Insulin Injection Technique is Negatively Correlate to Short- and Long-run Glycemic Control in Type 2 Diabetic Patients with Long-Acting Insulin Analogue

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Research Article

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Insulin Injection Technique is Negatively Correlate to Short- and Long-run Glycemic Control in Type 2 Diabetic Patients with Long-Acting Insulin Analogue

Running Title: Insulin injection technique affects glycemic control

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Abstract

Objective: To observe the effects of insulin injection technique (IT) on short- or long-run glycemic control in type 2 diabetic patients (T2D) with long-acting insulin analogue.

Methods: This was a single-center, cross-over, observational and open-labled study. Patients with T2D receiving long-acting insulin analogue insulin were enrolled as inpatients. The study period lasting for 5 days including a 1-day screen period and 4-day continuous glucose monitoring (CGM) period. During CGM period, patients injected insulin themselves from day 1 to day 2, and patient's insulin IT was given by two independent specialist nurses, with insulin injected by nurses from day 3 to day 4. The primary endpoint was the correlation between the insulin IT and the mean amplitude of glycemic excursion (MAGE).

Results: A total of 60 diabetic inpatients were recruited and completed the study. The mean score of patients' insulin IT of patients was lower than that of nurses ($p<0.05$). We observed that the MAGE value was significant different between the two injections period ($P<0.05$), and needle reuse and rotation of injection site were negatively correlated to MAGE and HbA1c values, respectively.

Conclusion: Insulin IT was negatively correlation to short- or long-run glycemic control in T2D patients with long-acting insulin analogue therapy.

Key words: type 2 diabetes; insulin injection technique; A1c; mean amplitude of glycemic excursion; continuous glucose monitoring

Introduction

Insulin resistance and hyperglycemia are two features of type 2 diabetes (T2D)[1]. If oral antidiabetic agents (OADs) are no longer sufficient to maintain glycemic control, insulin therapy will be a strategy of interest[2]. Available evidences indicates that more than half of T2D Asia population are on insulin therapy[3], with most of them are prescribed premixed insulin (77.3%) for maintaining their glycemic control[4-6], following by basal (11.8%) and prandial insulin (10.9%)[7].

Although study demonstrated premixed insulin analogue therapy has beneficial for glycemic variation in Chinese T2D patients[8]. Recently, a pilot study performed in China reporting that only 27% of type 2 diabetic patients receiving premixed insulin analogue therapy had adequate glycemic control (HbA1c ≤7%)[9], which was much lower than those the whole population in China[10] and the USA population[11]. Incorrect insulin injection technique (IT) is a common phenomenon worldwide, which may be the underline reason for the worsen of glycemic control [12, 13]. Lu Yuan, et al. further observed that Chines T2D patients had lower IT, and resuspension, needle reuse and pinching the skin were significantly correlation with glycemic variations (GV) in T2D patients receiving premixed insulin analogue[9]. GV, especially acute postprandial glucose, is an well known risk factor for microvascular and macrovascular complications[14], and GV increases circulating cytokines other than chronic glucose concentrations[15]. Which highlight the importance of IT on glycemic control in diabetic patients with insulin therapy.

More than one fifth Chinese T2D received basal and prandial insulin[7]. However, there are rare data regarding the impact of IT on GV in T2D patients receiving basal and prandial insulin. Continuous glucose monitoring (CGM) provides a potential opportunity to assess the 24-hrs GV in patients with T2D[16]. Therefore, we conducted the single-center, cross-over, observational and open-labled study to observe the relationship between GV and insulin IT in patients with T2D who received long-acting insulin analogue therapy.

Methods

This was a s single-center, cross-over, observational and open-labled study. The study protocol and patient consent forms were approved by the Institutional Ethical Committee of Yancheng third people's hospital, Yancheng, China. All procedures performed were in accordance with the ethical standards of Yancheng third people's hospital, and the Helsinki Declaration of 1964 as revised in 2013. Informed consent was obtained from all patients for being recruited in the study.

Between Jan. and Jun. 2019, patients with T2D who used basal and prandial insulin were enrolled as inpatients in Department of Endocrinology, Yancheng third people's hospital, Yancheng, China. The inclusion criteria were 1) Confirmed diagnosis of T2D; 2) patients aged between 18 and 80 years; 3) insulin administered by insulin pen themselves and insulin doses maintained stable for at least 3 months; and 4) patients were willing to perform CGM. The exclusion criteria were 1) patients with serious cognitive dysfunction; 2) patients with ketoacidosis or hyperosmolar state (coma); 3) patients with pregnancy, breast-feeding, or planning to have a baby; 4) patients with poor compliance and irregular eating and exercise; 5) patients with severe retinopathy or other eye problems.

The study period lasting for 5 days including a 1-day screen period and 4-day CGM period. Patients demography data were recorded at day 0, and fasting serum fasting plasma serum was collected for measurement of HbA_{1c} value on day 1 morning. All recruited patients injected insulin themselves from day 1 to day 2, and patient's insulin IT was given by two independent specialist nurses using a scale containing 15 skill-related items, with minor modification (Table 1), as previously described[9]. From days 3 to days 4, the same type (unopened) and dose of insulin was delivered by nurses.

