Beneficial Effects of Continuous Subcutaneous Insulin Infusion and Flexible Multiple Daily Insulin Regimen Using Insulin Glargine in Type 1 Diabetes

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ABSTRACT. Objective. The aim of this study was to evaluate the metabolic effects of continuous subcutaneous insulin infusion (CSII) with flexible multiple daily insulin (FMDI; premeal lispro + bedtime glargine) therapy as determined by glycosylated hemoglobin (HbA1c), body mass index (BMI), and hypoglycemic episodes in a group of patients who made the transition from multiple daily insulin (premeal lispro + bid ultralente) to either CSII or FMDI therapy.

Methods. Data from 40 (27 female and 13 male) patients (10.1–17.8 years of age) who were on CSII and 40 age- and gender-matched (27 female and 13 male) patients (10.3–17.3 years of age) who were on FMDI were collected during regularly scheduled visits at a similar frequency over a 1-year period.

Results. The total daily insulin dose did not change in CSII (0.97 ± 0.24 vs 0.91 ± 0.22 U/kg) and FMDI (0.98 ± 0.21 vs 0.97 ± 0.21 U/kg) patients, whereas the bolus:basal insulin ratio was significantly increased in both CSII (1.01 ± 0.43 vs 1.32 ± 0.92) and FMDI (1.07 ± 0.41 vs 1.29 ± 0.47) patients. The total cohort of CSII patients showed a decrease in HbA1c from 8.4 ± 1.0% to 7.8 ± 0.8%, whereas the FMDI cohort did not show a significant change in HbA1c (8.5 ± 1.1% to 8.2 ± 0.9%). However, 40% of the CSII group and 22.5% of the FMDI group showed ≥1.0% improvement in HbA1c. Also, a similar number of patients in CSII (52.5%; 8.0 ± 1.1 to 7.2 ± 0.5%) and FMDI (47.5%; 8.0 ± 0.5% to 7.5 ± 0.4%) maintained or achieved target HbA1c values <8.0%. The BMI increased significantly in the CSII group (21.6 ± 3.2 vs 23.0 ± 3.0 kg/m²) but did not change in the FMDI group (21.9 ± 3.9 vs 22.6 ± 3.8 kg/m²). There was a significant reduction in the rate of severe hypoglycemia (events/100 patient-years) in both cohorts: 20.6 to 8.2 in the CSII and 18.8 to 7.5 in the FMDI. Similarly, the rate of moderate hypoglycemia decreased in both CSII (68.3–35.4) and FMDI (56.3–30.4).

Conclusions. CSII therapy resulted in a significant improvement in HbA1c in the entire group, whereas FMDI therapy improved HbA1c in only a subgroup of patients. However, almost half of the patients in each of the treatment groups maintained or achieved target glycemic control. Both CSII and FMDI treatment groups demonstrated a decreased rate of hypoglycemia without an abnormal increase in BMI. Although the design of this study does not allow direct comparison of the metabolic effects of CSII and FMDI therapies, both regimens seem to be superior to basal ultralente and lispro multiple daily insulin regimen and offer desirable therapeutic alternatives in pediatric diabetes care.

In recent years, significant changes have occurred in the management of type 1 diabetes.1–2 Insulin replacement regimens now stress the importance of administering smaller doses of insulin throughout the day on the basis of flexibility in making food choices to fit individual lifestyles while focusing on improved metabolic control.2 The use of carbohydrate counting has been used in a number of diabetic management regimens to aid in this flexibility.2 Consequently, the goal of physiologic insulin replacement for type 1 diabetes has led to the development of better short-acting insulin analogues (lispro and aspart) that more closely mimic the sharp rise and short duration of pancreatic insulin secreted with nutrient intake.4,5 Lispro (Humalog; Lilly, Indianapolis, IN) or aspart (Novolog; Novo Nordisk Pharmaceuticals, Princeton, NJ) insulin has been shown, for this purpose, to be an ideal mealtime insulin.5–9

