

## Original article

# A 2-way cross-over, open-labeled trial to compare efficacy and safety of insulin Aspart and Novolin R delivered with CSII in 21 Chinese diabetic patients

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**Keywords:** rapid-acting insulin analogue; diabetes mellitus; continuous subcutaneous insulin infusion; capillary glucose

**Background** Subcutaneous absorption is accelerated by the monomeric conformation of insulin Aspart, which provides good glycemic control with a lower risk of hypoglycemia and less body weight increase. In the present study we investigated the efficacy and safety of a rapid-acting human insulin analogue (insulin Aspart) delivered with continuous subcutaneous insulin infusion (CSII) into Chinese diabetic patients.

**Methods** A total of 21 patients with type 1 or type 2 diabetes were recruited for the 2-way cross-over, open-labeled trial, and then randomized to Group A ( $n=10$ , treated with insulin Aspart) or Group B ( $n=11$ , treated with Novolin R). Insulin Aspart and Novolin R were administered by CSII. Capillary glucose concentrations were measured at 8 time points, pre-prandial and postprandial, bedtime (10 pm), midnight (2 am) every day during the treatment.

**Results** The average capillary glucose profiles for the day were much better controlled in Group A than in Group B ( $P<0.01$ ). The blood glucose levels were particularly better controlled in Group A than in Group B at pre-breakfast (( $6.72\pm 1.24$ ) mmol/L vs ( $7.84\pm 1.58$ ) mmol/L,  $P=0.014$ ), post-breakfast (( $8.96\pm 2.41$ ) mmol/L vs ( $11.70\pm 3.11$ ) mmol/L,  $P=0.0028$ ), post-supper (( $8.15\pm 2.10$ ) mmol/L vs ( $10.07\pm 2.36$ ) mmol/L,  $P=0.008$ ), bed time (( $7.73\pm 1.72$ ) mmol/L vs ( $9.39\pm 2.05$ ) mmol/L,  $P=0.007$ ) and midnight (( $6.32\pm 1.16$ ) mmol/L vs ( $7.48\pm 1.36$ ) mmol/L,  $P=0.0049$ ). There was no significant difference in the frequency of hypoglycemic episodes between the two groups.

**Conclusion** Insulin Aspart results in better control of blood glucose levels than regular human insulin (Novolin R) in diabetic patients during delivery by CSII.

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Intensive insulin treatment has been demonstrated to provide an ideal control of blood glucose and hemoglobin A1c (HbA1c) and to delay macro- and micro-vascular complications in diabetic patients.<sup>1</sup> However a therapeutic challenge remains to achieve an ideal blood glucose control with a minimal risk of hypoglycemic episodes. Endogenous insulin secretion is characterized by a mode of continuous basal and meal-related peaks.<sup>2</sup> Basal-bolus insulin therapy by continuous subcutaneous insulin infusion (CSII) aims to mimic physiological insulin secretion. Several studies of insulin Lispro versus regular insulin delivered by CSII in type 1 patients demonstrated that insulin Lispro performed better in lowering HbA1C levels.<sup>3,4</sup>

Proline at position B28 is substituted by aspartic acid in the rapid-acting insulin analogue Aspart (NovoRapid). Subcutaneous absorption is accelerated by a monomeric conformation of insulin Aspart, which provides good glycemic control with a lower risk of hypoglycemia and less body weight increase.<sup>5</sup> However, insulin Aspart is not widely used in delivery by CSII for diabetic patients in China; possibly due to lack of knowledge about its efficacy and safety. In the present study we investigated the efficacy and safety of insulin Aspart by CSII delivery

in 21 Chinese diabetic patients.

## METHODS

### Subjects

Twenty-one adult patients with type 1 or type 2 diabetes were enrolled in this study. All patients had been diagnosed with diabetes for at least 12 months and treated with human insulin (Novolin 30R) for at least 3 months before this study. All eligible patients met the following inclusion criteria: (1) HbA1c $>8.5\%$ ; (2) fasting blood glucose  $>8$  mmol/L and postprandial blood glucose  $>11$

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mmol/L. Patients were excluded if they had hypoglycemic unawareness, a body mass index (BMI) >30 kg/m<sup>2</sup>, pregnancy, lactation, abuse of drugs or alcohol, or use of glucocorticosteroids or oral anti-diabetic drugs.

