

Original Article

Changes in Glycemic Control and Quality of Life in Pediatric Type 1 Diabetics with Continuous Subcutaneous Insulin Infusion of Insulin Aspart Following Multiple Daily Injection Therapy

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Abstract. The efficacy of continuous subcutaneous insulin infusion (CSII) of the rapid-acting insulin analogue, insulin aspart, was evaluated in 26 patients with childhood-onset type 1 diabetes aged between 6 and 18 yr who had been on basal-bolus therapy (multiple daily injection (MDI) of regular human insulin or rapid-acting insulin and intermediate/long-acting insulin). The glycemic control in the patients was evaluated based on changes in the clinical parameters and the patient quality of life (QOL) was evaluated by using the insulin therapy-related QOL questionnaire. Twenty two patients continued CSII during the 6-mo study period. The mean HbA1c was $7.8 \pm 1.8\%$ at baseline and it decreased to $7.4 \pm 0.8\%$ at 6 mo after the start of the CSII. Overall, no decrease of the QOL post-CSII initiation was noted. The possible superiority of CSII as compared to MDI was suggested for patients who “eat out” or “have to look for an appropriate place for insulin injection.” Aside from an inadequate indwelling needle placement detected after the initiation of CSII in several patients, no adverse event associated with NovoRapid® was seen. In conclusion, CSII of rapid-acting insulin appears to be a useful therapy for patients with childhood-onset type 1 diabetes.

Key words: rapid-acting insulin, childhood-onset type 1 diabetes, continuous subcutaneous insulin infusion, HbA1c, insulin therapy-related QOL

Introduction

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Continuous subcutaneous insulin infusion (CSII) is a type of intensive insulin therapy in which basal and bolus insulin secretion is replaced by round-the-clock insulin supplementation via a pump attached to an infusion set inserted in the abdominal wall. The

recent advent of rapid-acting insulin analogues allows replacement of the bolus insulin secretion immediately before a meal in CSII, improving the convenience of insulin therapy. Unlike the traditional regular human insulin, rapid-acting insulin analogues contain buffers that reduce pump troubles, such as obstruction of the infusion tubing. The usefulness of rapid-acting insulin analogues in CSII has been reported both in Japan (1, 2) and other countries (3, 4).

Recent insulin pumps allow programming of various basal infusion doses at different times of day in order to accommodate changes in the required basal insulin level caused by the “dawn phenomenon” and other factors. Nowadays, indwelling needles, so-called infusion sets, are used in the infusion plastic tube inserted under the abdominal wall instead of the traditional winged needles, enabling continued tube placement for up to several days. Thus, the usefulness of CSII has been enhanced by a variety of improvements in its administration method.

With the improvement of infusion devices, an increasing number of studies have been conducted on CSII in patients with childhood-onset type 1 diabetes (5–7). Fox *et al.* (7) compared traditional insulin therapy (multiple daily injections (MDI) of intermediate-acting and regular insulin) and CSII allocated randomly to 23 patients of childhood-onset type 1 diabetes aged between 1 and 6 years. No difference in glycemic control was seen between the two treatment groups, and CSII was concluded to be comparable to traditional therapy based on the Pediatric Diabetes quality of life (QOL) questionnaire filled out by the parents of the study participants.

While CSII, an insulin injection therapy aimed at reproducing the endogenous insulin secretion seen in nondiabetics, has excellent therapeutic efficacy, the patient QOL may be compromised because of the need to wear of the infusion set and also of the need for the insulin pump to be carried by the patient all the time.

We evaluated the efficacy of the rapid-acting

insulin analogue NovoRapid® for CSII in patients with childhood-onset type 1 diabetes, based on the overall assessment of the medical (i.e., glycemic control) and psychological (QOL survey to determine patient satisfaction with the insulin therapy) aspects of the insulin therapy.

Study Design and Method

The current study was jointly conducted by the Departments of Pediatrics at Osaka City University Hospital, Surugadai Nihon University Hospital, Tokyo Women’s Medical University Medical Center East, and University of Yamanashi Hospital. The prospective intervention study was conducted for 48 wk between June 2004 and May 2005, after obtaining informed consent from the patients and their parents to participate in the study.

