

## Abstract

Children with type 1 diabetes mellitus often receive multi-injection therapy (MIT) with human insulin, but delayed absorption, along with unpredictable exercise and eating patterns, place this group at risk of frequent, severe hypoglycemia, and impaired neuropsychological development. Rapid-acting insulin analogs and continuous subcutaneous insulin infusion (CSII) more closely approximate physiological insulin delivery. This open-label trial in 61 preschool children using human insulin MIT for type 1 diabetes (mean age = 5.2–5.7 years; mean A1c = 7.4–7.7) compared efficacy, safety and caregiver quality of life (QoL) between the rapid-acting analogue insulin aspart (IAsp) in CSII, and IAsp or SHI plus NPH in MIT. After a 3-week human MIT run-in, patients were allocated to CSII (n=20), or randomized to MIT with SHI (15–30 min before meals; n=21), or IAsp (immediately premeal; n=20), plus NPH, for 26 weeks. ANOVA of mean A1c at 26 weeks showed no change from baseline in all groups, and no difference between groups (7.7% for CSII; 7.6% in MIT groups). ANOVA of glucose AUC over 24 hrs, reflecting mean overall glycaemic control, demonstrated equivalency in all groups (mean = 200.1–219.8 mmol/l/h). Of the 149 adverse events reported, only four were severe and none treatment-related. Most hypoglycemic episodes were minor, with three major episodes in the CSII group and one in the IAsp MIT group; mean hypoglycemic event duration was lower in the IAsp groups (p=NS). Using Kruskal-Wallis testing to analyze caregiver QoL questionnaires, total scores indicated superior QoL with CSII (4.0 versus 2.2 and 0.3 for IAsp MIT and SHI MIT, respectively; p=0.04), and notable satisfaction with low hypoglycemic frequency (CSII score +0.9 versus –0.6 and –1.1 in SHI and IAsp MIT groups, respectively; p=0.0002). Conclusions: IAsp CSII and MIT offer similar glycaemic control to SHI MIT, and are well tolerated, but caregiver satisfaction is greatest with CSII.

## Background and Aim

MIT using human insulin is an effective method of achieving glycaemic control in children with type 1 diabetes mellitus, but delayed insulin absorption, along with unpredictable exercise and eating patterns, increase the risk of hypoglycemia and impaired future neuropsychological development. Frequent injections can also raise issues of peer self-consciousness and self-esteem in pre-school and school-age children. Rapid-acting insulin analogs and CSII offer a more physiological pharmacokinetic profile and greater flexibility in dose timing, and CSII can improve patient QoL when correctly implemented.<sup>1,2</sup>

This study aimed to compare glycaemic control, safety and caregiver quality of life in pre-school children receiving insulin aspart CSII, and insulin aspart and human insulin MIT.

# Insulin Aspart Continuous Subcutaneous Infusion in Preschool Children: Superior Caregiver Satisfaction Versus Multi-Injection Therapy

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## Patients and Methods

This open-label trial in 61 preschool children using human insulin MIT for type 1 diabetes compared efficacy, safety and caregiver QoL between IAsp in CSII, and IAsp or SHI plus NPH insulin in MIT. After a 3-week human insulin MIT run-in, patients were allocated open-label to CSII (n=20) or randomized to MIT with SHI (15–30 min before meals; n=21) or IAsp (immediately pre-meal; n=20), plus NPH, for 26 weeks. Efficacy measures were A1c and 24-hour overall glycaemic control at study endpoint; safety endpoints included frequency of AEs, and frequency and duration of major and minor hypoglycemic episodes. QoL was evaluated using a questionnaire that offered 5-point scale answers and was derived, in part, from the Questionnaire for Parents of Children with Diabetes.<sup>3</sup> This trial was conducted in accordance with Good Clinical Practice.

## Results

Baseline demographics for age, weight and baseline A1c were similar in the three treatment groups (Table 1).

