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ORIGINAL ARTICLE

Long-Term Metabolic Effects of Continuous Subcutaneous Insulin Infusion Therapy in Type 1 Diabetes

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Abstract

Background: Continuous subcutaneous insulin infusion (CSII) and intensive multiple daily insulin injections (iMDI) program are treatment options in patients with type 1 diabetes not achieving optimal glycemic control. The long-term effects of CSII in patients with type 1 diabetes in comparison with those educated for iMDI are poorly documented.
Research Design and Methods: Medical records for patients commenced on CSII or undertaking an iMDI program between 2000 and 2011 were extracted. Change in hemoglobin A1c (HbA1c), hypoglycemia, and weight were analyzed. Prior to CSII or iMDI commencement, all patients were on basal bolus analog insulin. Data from blood glucose meter downloads before and 6 months after CSII and iMDI were also analyzed.
Results: One hundred twenty-six CSII and 121 iMDI patients were studied, with mean (±SD) follow-up of 39±26 and 48±26 months, respectively. For CSII, HbA1c was significantly lower than baseline at every time period up to 36 months. Peak HbA1c reduction was 0.64% at 6 months, following which the HbA1c change declined. For iMDI, HbA1c was significantly reduced only at 6 months, by 0.15%. Glucose meter data were available for 119 patients. CSII-treated patients had a significant decrease in mean glucose and glucose SD with no change hypoglycemia at 6 months compared with baseline; no differences were observed for iMDI-treated patients.
Conclusions: CSII in type 1 diabetes is associated with improved glycemic control with no increase in hypoglycemia. HbA1c improvement declined over time, suggesting a need for re-education after CSII commencement. The iMDI program did not have significant glycemic benefits.

Introduction

Insulin therapy using multiple daily insulin injections (MDI) is the treatment of choice in the majority of patients with type 1 diabetes. In patients not achieving adequate glycemic control, continuous subcutaneous insulin infusion (CSII) is an important treatment option. There is strong evidence from clinical trials that CSII is associated with improved glycemic control[1] and lower rates of severe hypoglycemia when compared with MDI.[2,3] There is debate regarding the magnitude of benefit in terms of hemoglobin A1c (HbA1c) and hypoglycemia reduction. There are several limitations in the clinical trial data available currently. Most of the trials are of relatively short duration, and therefore the longer-term metabolic effects of CSII versus MDI therapy in type 1 diabetes are unclear. Many of the older trials with CSII were performed in comparison with MDI using older insulins. There are few trials using newer insulin analogs as a comparison.[2,4–7]

It is also unclear whether the technology of an insulin pump, or the education that goes with insulin pump initiation, is responsible for the improvements seen in trials.[8,9] Insulin pump initiation involves many hours of teaching advanced insulin titration, including carbohydrate counting, adjusting for exercise, and reinforcing the need for frequent blood glucose monitoring. The Dose Adjustment for Normal Eating (DAFNE) program is a diabetes education program developed for patients with type 1 diabetes to assist with insulin adjustment in a similar manner to the diabetes education program associated with CSII initiation. There is evidence that

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DAFNE is associated with improved quality of life and glycemic control in type 1 diabetes.[10]

At the Baker IDI Heart and Diabetes Institute (Melbourne, Australia) there are specialized education programs for both CSII initiation and a DAFNE-style intensive MDI (iMDI) therapy. This retrospective study was conducted to determine the long-term metabolic effects of CSII initiation in patients with type 1 diabetes in comparison with a reference group of those who attended our iMDI program.

Subjects and Methods

Study design and patients

This retrospective observational analysis was undertaken in patients over 18 years of age with type 1 diabetes, from the diabetes clinics at the Baker IDI Heart and Diabetes Institute, who commenced CSII (or attended the iMDI program) in the period between 2000 and 2011.