Study subjects

Patients with childhood-onset type 1 diabetes who had been on intensive insulin therapy (basal-bolus therapy; MDI of regular human insulin or rapid-acting insulin and intermediate/long-acting insulin) were enrolled as subjects of the study (hereafter referred to as study subjects). The enrollment criteria included a chronological age of 6 to 18 yr, daily insulin requirement of 0.7 to 1.5 U/kg/day, HbA1c less than 12%, and currently practicing self-monitoring of blood glucose (SMBG) with a thorough understanding of the procedure. The exclusion criteria included occurrence of serious complications during the study therapy, request from the patient or his/her family for withdrawal from the study, occurrence of unexpected adverse reactions to the prescribed drugs, and other conditions based on which the patient was determined by the treating physician to be ineligible for the study.

Twenty-six patients were enrolled in the study; however, CSII had to be discontinued in 4 patients. The remaining 22 patients (4 male and 18 female) were included in the efficacy analysis. The patient background characteristics

Table 1 Patient background (n=22)

Item	Mean \pm SD	Range
Age (yr)	14.2 \pm 2.6	8.3–18.8
Height (cm)	155.7 \pm 10.3	126.0–172.6
Weight (kg)	50.3 \pm 11.3	27.0–66.6
BMI (kg/m ²)	20.5 \pm 2.8	16.5–25.2
Percent overweight (%)	3.1 \pm 8.9	–16.4–12.5
Age at the time of onset (yr)	6.8 \pm 3.9	0.0–14.0
Duration of DM (yr)	7.5 \pm 3.8	1.0–17.0

Percent overweight was determined on the basis of Japanese standard body weights for height by age and sex, $100\% \times (\text{actual body weight} - \text{standard weight})/\text{standard weight}$, and overweight exceeding 20% of ideal weight is defined as obesity in Japan.

Table 2 Pre-CSII insulin dosages and administrations and number of patients

Dosage and administration	Number of patients
Q-(Q&R)-Q-N	1
Q-Q-Q-L	13
Q-Q-Q-N	2
R-R-Q-Q-20R	1
R-R-R-N	5

N, intermediate; 20R, 20% regular; Q, rapid-acting; R, regular; L, long-acting.

are shown in Table 1.

Table 2 shows the pre-CSII insulin dosages and patterns of administration in the study subjects based on the available data.

Grouping of study subjects

The pre- and post-CSII parameters were compared without grouping of the study subjects.

Dosing method

CSII introduction: Inpatient-based introduction of CSII was performed generally in order for the patients to learn how to use the insulin infusion pump and circuit (infusion set) with a thorough understanding of the principles, how to prepare the insulin, about the characteristics of insulin aspart NovoRapid[®],

about potential pump and circuit troubles, how to cope with hypoglycemia, how to deal with and the causes of hyperglycemia, and how to contact their physicians in case of emergency. CSII was also introduced on an outpatient basis for patients for whom inpatient-based introduction was not possible.

Eighty percent of the daily dose of insulin used prior to the introduction of CSII was used as the starting dose for the CSII. Half of this starting daily dose was administered as the basal dose (A) and the remaining half as the pre-meal bolus dose (B). The initial basal infusion rate was A/24 (U/h) and the initial pre-meal bolus dose was B/3 (U).

As a general rule, the study subjects were instructed to visit the clinic once a month. They could consult their physicians for insulin dose adjustment as frequently as possible during the first several days of the study therapy. Emergency contact information (ex. telephone and fax numbers, e-mail address) was provided to the study subjects at the beginning of the study.

Insulin dose adjustment: With the initial target blood glucose of 80 to 200 mg/dl, the basal infusion was adjusted every hour (by 0.1 U/h). At 1 mo post-CSII introduction, the basal infusion was fine-tuned every hour so that the blood glucose before meals, at bedtime, and at 3 a.m. was maintained between 70 to 150 mg/dl. The

bolus dose was adjusted by 1 unit at a time to keep the blood glucose at 90 min postprandial at 180 mg/dl or less in patients who had achieved the target blood glucose (70 to 150 mg/dl) at 1 mo post-CSII introduction.