Table 1. Mean baseline demographics for the study population

	IAsp CSII	IAsp MIT	HI MIT
Age (years)	5.7	5.2	5.4
Weight (kg)	21.1	20.1	21.5
A1c (%)	7.7	7.4	7.5
Duration of diagnosed diabetes (months)	30.2	23.2	24.0
Duration of exposure to trial drug (days)	208	195	208

## Similar glycaemic control

Mean A1c values after 26 weeks of treatment remained unchanged from baseline in all three groups. Mean overall glycaemic control over 24 hours was comparable in all groups, although the absolute value was lower in the CSII group (CSII, IAsp MIT and HI MIT groups: 200.1, 219.8 and 211.8 mmol/L\*hrs, respectively; p=0.55). In the CSII group, diurnal fluctuation in blood glucose levels (approximately

3.0 mmol/L) was less than that in both MIT groups (4.0 mmol/L), and mean glucose levels between 07:00 and 19:00 were also lower.

## Superior carer QoL and reduced hypoglycemia with CSII

While all groups demonstrated an increase in QoL during the trial, the increase in mean total QoL score was significantly greater for CSII, compared with IAsp and HI MIT (p=0.04 between groups) (Table 2). Carers of children receiving IAsp CSII found the frequency of hypoglycemic events acceptable, whereas a decrease in scores among carers of children in the IAsp and HI MIT groups suggested an unacceptably high frequency of hypoglycemia (Table 3).

Table 2. Quality of life (QoL) total scores for carers of children receiving treatment indicated the greatest satisfaction when children were switched to IAsp CSII. p=0.04 for changes between treatment groups.

	IAsp CSII	IAsp MIT	HI MIT
At randomization			
Median	28	28	28
Range	16–36	14–33	20–34
At end of trial			
Median	32	29.5	28.5
Range	23–36	23–34	22–33
Mean change during treatment (SD)	+ 4 (5.1)	+ 2.2 (5.6)	+ 0.3 (4.4)

Table 3. Carer responses to the question ‘How often have you felt your child’s blood sugar to be unacceptably low?’ indicated the greatest satisfaction in carers of children switched to IAsp CSII. p=0.0002 for changes between treatment groups using the Kruskal-Wallis test.

	IAsp CSII	IAsp MIT	HI MIT
Median score at randomization (SD)	3.2 (1.4)	4.1 (1.0)	3.7 (1.3)
Median score at trial endpoint (SD)	4.1 (1.2)	3.1 (1.1)	3.2 (1.1)
Mean change from randomization to trial endpoint (SD)	0.9 (1.2)	–1.1 (1.3)	–0.6 (1.4)

Frequency of hyperglycemic events was acceptable to carers in all groups; those whose children received IAsp CSII reported greater satisfaction, although this was not statistically significant.

## Good tolerability with few episodes of hypoglycemia

A total of 55%, 50% and 71% of patients in the IAsp CSII, IAsp MIT and HI MIT groups, respectively, reported at least one AE. The majority were mild in severity and unrelated to trial products; of the four serious AEs reported, two in each IAsp group, only one (a brief hypoglycemic episode in an MIT patient) was thought to be treatment-related. There were no withdrawals due to AEs.

The majority of hypoglycemic episodes were minor in severity, although one CSII subject reported three major events, and one IAsp MIT subject, one major event. The incidence and duration of minor hypoglycemic events were equivalent between groups.

## Conclusions

- CSII with insulin aspart offers equivalent glycaemic control to multi-injection therapy (MIT) in preschool children, with a low rate of hypoglycemic events
- Carers describe improved quality of life and acceptable frequency of hypoglycemic events when insulin aspart CSII replaces MIT

## References

- Maniatis A, Klingensmith G, Slover R, et al. Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. *Pediatrics* 2001;107:351–6.
- Boland E, Grey M, Oesterle A, et al. Continuous subcutaneous insulin infusion: a new way to lower risk of severe hypoglycaemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999;22:1779–84.
- Gerber R, Cappelleri J, Abertz L, Quattrin T. Development and validation of the Parents of Children with Diabetes Questionnaire – a questionnaire to assess treatment satisfaction and well-being. Presented as a poster at the 18th International Diabetes Federation Congress, August 24–26, 2003, Paris, France.

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