During the insulin injection period (from day 1 to day 5), all recruited patients were subjected to a 96-hrs retrospective CGM (Medtronic Incorporated, Northridge, USA), as previously described[17, 18]. All patients were instructed to perform self-monitored blood glucose measurements, using OneTouch Ultra Vue blood glucose monitor (LifeScan, Milpitas, CA), before breakfast, lunch, and dinner and before going to bed,

respectively. During the CGM period, three meals per day consisting of a total daily caloric intake of 25 kcal/kg/day were served at 0700, 1100 and 1700 by research nurses, respectively. At the endpoint, CGM data including the mean amplitude of glycemic excursion (MAGE), the 24-hrs mean glucose concentration (MG), the 24-hrs standard deviation of the MG (SD), the incremental area under the curve (AUC) of glucose >10.0 mmol/L and the incremental area over the curve (AOC) of glucose <3.9 mmol/L were recorded and analyzed. The primary endpoint was the correlation between the insulin IT and the MAGE. The secondary endpoints were the differences in glycemic profiles between patient and nurse injection period.

Statistical analysis

The analyses were performed using the SPSS 18.0 (SPSS, Science, Chicago, USA) statistical package. All normal distribution of the data were presented as the means ± SD, and non-normally distributed data were presented as median (25^{th}, 75^{th} percentile). Pearson's analysis or Spearman's analysis in nonparametric variable were performed to analyze correlation relationships between two variables. A two-way ANOVA for repeated measurements was used in the comparison of indices between two groups. Multiple linear stepwise regression analysis was performed to identify factors which correlation with MAGE or HbA_{1c}. All comparisons were 2-sided at the 5% significance level. P value less than 0.05 was considered to be statistical significance.

Results

Between Jan. and Jun. 2019, a total of 65 patients with T2D who used long-acting insulin analogue were enrolled as inpatients in Department of Endocrinology, Yancheng third people's hospital, Yancheng, China. all recruited subjects completely fulfilled the study, with 1patient was excluded due to unfulfilled of self-injection, and 4 patients were excluded because of missing CGM data (>30%). The remaining data from 60 patients (34 males and 26 females) were analyzed at the endpoint. The demographic data were: patients age was 58.4±14.3 years, HbA_{1c} value was 8.6±1.1%, body mass index (BMI) was 23.7±2.8 kg/m^2 and diabetic duration was 13.2±7.6 years, respectively. The duration for using insulin was 7.2±7.6 years, with 2.2±1.4 injection daily, and the mean insulin dose was 0.4±0.4 U/kg/day.

In this study, we assumed scores of insulin IT gained by specialist nurses were 28 points, because they were all trained for diabetic patients care for at least 5 years. We observed that the mean score of patients' insulin IT was significantly lower than those mean score of specialist nurses (22.3±3.6 vs. 28, $p<0.05$). In addition, there was no differences in score of insulin IT between male and female patients (21.6±1.7 vs. 23.8±4.1, $p>0.05$). In the present pilot study, we expected to see a significant improvement in GV during diabetic patients receiving insulin delivered by specialist nurses compared to those who injection themselves period. Our CGM data showed that the GV, in terms of MAGE, SD, CV%, and AUC >10 mmol/L in patient injection period were significantly higher than those of nurse injection period ($P<0.05$, respectively). Although we did not observe significant differences in the MG and the AOC <3.9 mmol/L between the two injection periods (Table2).

To identify whether score of insulin IT was the independent risk factor for short-run and long-run glycemic control in diabetic patients receiving prandial. Multiple linear stepwise regression analysis showed that insulin IT score was significantly negatively correlated to MAGE ($B=-0.18$, $p<0.05$), and HbA1c ($B=-0.31$, $P<0.05$), controlling for gender, age, BMI, duration with insulin, times of insulin injections daily, doses of insulin daily, duration of diabetes. Of importance, in this study, our data indicated that

156 subitems of insulin IT, such as needle reuse, were significantly correlated to MAGE
157 value ($r=-0.42$, $p<0.05$), and the score of rotation of insulin injection site was negatively
158 correlated to HbA1c level ($r=-0.25$, $P<0.05$).
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Discussion

In this pilot study, we observed that nearly half patients with T2D receiving long-acting insulin analogue therapy had their glycemic control. We also found that patients mean IT scores were lower than that of nurses, and the lower IT scores were significantly negatively correlated to the GV, in terms of MAGE, SDBG, and CV%.

Inject site choice, needle use, insulin suspension, and other profile regarding insulin injection, are common problems affect insulin efficacy in outpatient diabetic patients worldwide[12, 13]. In this study, each patient scores of insulin IT were the sum of each subitem score given by two special diabetic nurses according to them performance. we observed that T2D patients with insulin therapy gained dramatically lower IT in the real world, with the scores lost mainly focused on the rotation of injection site and needle reuse.