Self-monitoring of blood glucose: Blood glucose was measured 3–5 times a day: before each meal, at bedtime, and ad lib at 3 am.

Study drug and device

Study drug: NovoRapid® Injection 100 U/ml/vial (10 ml) of Novo Nordisk Pharma was used as the study drug.

The patients were instructed to abstain from using other insulins, drugs that promote insulin secretion (e.g., SU, nateglinide), and drugs that greatly affect glycemic control (e.g., steroids). However, other concomitant medications were allowed, and the study subjects were instructed not to change their medications and to continue with their usual diet and exercise during the study period.

Study device: The study device was composed of the following components. MMT-508 Minimed Insulin Pump, and Silhouette or Quick Set as infusion sets.

All components were manufactured by Medtronic Japan Co. Ltd.

Test/Survey Items (once a month)

Study subjects' height, weight and HbA1c were measured, and the occurrence of inflammation/infection at the site of insertion of the infusion set and device/infusion set troubles were monitored. The patient QOL was surveyed using the insulin therapy satisfaction questionnaire (ITR-QOL) (8).

Percent overweight was determined on the basis of Japanese standard body weights for height by age and sex using the following formula (9), $100\% \times (\text{actual body weight} - \text{standard weight})/\text{standard weight}$, and overweight exceeding 20% of ideal weight is defined as obesity in Japan.

Hypoglycemia was defined as the development

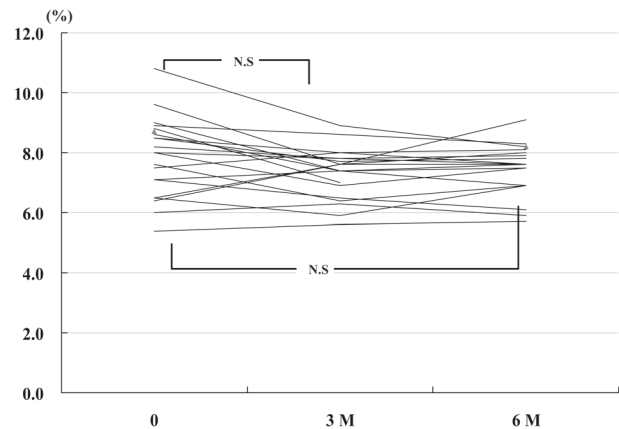


Fig. 1. Pre- and post-CSII differences in HbA1c. HbA1c (mean \pm SD: $7.8 \pm 1.8\%$, $n=22$) at the beginning of CSII was measured and compared at 3 mon ($7.3 \pm 0.8\%$, $n=20$) and 6 mon ($7.4 \pm 0.8\%$, $n=21$) later. CSII therapy has slightly improved HbA1c. However, there were no significant differences among the data. NS: not significant.

of symptoms of hypoglycemia (sweating, anxiety, palpitation, tachycardia, finger tremor, pallor, headache, hunger, sleepiness, convulsion, coma) necessitating a supplemental meal or a self-measured casual glucose value of 70 mg/dl or less. The hypoglycemia was classified in severity as serious (requiring assistance of others and/or glucagon injection) and non-serious (able to recover from hypoglycemia on one's own).

Statistical analysis

The pre- and post-CSII parameters were evaluated by the paired t-test and the QOL survey results by Wilcoxon's signed rank sum test. A P value of less than 0.05 was considered to be statistically significant.

Results

Effect on HbA1c

As shown in Fig. 1, the HbA1c decreased from $7.8 \pm 1.8\%$ ($n=22$) at baseline to $7.3 \pm 0.9\%$ ($n=20$) at 3 mo, and increased slightly again to $7.4 \pm 0.8\%$ ($n=21$) at 6 mo. The data showed