The use of the new long-acting basal insulin glargine (Lantus-Aventis Pharmaceuticals, Bridgewater, NJ) in a flexible multiple daily insulin (FMDI) regimen has been shown to enhance further the flexibility in insulin delivery and patients’ lifestyle.10 Intensive replacement of basal insulin using glargine with premeal insulin analog resulted in lower glycosylated hemoglobin (HbA1c) and reduced frequency of hypoglycemic episodes when compared with premeal analog and bedtime neutral protamine Hagedorn insulin.11

Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps was introduced to treat
type 1 diabetes >20 years ago. Because CSII provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens, there has been a growing interest in the pediatric diabetes community for the use of CSII in the treatment of children and adolescents with type 1 diabetes. Insulin pump therapy has been shown to result in improved metabolic control and reduced frequency of severe hypoglycemia.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy with either multiple daily insulin (MDI) or CSII resulted in dramatic risk reductions for the development and progression of microvascular complications compared with conventional treatment. Although CSII therapy is used increasingly in pediatric patients to achieve meticulous glycemic control, insulin injection regimens remain the mainstay of diabetes care for the majority of patients. Therefore, we evaluated the metabolic effects of CSII and FMDI (premeal lispro + bedtime glargine), as determined by HbA1c, body mass index (BMI), and hypoglycemic episodes, in 2 groups of age- and gender-matched pediatric patients who made the transition from MDI (premeal lispro + bid ultralente) to either CSII or FMDI therapy.

METHODS
Eighty white children and adolescents (age 10.1–17.8 years) were included in the study. All patients were cared for in the Children’s Hospital of Wisconsin Diabetes Center (affiliated with Medical College of Wisconsin). For each patient, data were collected retrospectively for 1 year before CSII or FMDI initiation and for the first year of CSII and FMDI therapy. The majority of our patients were transferred from MDI to FMDI using glargine insulin between July 2001 and September 2002. In addition, some patients requested CSII during the same period. Before initiation of CSII, patients underwent an extensive diabetes care skills and psychosocial screening to minimize nonadherence on insulin pump therapy. Of 51 patients who were initially screened, 40 (78%) were selected for the CSII regimen. We therefore selected an age- and gender-matched cohort of patients who had made the transition from MDI (premeal lispro + bid ultralente) to either CSII or FMDI therapy.

Transition to CSII or FMDI
Before initiation of the FMDI (lispro + glargine) or CSII regimens, all patients were on mealtime lispro and long-acting Humulin U (ultralente) insulin (prebreakfast: lispro + ultralente; prelunch: lispro; and presupper: lispro + ultralente) and applied principles of mealtime carbohydrate adjustment using insulin to carbohydrate ratio (ICR). Patients were switched to FMDI using glargine or CSII in an attempt to achieve optimal glycemic control, to reduce hypoglycemic events, and to provide a more flexible lifestyle by allowing variable mealtime insulin dosing. Before initiation of FMDI or CSII therapy, patients and their parents were evaluated by the diabetes team for ability to manage intensive therapy, which included diabetes self-management and insulin adjustment. Dietary strategies to calculate insulin bolus dosing on the basis of the ICR were again reviewed and included insulin adjustment techniques that included postprandial blood glucose determinations. Patients were evaluated at quarterly diabetes clinic visits. Most patients also contacted the team every 6 to 8 weeks to review blood glucose records.

Data were collected retrospectively for 1 year before FMDI or CSII initiation and for the first year of FMDI or CSII therapy. At each clinic visit, HbA1c, BMI, and Tanner stage were obtained, and the number of hypoglycemic episodes in the preceding 3 months was determined. However, we did not use any tool to assess patient compliance with the 2 new treatment regimens. Severe hypoglycemic episodes were defined as blood glucose <50 mg/dL (<2.8 mmol/L) associated with unconsciousness with or without seizure, expressed as events per 100 patient-years. Moderate hypoglycemia was defined as blood glucose <60 mg/dL (<3.3 mmol/L) with or without behavioral impairment and was also expressed as events per 100 patient-years. This study was approved by the Institutional Review Board of Children’s Hospital of Wisconsin for the retrospective review of patients’ clinical charts and, therefore, informed consent was not required. The details that might disclose the identity of the subjects under chart review were omitted.