In this observational study, we observed that only 20% of T2D patients had HbA_{1c} less than 7%. HbA_{1c} is an established index employed for judging long-term glycemic control[19-21]. However, HbA_{1c} value itself can't describe well the glycemic variation, especially acute glucose fluctuation[22-24]. CGM employee is one strength of this study, our data showed that insulin IT not only negatively correlated to HbA_{1c} value, but also negatively correlated to GV. Our findings were in accordance with previous study reporting that patients receiving pre-mixed insulin analogue with lower insulin IT had significantly increase in GV and HbA_{1c} value[9].

Unlike premixed insulin analogue, insulin did not need resuspension before injection[25, 26]. However, other injection problems remain to be resolved. Study revealed that reuse of needles may lead to bad short-run and long-run glycemic control, such as increased in GV and HbA_{1c} levels[13], and lipohypertrophy (LH)[27]. Using self-monitoring of blood glucose data, researchers observed that LH was an independent risk factor for the increase in GV [27, 28]. Unfortunately, nearly half of patients with insulin therapy reuse their needles more than once throughout the world[12]. In this study, only 4.2% patients used their needles once, with most of them had their needles use more than 5 times. Of importance, we found that the needle reuse score was significantly negative related to

MAGE. Much indices delivered from CGM were used to assess GV, such as MAGE, SD, and CV%, in pre- or onset diabetic patients[29-31], of which, there exist a high degree of correlation between SD and MAGE [32, 33]. Interestingly, our data also revealed that the score of needle reuse was negatively correlated to SD.

Rotate of injection site is one of the independent risk factor for induction of HbA_{1c} level, the underline mechanism may partially be the reason of the LH[12, 13, 34, 35]. In this study, we observed that patients with insulin with lower rotation injection site score had significantly increase in MAGE, and HbA_{1c} value, which was slightly different to previous study reporting that score of rotation of injection site was negative correlation with HbA_{1c} value in patients with premixed insulin analogue, rather than MAGE[9]. Future studies identifying the relationship between score of rotation of injection site and HbA_{1c} or MAGE are warranted. Lifted a skinfold is most important in the past decade during insulin injection. However, the score of lifted a skinfold of insulin IT may be not importance as before, because 4 mm needle was used predominately nowadays in China. In this study, all recruited patients lifted their skinfold well.

Several limitations should be addressed in this study. First, the sample size was modest; Second, it was an observational study, not a perspective study, Third, the study population may not be the same as other geography.

In conclusion, our data indicates that insulin IT was negatively correlation to short-or long-run glycemic control in T2D patients with long-acting insulin analogue therapy in Chinese population.

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Authors' Contributions Statement

Y. C., and QH. L. contributed to the conception and design of the study. FD. Y., LP. C., and L. Y. conducted the study and collected data. JQ. Y., L. G., YX. Q., and Q. S. contributed to the data analysis. FW. W., and DP. W. prepared and finally approved the manuscript.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Declaration of conflict of interest:

None.

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342 **Legends**

343 **Table 1** The items and scores of insulin injection technique

344 **Table 2** The 24-hrs glucose profiles between the two different injection groups

345

346

347 **Table 1** The items and scores of insulin injection technique

Items	Scores
Injection at indicated time	2
Yes	2
No	0
Warming up to room temperature before injection	2
Yes	
>30 min	2
<30 min	1
No	0
Checking insulin (dosage and liquid) before injection	2
Yes	2
Partly	1
No	0
Attaching a pen needle	2
Correct	2
Incorrect	0
Priming before injection	2
Yes	2
No	0
Inspection of injection sites	2
Yes	2
No	0
Rotation of injection sites	2
Correct	2
Incorrect	0
Disinfection the skin and injection after disinfection being dried	2
Yes	
Correct	2
Incorrect	1
No	0
Pinching the skin	2
Yes	2
No	0
Needle entry angle	2
Correct	2
Incorrect	0
The time(s) the pen needle under the skin	2
>10	2
5-10	1
<5	0
Pulling needle out while holding dose knob	2
Yes	2
No	0

Needle reuse (times)	2
1	2
2-5	1
>5	0
Insulin (opened and unopened) storage	2
Yes	2
Partly	1
No	0
Total scores	28

348

349

Table 2 The 24-hrs glucose profiles between the two different injection groups

Parameters	Patient	Nurse	P value
MG (mmol/L)	8.4±3.5	8.2±1.1	0.63
SD (mmol/L)	4.2±3.3	2.5±2.2	0.02
MAGE (mmol/L)	6.4±4.0	4.3±1.80	0.01
AUC>10 (mmol/L per day)	0.5 (0.0, 0.8)	0.2 (0.0, 0.3)	0.01
AOC<3.9 (mmol/L per day)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.43

MG: the 24-hrs mean glucose concentration, SD: the standard deviation of MG, MAGE: the 24-hrs mean amplitude of glycemic excursion, AUC>10 mmol/L: the incremental area under curve of plasma glucose >10.0 mmol/L, AOC<3.9 mmol/L: the incremental area over curve of plasma glucose <3.9 mmol/L. Normal distribution data were presented as mean ± SD and non-normal distribution data were shown as median (25^{th}, 75^{th} percentile).