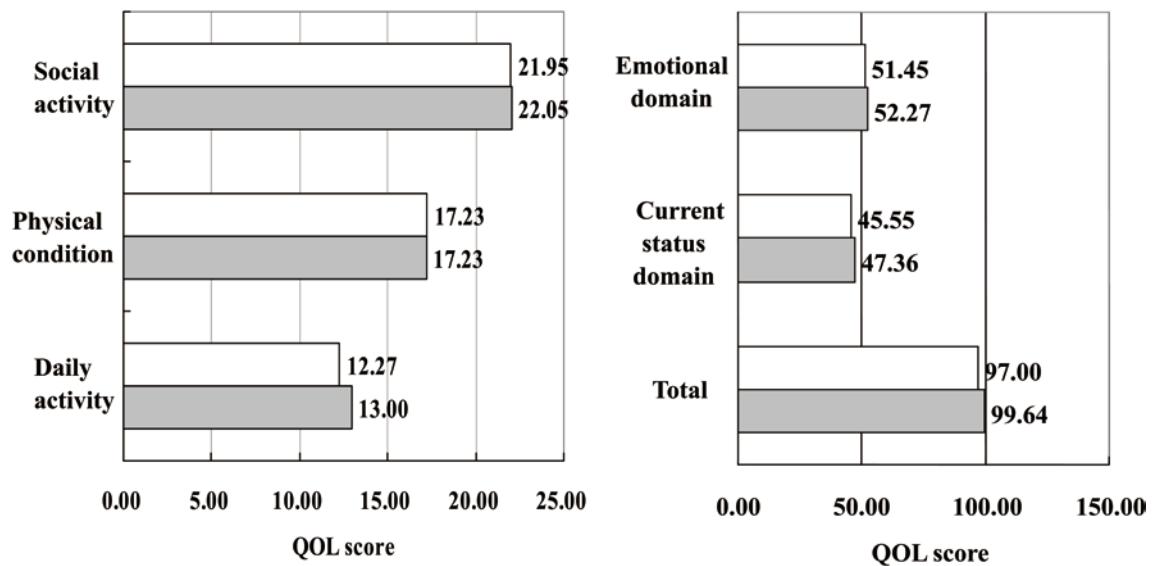


Fig. 2. Pre- and post-CSII comparison of the patient QOL scores based on the ITR-QOL questionnaire. The patient QOL was surveyed using the insulin therapy satisfaction questionnaire (ITR-QOL) at the beginning of CSII and at the end of this study. The mean total scores in the pre- and post CSII ITR-QOL surveys are shown. There were no significant differences between the scores.

overall improvement of glycemc control, although the difference was not significant.

Effect on the insulin dose (basal, bolus, and daily dose)

The mean of the pre-CSII basal dose was 21.6 U/day. After slightly increasing to 22.8 U/day at 3 mo, the basal dose returned to the baseline 21.6 U/day at 6 mo. The bolus dose increased from the pre-CSII 24.2 U/day to 27.7 U/day at 3 mo and 27.5 U/day at 6 mo, with no significant change. The increase in daily dose from the baseline 45.7 U/day to 49.3 U/day at 3 mo and 49.0 U/day at 6 mo was not statistically significant either.

Effect on BMI and percent overweight

The patients' BMI were not affected by the CSII therapy: 20.5 kg/m² at baseline, 20.3 kg/m² at 3 mo, and 20.4 kg/m² at 6 mo. The mean of percent overweight also was not changed by the CSII therapy: 3.1 ± 8.8% at baseline, 3.8 ± 12.2