Nutritional Assessment
All patients and their families were using carbohydrate counting for at least 12 months before initiation of flexible insulin therapy. However, the FMDI group was advised to limit snack size to 1 carbohydrate exchange if they wanted to avoid additional insulin injections. Each subject and family received nutrition and meal planning recommendations and education on the use of carbohydrate counting with CSII and FMDI regimen, based on established guidelines. Food labels, exchange lists, food models, and restaurant reference guides were used as educational tools.

Implementation of FMDI
All patients received lispro insulin (Humalog vial or Humalog Pen; Lilly) before meals for FMDI (bolus) or CSII (bolus and basal). The total daily dose (TDD) of insulin from the lispro + ultralente regimen was used to calculate bolus and basal doses of the FMDI regimen. The lispro insulin dosage for meals was calculated by dividing one half of the TDD of insulin by the total number of mealtime carbohydrate exchanges (1 carbohydrate exchange = 15 g), thus estimating the lispro ICR. A correction or supplemental dose of lispro insulin was also based on this ICR. For instance, the correction dose of lispro insulin was estimated as 0.5 U if the ICR was 0.5 or 1 U if it was 1.0. This 0.5 U or 1 U of lispro was added for every 50 mg/dL (2.8 mmol/L) that the blood glucose level was greater than the upper limit of the target range of 80 to 150 mg/dL (4.4–8.3 mmol/L). This initial insulin dosage algorithm was individualized in most patients during the year to accommodate variable insulin sensitivity. The insulin dosage algorithm also instructed the patients to subtract 0.5 U or 1.0 U of lispro insulin when the blood glucose was less than the lower limit of the target range. In addition, families were instructed to adjust unit per carbohydrate ratio and correction dose on the basis of 2-hour postprandial blood glucose determinations.

The other half of the previous TDD of insulin was given as a bedtime dose of glargine (Lantus–Aventis Pharmaceuticals). All insulin dose changes were initially made through consultation with clinic at first every 2 weeks for the first 1 to 2 months by fax or telephone contact and then independently by families of patients according to the basic guidelines taught.

Implementation of CSII
The Children’s Hospital of Wisconsin Diabetes Center has an outpatient insulin pump program. Before the initiation of pump therapy, all patients and families were instructed in the mechanics of pump use and were a demonstrator pump with saline for 3 days. The patient and the family chose the pump brand (MiniMed; Northridge, CA, or DiSetronic, St. Paul, MN). Patients and families were instructed on risks of pump use, including catheter-site infection, hyperglycemia, hypoglycemia, ketosis, and diabetic ketoacidosis (DKA), and potential mechanical problems (eg, kinked infusion sets, air bubbles, dislodged tubing) that could interfere with insulin delivery.

On the day before pump placement, all patients discontinued their basal insulin (ultralente) the night before and used correction doses of lispro insulin every 4 hours until the morning of pump
start. The new TDD was calculated as 75% of previous TDD (lispro + ultralente regimen). Lispro insulin was used in all pumps. Fifty percent of the daily dose was used for bolus dosing, and the remainder was used for basal rates. During the first 2 weeks of pump therapy, patients were instructed to perform frequent blood glucose monitoring (almost every 2 hours, including preprandial, postprandial, and overnight levels). Most patients were started on 2 to 3 basal rates, and correction doses were calculated for each patient as described in the FMDI regimen. All patients had daily telephone contact with a diabetes nurse educator for 7 to 14 days followed by fax or telephone contact (2-5 times/week) for at least 1 to 2 months. The HbA1c was determined using the Bayer DCA (Bayer Diagnostics Inc, Tarrytown, NY) 2000 instrument, with a nondiabetic range of 4.5% to 5.7%.

Statistical Analysis

The reported values represent the mean ± standard deviation. Baseline characteristics were compared with t test and $\chi^2$ analyses, and when differences were found, they were controlled for in additional analyses. The HbA1c data were analyzed using paired t test and 1-way analysis of variance. The rate of moderate and severe hypoglycemia was analyzed using a generalized estimating equation approach with a Poisson regression. $P < .05$ was considered significant.