The two groups had identical baseline BMI, waist-to-hip ratio (WHR), serum triglycerides, cholesterol, fasting and postprandial glucose levels and HbA1c. This study had been approved by the Ethical Committee of Ruijin Hospital and the informed consent was obtained from each subject.

**Research design**

This study was a three-week, open-label, randomized and 2-period cross-over trial (Fig. 1). Patients were randomly allocated into two groups. In group A (n=10), patients received subcutaneous Novolin 30R continuously for three days and then switched to receive Aspart by CSII on the fourth day. The initial Aspart dose was given at 75 to 80 percent of previous Novolin 30R and increased by 0.1 U·kg<sup>-1</sup>·d<sup>-1</sup> until fasting blood glucose was <8.0 mmol/L. In sequence A the Aspart dose was fixed for three days after the adjustment was completed (7–10 days). In sequence B insulin Aspart was replaced by Novolin R, which was maintained for 5 days following sequence A.

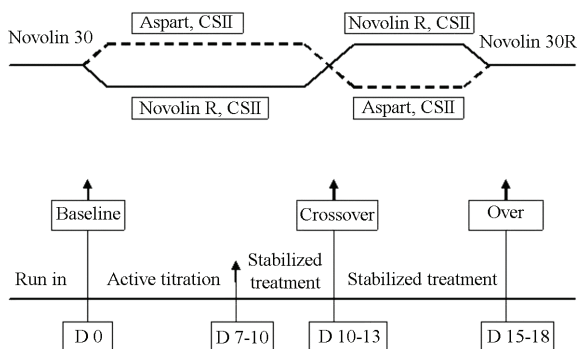


Fig. 1. Research design. The study was plotted as a cross-over, open-label and randomized trial.

In Group B (n=11), patients continued to receive subcutaneous Novolin 30R for three days and switched to receive Novolin R by CSII on the fourth day. The dose of Novolin R was initially given at 75 to 80 percent of the previous Novolin 30R and increased by 0.1 U·kg<sup>-1</sup>·d<sup>-1</sup> until fasting blood glucose was <8.0 mmol/L. In sequence A the dose of Novolin R was fixed for three days after the dose adjustment was finished (7–10 days). In sequence B Novolin R was replaced by insulin Aspart, which was maintained for 5 days following sequence A. 8-point capillary glucose measurements were performed for patients in both groups at pre-, post-prandial and at bedtime at 10 pm, midnight at 2 am every day during the treatment.

Half of the daily insulin dose was administrated as basal and the other half as meal bolus. The insulin dose was

reduced by 0.05 U·kg<sup>-1</sup>·d<sup>-1</sup> if hypoglycemic episodes occurred more than twice a day. The target of blood glucose control was 5.0–8.0 mmol/L for fasting and <10.0 mmol/L for post prandial.

MiniMed 508 insulin pump (Medtronic Inc., MN, USA) was used for CSII. One Touch blood glucose meter (Lifescan, Inc., Milpitas, CA, USA) was used for capillary glucose measurement.

**Statistical analysis**

A comparison of insulin Aspart and Novolin R was carried out in Group A and Group B using a 2-tailed test with a significance level of 0.05. Data from all patients enrolled in this study were taken into account. The baseline characteristics in each group were shown by mean ± standard error (SE) and compared with the *t* test. The efficacy and safety variables were displayed by numerical scales.

**RESULTS**

**Baseline data**

A total of 21 patients (14 males, 7 females; 15 type 1 diabetes, 6 type 2 diabetes) were studied. None of the patients discontinued. There were no statistically significant differences between the two groups with respect to clinical characteristics, baseline, fixed or total daily insulin doses (Table 1).