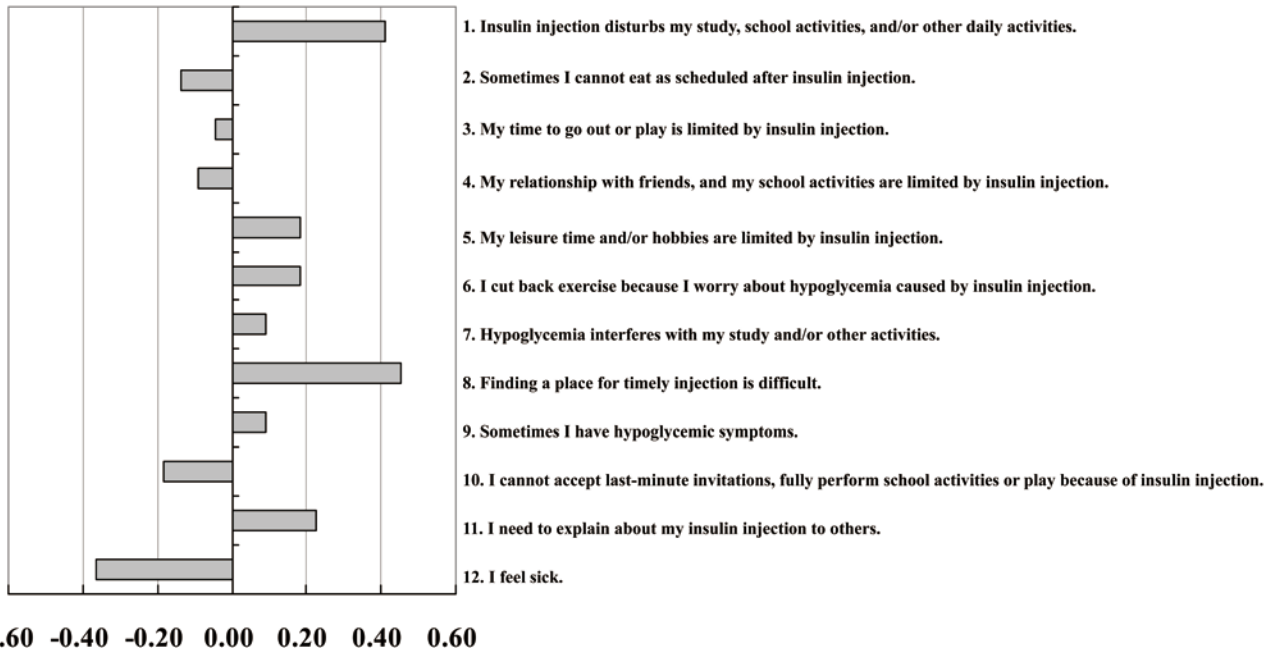
at 3 mo, and 2.7 ± 10.5 at 6 mo.

Effect on insulin therapy-related QOL

The effects of the CSII therapy on the patient QOL was evaluated based on the mean scores in the pre- and post-CSII ITR-QOL questionnaire surveys. The pre- and post-CSII scores were mostly comparable for all the domains and subdomains of the questionnaire, as shown in Fig. 2.

The mean pre- and post-CSII scores for individual questionnaire items are graphically compared in Fig. 3. The QOL scores for 13 of the 23 items in the questionnaire were improved following the CSII therapy. Increase in the mean QOL scores by 0.2 or more above the baseline was seen for 6 items: 1) Insulin injection prevents my study, school activities, and/or other daily activities; 8) Finding a place for timely injection is difficult; 11) I need to explain about my insulin injection to others; 17) It is a burden to get up early in the morning for insulin injection; 21)