RESULTS

Table 1 summarizes general characteristics and age of onset and duration of diabetes. The patients were stratified into 2 subgroups of target (achieved or maintained HbA1c <8.0% and above target (achieved or maintained HbA1c ≥8.0%). An HbA1c <8.0% target was deemed more realistic for children compared with the suggested level of <7.0% for adults because of high risk of severe hypoglycemia in prepubertal children. The CSII cohort had similar age of onset and duration of diabetes compared with FMDI group, and there were no differences among baseline HbA1c subgroups within each treatment group.

Table 2 summarizes number of clinic visits, TDD of insulin (U/kg/day), bolus:basal insulin ratio, HbA1c, BMI, and the rate of severe hypoglycemia. Both groups were well matched, with a similar number of clinic visits (3.5 ± 0.6 vs 3.6 ± 0.4), BMI (21.6 ± 3.2 vs 21.9 ± 3.9 kg/m²), HbA1c (8.4 ± 1.0 vs 8.5 ± 1.1%), daily insulin requirement (0.97 ± 0.2 vs 1.1 ± 0.2 U/kg/day), bolus:basal insulin ratio (1.0 ± 0.4 vs 1.07 ± 0.4), and frequency of severe (20.6 vs 18.8 events/100 patient-years) and moderate (not shown in Table 2) hypoglycemic episodes before initiation of CSII and FMDI therapy. There was no significant difference between the number of clinic visits in CSII (3.5 ± 0.6 vs 3.7 ± 0.5) and FMDI (3.6 ± 0.4 vs 3.6 ± 0.5) groups and their stratified subgroups (data not shown) during 1-year follow-up. Although the TDD was not significantly affected by either therapy, the bolus:basal insulin ratio was increased in both the CSII ($P < .005$) and FMDI ($P < .03$) groups.

Using the National Center for Health Statistics criteria, 27.5% of CSII (9 girls and 2 boys) and 37.5% of FMDI (9 girls and 6 boys) were overweight at baseline. After 1 year, there was a modest but not significant increase in the number of overweight patients on CSII (37.5%; 11 girls and 4 boys) but no increase in the number of overweight FMDI subjects (9 girls and 6 boys). Four CSII subjects who became overweight had either target (1 girl and 1 boy) or above-target (1 girl and 1 boy) HbA1c. The CSII cohort BMI increased (21.6 ± 3.2 vs 23.0 ± 3.0 kg/m²; $P < .05$), the FMDI group BMI did not (21.9 ± 3.9 vs 22.6 ± 3.8 kg/m²). There was no significant difference in BMI changes within the stratified subgroups (data not shown). Additional analysis of subgroups also revealed that patients with target control had significantly higher bolus:basal insulin ratio only in the CSII ($P < .03$) treatment group compared with their respective baseline ratios.

After 6 months, the CSII group showed a significant change in HbA1c (8.4 ± 1.0% to 7.5 ± 0.7; $P < .0001$); the FMDI group did not (8.5 ± 1.1% to 8.4 ± 1.0; data not shown in Table 2). After 1 year, the CSII patients again showed a decreased HbA1c compared with baseline (8.4 ± 1.0% to 7.8 ± 0.8%; $P < .002$), whereas the FMDI cohort did not (8.5 ± 1.1% to 8.2 ± 0.9%). However, 40% of the entire CSII group (9.1 ± 0.9% to 7.6 ± 0.9%; $P < .0001$) and 22.5% of the entire FMDI group (9.9 ± 1.1% to 8.6 ± 1.1%; $P < .02$) showed ≥10% improvement in HbA1c. Also, a similar number of patients in CSII (52.5%; 7.9 ± 1.1% to 7.2 ± 0.5%) and FMDI (47.5%; 8.0 ± 0.5% to 7.5 ± 0.4%) maintained or achieved HbA1c values <8.0% after 1 year of treatment. There were no significant differences between baseline values of target and above-target groups within CSII and treatment regimens.