**Eight-point capillary glucose profiles**

The results of eight-point capillary glucose profiles were shown in Table 2. The average glucose levels in patients treated with insulin Aspart were significantly lower than those treated with Novolin R. The glucose levels were particularly better controlled in the insulin Aspart group than in the Novolin R group at pre-breakfast ((6.72±1.24) mmol/L vs (7.84±1.58) mmol/L, *P*=0.014), post-breakfast ((8.96±2.41) mmol/L vs (11.70±3.11) mmol/L, *P*=0.0028), post-supper ((8.15±2.10) mmol/L vs (10.07±2.36) mmol/L, *P*=0.008), bed time ((7.73±1.72) mmol/L vs (9.39±2.05) mmol/L, *P*=0.007) and 2 am ((6.32±1.16) mmol/L vs (7.48±1.36) mmol/L, *P*=0.0049) (Table 2 and Fig. 2). Glucose fluctuation during the mutual switch between insulin Aspart and Novolin R did not show any difference between the two groups (data not shown).

**Hypoglycemic episodes**

Seven hypoglycemic episodes occurred in five patients treated with insulin Aspart and four episodes in three patients treated with Novolin R. There was no significant difference in the frequency of hypoglycemic episodes between the two groups.

**DISCUSSION**

Human insulin analogues are developed by DNA recombination technology. Both rapid-acting and long term insulin analogues are available for diabetic patients. Three rapid-acting insulin analogs are currently available:

**Table 1.** Clinical characteristics of patients with diabetes at baseline

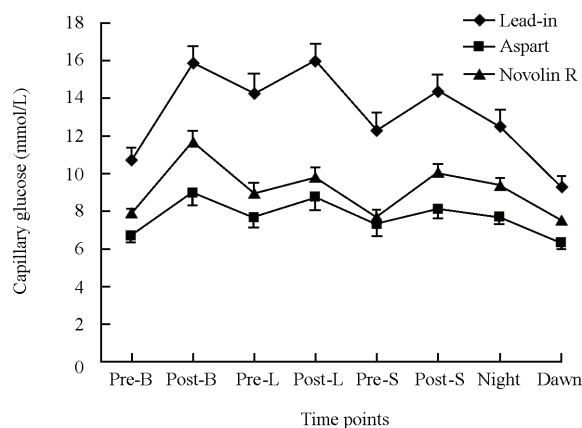
Parameters	Group A (n=10)	Group B (n=11)	t values	P values
Type 1/Type 2	4/6	2/9	–	–
Female/Male	3/7	4/7	–	–
Age (yr)	45.60±22.58	53.00±15.32	0.8862	>0.05
DM duration (yr)	6.22±8.18	8.20±5.12	0.6748	>0.05
BMI (kg/m <sup>2</sup> )	22.40±6.20	22.33±2.04	0.0354	>0.05
WHR	0.90±0.08	0.90±0.06	0.1981	>0.05
TG (mmol/L)	1.24±0.61	1.53±0.80	0.9265	>0.05
TC (mmol/L)	4.77±0.46	5.43±1.09	1.7733	>0.05
FBG (mmol/L)	11.13±3.44	13.99±7.71	1.0776	>0.05
PBG (mmol/L)	18.98±6.40	20.73±9.31	0.4967	>0.05
HbA1c (%)	9.65±2.71	9.25±1.05	0.4543	>0.05
Initial Novolin 30 R (U·kg <sup>-1</sup> ·d <sup>-1</sup> )	0.76±0.28	0.71±0.21	0.4658	>0.05
Fixed Aspart or Novolin R (U·kg <sup>-1</sup> ·d <sup>-1</sup> )	0.75±0.27	0.72±0.26	0.2593	>0.05
Basal Novolin R (U/d)	23.40±11.87	21.87±9.02	0.3345	>0.05
Bolus NovolinR (U/d)	20.50±7.23	22.55±8.86	0.5771	>0.05
Basal Aspart (U·kg <sup>-1</sup> ·d <sup>-1</sup> )	23.44±11.86	21.87±9.02	0.3434	>0.05
Bolus Aspart (U·kg <sup>-1</sup> ·d <sup>-1</sup> )	20.50±7.23	22.55±8.86	0.5771	>0.05

DM: diabetes mellitus; BMI: body mass index; WHR: waist-to-hip ration; TG: triglyceride; TC: total cholesterol; FBG: fasting blood glucose; PBG: postprandial blood glucose; HbA1c: hemoglobin A1C.