A



B

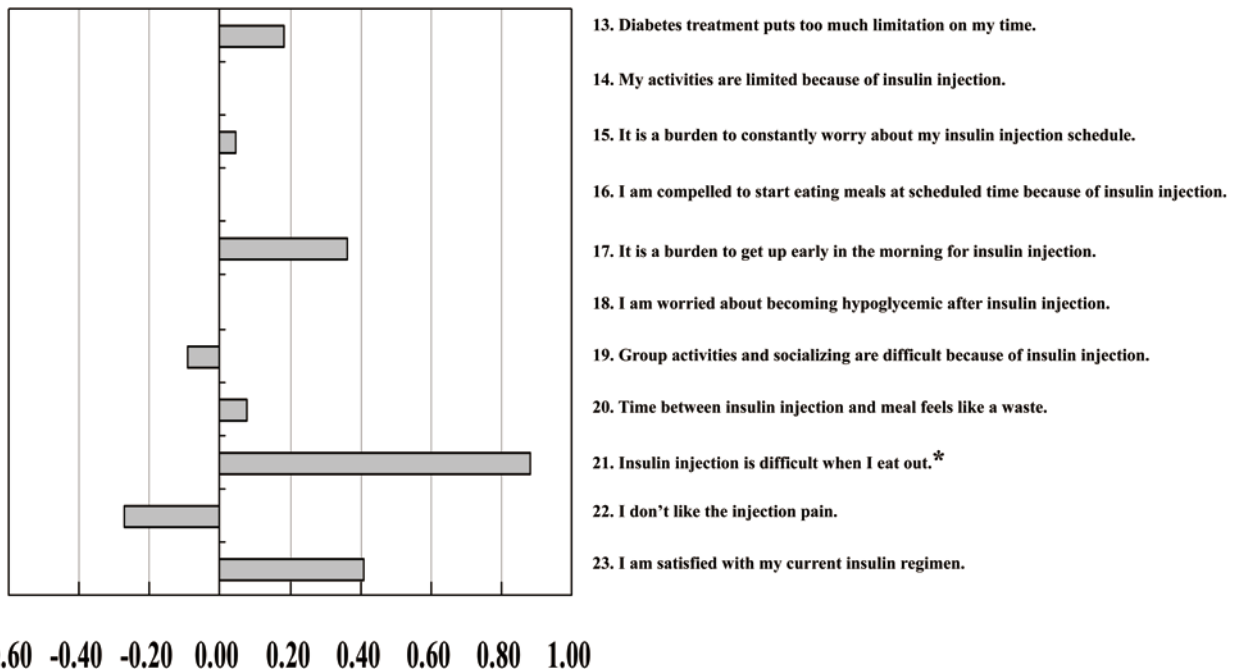


Fig. 3. Changes in the QOL scores for individual items of emotional domain and current status domain. The data of (the QOL scores of post CSII) – (the QOL scores of pre CSII) was shown. Positive scores indicate the post-CSII QOL score is higher than the pre-CSII QOL score. A. Emotional domain. B. Current status domain. *P<0.01.

Insulin injection is difficult when I eat out; and 23) I am satisfied with my current insulin regimen. The score for item 21 "Insulin injection is difficult when I eat out," significantly increased after the institution of the CSII therapy ($P < 0.01$).

Frequency of hypoglycemia

Eight of 22 patients had a history of experiencing hypoglycemia in the 6 mo prior to the institution of the CSII therapy. Most of these pre-CSII hypoglycemic symptoms, such as hunger and finger tremor, were mild, except for convulsion in 1 patient.

Hypoglycemia occurred in 7 of the 22 patients in the 6 mo after the institution of CSII therapy; however, none of the patients had severe symptoms.

Other adverse events

One each of three patients described the following adverse events: "pain." "the needle insertion site became bumpy and indurated." and "discoloration." The "pain" disappeared on the day after the needle was replaced. The "induration" was treated with topical steroid-antimicrobial ointment after removal of the needle, and disappeared in 2 days. The "discoloration" was left untreated and disappeared in 2 days.

Withdrawn patients

The CSII therapy was discontinued in 4 of the 26 patients during the study. The reasons for the discontinuation included inadvertent withdrawal of the needle due to bending of the insertion site (1 patient), interference of daily activities by the pump (1 patient), tube trouble (1 patient), and injection pain (1 patient).

All of the 22 patients in whom the CSII therapy was continued for the entire study period of 6 mo wished to continue with the therapy.

Device defects

A total of 18 CSII device defects were

encountered during the study period, although none necessitated discontinuation of the CSII therapy. In 16 of the 18 cases, the defect was related to infusion set trouble (inadequate infusion due to bending of the insertion site, 13; circuit detachment, 3), and in three of these 16 cases, DKA developed, necessitating inpatient care. Other defects included damaged liquid-crystal display (1) and auto-off due to incorrect set-up of the pump (1).

Discussion

CSII is, together with MDI, one of the important strategies for intensive insulin therapy in cases of type 1 diabetes mellitus. After rapid-acting insulin analogues became available for clinical use, the usefulness of these insulin analogues in CSII therapy has been reported in a number of studies. The usefulness of this drug in the treatment of childhood-onset type 1 diabetes has also been reported frequently in recent years. However, few studies have evaluated the QOL of the patients of childhood-onset type 1 diabetes treated by CSII therapy.

We instituted CSII of rapid-acting insulin analogue in patients with childhood-onset type 1 diabetes aged between 6 and 18 yr (mean age, about 14 yr) who had been on basal-bolus therapy, and followed them for 6 mo.

HbA1c, which reflects the glycemic control status had decreased at 6 mo after the CSII initiation of CSII therapy in 16 of 22 patients; however, no statistically significant change of the mean HbA1c was observed in the patients. We reported a decrease of the HbA1c at 3 mo after the initiation of CSII of rapid-acting insulin analogue in 8 of 10 patients with type I diabetes (mean age, 18 ± 3.9 years) in a previous study (1).