The rate of severe hypoglycemia significantly decreased in the CSII ($P < .05$) and FMDI ($P < .05$) groups. Both CSII and FMDI groups with target control showed a significant reduction in the rate of severe hypoglycemia ($P < .05$) compared with their baseline rates, respectively; no other subgroup differences in the frequency of severe hypoglycemia were observed. The rate of moderate hypoglycemia decreased in the entire cohorts of CSII (68.3-35.4; $P < .03$) and FMDI (56.3-30.4; $P < .05$) groups but not in the target or above-target HbA1c CSII and FMDI subgroups.

While the number of emergency department visits

| TABLE 1. General Characteristics of Children and Adolescents With Type 1 Diabetes Mellitus |
|------------------------------------------|----------------|----------------|----------------|
| Characteristics | CSII | | FMDI |
| | All | Target | Above-Target | All | Target | Above-Target |
| Mean age, y | 14.7 ± 1.9 | 15.2 ± 2.2 | 14.2 ± 1.4 | 14.6 ± 2.0 | 14.9 ± 1.9 | 14.3 ± 2.1 |
| Female, % | 67.5 | 61.9 | 73.7 | 67.5 | 73.7 | 61.9 |
| Age of onset, y | 8.5 ± 3.5 | 9.2 ± 3.1 | 7.7 ± 3.7 | 7.4 ± 3.2 | 7.7 ± 3.1 | 7.3 ± 3.2 |
| DM duration, y | 6.2 ± 3.1 | 5.9 ± 2.8 | 6.5 ± 3.3 | 7.2 ± 3.0 | 7.2 ± 3.1 | 7.1 ± 3.0 |

Data are mean ± SD. Target HbA1c < 8.0%, and above-target ≥ 8.0%.

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TABLE 2. Clinical Characteristics of Patients Before and 1 Year After CSII and FMDI Therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CSII</th>
<th>FMDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (N = 40)</td>
<td>Target HbA1c (N = 21)</td>
</tr>
<tr>
<td>Pre-TDD, U/kg</td>
<td>0.97 ± 0.2</td>
<td>0.93 ± 0.3</td>
</tr>
<tr>
<td>Post-TDD, U/kg</td>
<td>0.91 ± 0.2</td>
<td>0.88 ± 0.2</td>
</tr>
<tr>
<td>Prebolus: basal</td>
<td>1.0 ± 0.4</td>
<td>0.97 ± 0.4</td>
</tr>
<tr>
<td>Postbolus: basal</td>
<td>1.32 ± 0.5*</td>
<td>1.28 ± 0.5†</td>
</tr>
<tr>
<td>Pre-HbA1c, %</td>
<td>8.4 ± 1.0</td>
<td>8.0 ± 1.1</td>
</tr>
<tr>
<td>Post-HbA1c, %</td>
<td>7.8 ± 0.8§</td>
<td>7.2 ± 0.6‖</td>
</tr>
<tr>
<td>Pre-SH†</td>
<td>20.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Post-SH†</td>
<td>8.2‡</td>
<td>8.6‡</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Target HbA1c < 8.0%, and above-target ≥ 8.0%.
Pre-CSII versus post-CSII: *P < .005; †P < .03; ‡P < .05; §P < .002; ||P < .008. Pre-FMDI versus post-FMDI: *P < .005; †P < .03; ‡P < .05.
§ The severe hypoglycemia (SH) rate is expressed as events per 100 patient-years.

for ketosis and hyperglycemia were similar in CSII (4: 2 girls and 2 boys) and FMDI (3: 1 girl and 2 boys) groups, DKA (pH < 7.30) was documented only in 2 of 4 emergency department visits in the CSII group (as a result of catheter blockage and dislodgement), both of whom required hospitalization. Three CSII patients developed catheter site skin infection, which was treated with topical antibiotics.

