983.2	0.105
$AUC_{insulin}$ of insulin aspart	12,151.9±8749.8	13,116.7±9365.7	0.350

AUC_{glu} = area under the glucose curve, $AUC_{insulin}$ = area under the insulin curve.

insulin levels at the time points of 2.0 and 3.0 hours between these 2 treatment devices. In terms of insulin aspart, postprandial insulin concentrations were determined during a time period of 0 to 3.0 hours, and the results are shown in Fig. 4B. In contrast to the pen, treatment with the jet displayed an increase in the insulin level at 0.5 hours and gradual decreases at the time points of 1.0, 2.0, and 3.0 hours after insulin aspart administration (all $P < 0.05$). Average concentrations (μIU/mL) at the indicated times were shown as 81.2±63.2 and 68.8±58.1, 78.5±60.1 and 87.8 ±66.9, 73.8±55.3 and 83.1±63.5, and 48.8±39.6 and 59.6± 49.8 in the jet- and the pen-treated patients.

3.4. Effects of injection devices on AUC_{glu} and $AUC_{insulin}$

AUC_{glu} and $AUC_{insulin}$ were determined with treatments of the 2 devices, and the results are shown in Table 2. The value of AUC_{glu} for regular insulin but not insulin aspart administration manifested a significant decrease in the blood samples from the jet-treated patients as compared to the pen-treated ones ($P < 0.01$). However, there were no differences in measurement of $AUC_{insulin}$ for regular insulin and insulin aspart injections between the patients treated with the jet injectors and the insulin pens.

3.5. Safety and tolerability

In the cohort of 60 subjects, the results of survey feedback showed 46.6% accompanying with uncomfortable feeling for the insulin pen use, 70% with 1 to 3 degrees of pain at the injection site, and 78.3% with skin injuries, bruise, needle break, and injection failure when using the pen. In general, 67.5% of the patients did not like the insulin treatment of the pens. In contrast, 95% of the jet-treated patients did not have the fear factor for the device use. Despite 4 of the patients being taken off from the study because of an inappropriate insulin jet injection and skin bruise, 93.8% of the patients successfully finished treatment of the jets. Only 21.7% of the patients did not show their interests in use of the jet injector with reasons including a relatively large size of the device and a higher cost. In addition, hypoglycemia occurred in 4 and 6 patients in treatments with the pens and the jets, respectively. However, all of the patients reached to normal blood sugar levels following eating. Overall, there were no serious adverse events observed in the study cohort.

4. Discussion

In this study of 64 patients with type 2 diabetes, 4 patients were removed from the list due to pain and obvious bruising at the site of drawing venous blood and personal requests. Sixty patients completed all test cycles with a success rate of 93.8%. The data revealed that insulin and insulin aspart administration by the jet injectors rapidly decreased postprandial plasma glucose levels at 0.5 hours as compared to the pen use. Insulin jets by the injectors also markedly lowered the glucose levels at the time points of 1.0 and 2.0 hours. These results indicated that efficacy of the jet injectors in treatment of the diabetes was obviously superior to the pen injection, which not only reduced the glucose levels but also shortened the time achieving effectiveness of treatment. Since the jet injects insulin through skin by forcing a high-pressured stream of insulin which can be allowed to spread out more in the subcutaneous layer of skin than the typical pen or needle,[2,12] it is reasonable to speculate that the observed effects accounted for the cause that the insulin jet injector can spread over a larger area of tissue and into bloodstream faster than a subcutaneous injection by the pens.

Postprandial plasma glucose excursion was examined based on the consideration that it is a significant determinant of overall metabolic control as well as an increased risk for diabetic complications. Our results manifested that treatment with insulin jets resulted in reducing postprandial glucose excursion at the time point of 0.5 hours for both target drugs and 1.0 to 3.0 hours for the insulin alone, suggesting that the jet device can lead to the rapid effect of the target drugs on reducing hyperglycemic burden after the meal, which was consistent with previous reports that insulin and insulin analog administration by the jet injectors may achieve to a maximum insulin concentration within a shorter time as compared to the pens.[8,13] It has been reported that the time reaching to the maximum concentration delayed in the obese patients as compared to the lean patients when using the conventional injection.[14,15] However, our patients who had a higher or low body mass index showed a similar time–-concentration response to the jet therapy, suggesting that this dosing device may not only control blood glucose in a normal range but also raise treatment efficacy for these subjects who have a higher body weight.[14]

Changes in plasma insulin concentrations are an important parameter in evaluating treatment effectiveness. Our data showed that plasma insulin levels in the jet-treated patients rapidly elevated at 0.5 hours for both target drugs and 1.0 hour for insulin alone as compared to the pen-treated ones, indicating that the jet injection can enhance the rate of insulin absorption and shorten the time to achieve its effect. In addition, we also noted that the concentration of insulin apart in plasma gradually decreased with extending time in the jet-treated patients, suggesting that insulin aspart administrated by the jet injector has a faster onset and shorter duration of action than regular insulin.[16] Hyperglycemia affects people with diabetes and requires emergency care since it can lead to serious complications. The prompt time–concentration response to insulin therapy would be beneficial in controlling occurrence of complications. Therefore, it is reasonable to consider that the jet injector as a dosing device would be better than the pen in rapidly lowering risk of hyperglycemia. Effects of both treatment devices on AUC_{glu} and $AUC_{insulin}$ were compared with a significant decrease detected in the value of AUC_{glu} of regular insulin. This finding supported the consideration that intervention of the jet injectors was more effective than the pens in reducing the plasma glucose level.[17]

The results of survey feedback indicated that most patients preferred a prescribed insulin dose delivered by the jet injector but not the insulin pen since the jet injection is needle-free with less tissue injury and pain as compared to the pen injection. A cross-sectional survey regarding use of the insulin pens also revealed that 35.26% of type 2 diabetic patients had lipohypertrophy and 58.68% of the patients had symptoms of bleeding and bruising at the injection site,[18] suggesting that the insulin pens used for glycemic control may cause undesirable effects in some of the patients. In addition, the needle-free, easy-to-use jet injectors indeed showed high merits in avoiding the reuse of injection needles and simplifying procedures of insulin delivery. Despite 4 patients who failed to the jet injection with the abovestated reasons, over 93% of the study cohort successfully underwent treatments with insulin and insulin aspart by the jet injectors.

In this study, we investigated efficacy of an insulin jet injector in treatment of type 2 diabetes, emphasizing that intervention of the injector was obviously superior to the traditional insulin pen in controlling postprandial glucose and insulin concentrations. It was worth to point out that use of jet injector would increase health cost for patients at certain degree. In addition, patient training on the operation of insulin jets would be necessary for achieving performance of the medical device.

In conclusion, our study indicates that an insulin jet injector is more effective than an insulin pen in improving plasma glucose and insulin levels in type 2 diabetic patients. Furthermore, the jet injector in the process of insulin delivery conveniently operates with high acceptance and tolerance observed in the investigated cohort.

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