One of the possible reasons for the only slight decrease of the HbA1c in the current study is that in many of the patients a combination of rapid-acting and long-acting insulin analogues switched to CSII. Some studies have shown that

the long-acting insulin analogue has some effects on improving HbA1c compared with intermediate acting insulin. Hirsch *et al.* (10) compared MDI of rapid-acting and long-acting insulin analogues with CSII and reported greater improvement of the glycemic control with CSII in a randomized cross-over study. The current study failed to show a significant improvement of HbA1c after the initiation of the CSII therapy, possibly due to the small sample size. Whether the basal dose was determined appropriately and whether the number and amount of bolus doses was adequately adjusted based on the intake of meals and blood glucose levels were not evaluated in the current study. We started CSII therapy with a daily dose of insulin which was 80% of that used prior to the introduction of CSII. However, 6 mo later, an increase in the total daily insulin dose from the baseline was observed. A possible reason for this might be because the patients could increase bolus dose according to foods and blood sugar levels without experiencing hypoglycemia. The MMT508 pump has various functions to temporarily change the basal insulin dose or adjust the bolus dose, enabling more appropriate treatment than MDI. More thorough education and training of the medical staff and the patients about the insulin pump therapy may have led to a more significant improvement of the HbA1c in the current study.

During puberty periods, it is difficult to assess the obesity of adolescent subjects. In this study, we examined the BMI and the percent overweight of subjects. The results show that the CSII therapy did not induce obesity during the 6-mo study period.

As described earlier, the usefulness of insulin pump therapy has been greatly enhanced with improved designs of insulin pumps and infusion sets, as well as the development of rapid-acting insulin analogues. With the currently available devices, bolus insulin can be infused immediately before a meal. Pump troubles, such as obstruction of the infusion tubing are reduced due to the additional buffer for the insulin, and an infusion

set requires replacement only once every few days. With the enhanced convenience of CSII therapy, an improvement of patient QOL was expected. According to Tsui *et al.* (3) and Hoogma *et al.* (4), there were no significant differences in the QOL scores between CSII and MDI therapy. The mean total QOL scores showed no decrease from the baseline in the current study in which the ITR-QOL questionnaire developed by Ishii *et al.* (8) was used. The mean QOL scores for individual questionnaire items such as "Insulin injection prevents my study, school activities, and/or other daily activities," "Finding a place for timely injection is difficult," "I need to explain about my insulin injection to others," "It is a burden to get up early in the morning for insulin injection," "Insulin injection is difficult when I eat out," and "I am satisfied with my current insulin regimen," were higher after the initiation of CSII than while receiving MDI therapy. Most patients wished to continue with the CSII treatment after the study and this also suggests an improved QOL for the patients on CSII therapy. An apparent improvement of QOL for the patients receiving CSII therapy may have been demonstrated if the ITR-QOL questionnaire had been developed for patients on insulin injection therapies and included questions concerning the features of CSII.

The number of device/infusion set defects that occurred was rather large. CSII had to be discontinued in 4 of 26 patients because of device/infusion set defects. In particular, the frequency of hyperglycemia was high, and 3 patients eventually developed DKA. Danne *et al.* (11) reported a DKA frequency of 6.6/100 person years in 1041 pediatric patients on CSII therapy in 17 European countries. The DKA frequency in the current study was higher than the frequency reported in the aforementioned European study. As described by Hanas *et al.* (12) in their general statement: in general, DKA occurs immediately after the initiation of CSII therapy; post-CSII DKA is usually mild and can be avoided by appropriate patient education. Infusion set

troubles that led to hyperglycemia or DKA in the current study also occurred soon after the initiation of CSII and could probably have been prevented by careful infusion set replacement. The incidence of infusion set troubles would decrease if healthcare providers provided excellent patient education at the time of institution of CSII therapy. No adverse effects of insulin occurred, except for hypoglycemia, which also did not occur at a higher frequency than at the baseline. CSII appears to be favorable in terms of patient tolerability as well.

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