**DISCUSSION**

The present study evaluated the metabolic effects of 2 regimens of insulin replacement in the intensively treated CSII and FMDI patients with type 1 diabetes during a period of 1 year. The results indicate that the CSII cohort improved their glycemic control, whereas only a subgroup of FMDI patients demonstrated improved metabolic control. However, the frequency of severe and moderate hypoglycemia decreased significantly in both CSII and FMDI groups.

Similar to other studies, our CSII group demonstrated significant reduction in HbA1c at 6 months and 1 year.13 Forty percent of the total cohort (16 patients) demonstrated a clinically significant reduction (≥ 1%) in HbA1c. However, only 22.5% (9 patients) of our FMDI patients showed ≥ 1% improvement in HbA1c. This degree of reduction in HbA1c was associated with a 21% to 49% decreased risk of microvascular complications in the DCCT.17,22 Furthermore, almost half of the patients in both treatment groups maintained or achieved target glycemic control as defined by HbA1c < 8.0% in pediatric patients.20 In both groups, 60% to 77.5% of patients did not achieve at least 1.0% reduction in HbA1c, which implicates factors such as failure to administer insulin bolus doses at meals or snacks on CSII and suboptimal lispro coverage of meals or larger than 1-carbohydrate snacks on FMDI. It is interesting that the number of emergency department visits for ketosis in the CSII group was similar to FMDI, whereas DKA episodes occurred only in CSII patients as a result of interruption of insulin infusion.

Intensive insulin therapy has been commonly associated with excess weight.14,17,23 Our CSII patients experienced a statistically significant increase in BMI, which was anticipated among growing children and adolescents, but this increase in BMI was not clinically significant.

Hypoglycemia has often been regarded as an almost unavoidable consequence of good metabolic control, and this view has been underlined by the DCCT study.24,25 Some, however, have not reported such a risk.14–16,26,27 In our study cohort, the rate of severe hypoglycemia decreased significantly and equally in both CSII and FMDI cohorts as well as their target control subgroups. Although the cause of severe hypoglycemia in type 1 diabetes is multifactorial, it is usually associated with self-management errors, vigorous physical activities, psychosocial stresses, fewer than 3 injections a day, and a low bolus:basal ratio.28 Consistent with other studies,28–30 appropriate physiologic replacement of insulin with CSII or FMDI, frequent blood glucose monitoring, combined with adequate self-management, and active problem-based training were the likely reasons for decreased severe hypoglycemia. However, 1 limitation to our study was bedtime dosing of glargine because a recent study suggested that morning dosing instead would further reduce hypoglycemia frequency.31

Increased risk of frequent mild to moderate hypoglycemia in individuals with type 1 diabetes is usually associated with high blood glucose variability, low average blood glucose concentration, diabetes of long duration, low BMI, self-reported hypoglycemia unawareness, and vigorous physical activity.32 In our patients, there was no correlation between hypoglycemia frequency and BMI and/or duration of diabetes. However, the reasons for decreased rate of hypoglycemia frequency in CSII and FMDI were likely attributable to motivated families and improved insulin dosing strategies using ICRs allowing for limitations on the amount of required basal insulin. This study was undertaken to evaluate metabolic effects of CSII and FMDI using glargine insulin in a general pediatric diabetic population. Because the study patients were not randomized to the treatment regimens, we could not directly compare the metabolic outcomes of the 2 treatment groups. This is mainly because the CSII cohort was selected from among a group of highly motivated patients who were interested in improving their metabolic control.
and received more attention from the diabetes team than FMDI group, whereas the patients in the FMDI group were age and gender matched to the CSII group without necessarily similar psychosocial profiles and attention from the diabetes team.

In conclusion, CSII therapy resulted in a significant improvement in HbA1c in the entire cohort, whereas FMDI therapy improved HbA1c in only a subgroup of patients. However, almost half of the patients in each of the treatment groups maintained or achieved optimal glycemic control. Both CSII and FMDI treatment groups demonstrated a decreased rate of hypoglycemia without an abnormal increase in BMI. Although metabolic effects of CSII and FMDI regimens cannot be compared directly with each other, both regimens seem to be superior to basal ultralente and lispro MDI regimen and offer desirable therapeutic alternatives in pediatric diabetes care.

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