**Table 2.** Eight-point capillary glucose profile

Time points	Lead-in (n=21)	Aspart (n=21)	Novolin R (n=21)	t values	P values*
Pre-breakfast	10.79±2.53	6.72±1.24	7.84±1.58	2.5554	<0.05
Post-breakfast	15.88±4.00	8.96±2.41	11.70±3.11	3.1913	<0.01
Pre-lunch	14.26±4.77	7.68±2.69	8.93±2.67	1.5113	>0.05
Post-lunch	15.97±4.25	8.75±2.47	9.82±3.20	1.2129	>0.05
Pre-supper	12.31±4.27	7.26±1.76	7.72±2.42	0.7044	>0.05
Post-supper	14.35±4.17	8.15±2.10	10.07±2.36	2.7851	<0.01
Bedtime	12.51±3.93	7.73±1.72	9.39±2.05	2.8427	<0.01
2 am	9.27±2.74	6.32±1.16	7.48±1.36	2.9738	<0.01

\*Comparison between Aspart and Novolin R groups.



**Fig. 2.** Eight-point capillary glucose profiles during CSII treatment with Aspart or Novolin R. The data was shown as mean ± SE. Pre-B: Pre-breakfast; Post-B: Post-breakfast; Pre-L: Pre-lunch; Post-L: Post-lunch; Pre-S: Pre-supper; Post-S: Post-supper.

insulin Lispro (Eli Lilly), insulin Aspart (Nova Nordisk) and insulin Glulisine. They are all safe, flexible and effective in achieving target postprandial glycemic control. In insulin Lispro the normal sequence of proline at position 28 of the B chain and lysine at position 29 are reversed (LysB28, ProB29; Lispro).<sup>6</sup> Insulin Aspart is made from insulin molecules by substitution of proline at position B28 with negatively charged aspartic acid (AspB28; Aspart). The B28 aspartic acid substitution only results in a small local conformational alteration at the

C-terminus of the B-chain. Insulin Glulisine (LysB3, GluB29; Glulisine) is the most recently approved rapid-acting insulin analogue.<sup>7-9</sup> Such conformational changes enhance subcutaneous absorption compared to conventional human insulin. Physiological pharmacokinetics showed an obvious role for rapid-acting insulin in reducing postprandial glucose to a greater extent.<sup>10</sup>

Human rapid-acting insulin analogues have a quicker start and a shorter duration of action than regular insulin. Several studies showed that human rapid-acting insulin analogues could lower HbA1c and postprandial blood glucose,<sup>11</sup> raise treatment satisfaction and life quality when compared with regular human insulin.<sup>12,13</sup> Rapid-acting insulin analogues can be injected immediately before meals and are considered as a safe and effective alternative of regular insulin.<sup>14</sup> So patients benefit from greater compliance to the insulin regimen with increased flexibility and freedom in daily activities. CSII is based on a pump that works like a pancreas which can provide a reasonable basal and bolus insulin supplementation. Rapid-acting insulin is considered as an ideal insulin for CSII use.<sup>15</sup> Several open-label randomized cross-over trials demonstrated that CSII with insulin Liapro had better control of postprandial hyperglycaemia and slightly, but significantly, reduced glycated haemoglobin, with a lower daily insulin requirement and similar, or even fewer, hypoglycaemic episodes.<sup>16-20</sup>

In some other clinical trials on CSII therapy with insulin Aspart showed better glycemic control than MDI therapy with insulin Aspart/insulin Glargine. The glycemia improvement with CSII did not parallel an increase of the insulin dose.<sup>21</sup> In our study, the average glucose levels were controlled much better in the insulin Aspart group than in the Novolin R group. The hypoglycemic episodes with insulin Aspart were also similar to episodes with Novolin R. Insulin Aspart was well-tolerated by our study subjects.

Our study demonstrated that the rapid-acting human insulin analog Aspart not only showed a better blood glucose control, but also had similar hypoglycemic events when compared with regular human insulin Novolin R when delivered with CSII. It suggests that rapid-acting human insulin analogues could be widely used with CSII in type 1 and type 2 diabetic patients.

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