All patients starting CSII attended an education program with our diabetes education team, both prior to and following insulin pump commencement. They attended a standard pump initiation program that included group meetings and individual appointments with credentialed diabetes educators and dieticians, totalling approximately 6.5 h prior to pump commencement and 4 h following pump commencement (1-h diabetes education at 1, 2, 4, and 6 weeks). Patients referred to the iMDI education attended a DAFNE-style 5-week education program with group meetings of 2.5 h every week. This program is based on insulin pump principles and focuses on insulin dose calculations according to insulin sensitivity factors, on carbohydrate counting, and on sick day management. The education programs in both groups were essentially the same in basic principles, with the exception of the additional training in CSII patients for the skills associated with insulin pump technology. The criteria for patients to be offered either pump or iMDI treatments were similar: inadequate glycemic control, frequent hypoglycemia, glycemic variability, patient motivation, and their agreement to attend education sessions. As the patients in this clinic are mostly covered by private health insurance, they would be reimbursed for the purchase of a pump, and the disposables would be supported by regular health coverage.

All patients included in this analysis of CSII and iMDI and were treated with at least three injections of insulin (Humalog® [Eli Lilly, Indianapolis, IN] or Novorapid® [Novo Nordisk, Bagsvaerd, Denmark]) before meals and at least one injection of basal analog insulin (Lantus® [sanofi aventis, Paris, France] or Levemir® [Novo Nordisk]), for a minimum of 6 months prior to starting the iMDI program. They all had long-standing diabetes, on average 19 years, with a long experience of insulin treatment. Six of the patients who were initially treated with iMDI changed to pump treatment, but only their data from the iMDI treatment are included in these analyses up until the time that CSII was commenced.

Pregnant women were excluded from this study.

Outcome measures

Data from patient files were used to analyze HbA1c, hypoglycemia, and weight prior to and at regular time intervals following commencement of either CSII or iMDI. HbA1c was recorded as the initial value if it fell within a 6-month period prior to treatment. The mean of HbA1c readings in the first 6 and 12 months and the mean of HbA1c for every subsequent year of follow-up were calculated and analyzed. We also measured weight at the beginning and every 6 months during the study period.

As part of CSII and iMDI education, patients were advised to obtain self-measured blood glucose at least four times per day. Downloaded glucose values from patients' glucose meters were available from the Precision Link 2.5 system (Abbott Diabetes Care, Alameda, CA), Accu-Chek® (Roche Diagnostics, Indianapolis) Camit Pro databases, and the Abbott CoPilot Health Management System-HCP version 4.1 INTL. The normoglycemic target range was defined as 3.5–8.0 mmol/L, hyperglycemia was defined as >8.0 mmol/L, and hypoglycemia was defined as <3.5 mmol/L. For hypoglycemia event rates, the percentage and total number of blood glucose readings in the hypoglycemic range were calculated, over a period of 1 month before CSII or iMDI and at 6 months. The SD of glucose values was calculated over the same 1-month period for each patient as a marker of glucose variability.

Statistical analysis

IBM® SPSS® statistics software (version 19.0, 2010; SPSS, Inc. an IBM Company, Armonk, NY) and SAS (version 9.2; SAS Institute, Inc., Cary, NC) were used for statistical analyses.

Characteristics of the patients are presented as mean ± SD and n (%) and compared by Student's t test and Fisher's exact test according to CSII and iMDI treatment groups. The change since baseline for the three outcome variables (HbA1c, weight, and hypoglycemia) were compared for each time interval by Wilcoxon signed rank tests.

Data from blood glucose monitoring are presented on the subgroup of patients who had glucose meter download records available at both baseline and 6 months following commencement of CSII or the iMDI program. Characteristics at baseline and at 6 months and changes in characteristics are presented as medians (first and third quartiles), and the 6-month changes are tested by Wilcoxon signed rank tests. The differences between treatments of these changes, are compared by Mann–Whitney U tests.

Results

Demographic data

One hundred fifty-eight patients commenced CSII in the time between March 2000 and March 2011. Of these, 29 patients were excluded because of a lack of data, and three were excluded because of pregnancy. There were 131 patients who attended the iMDI program in the same time period; seven patients were excluded because of a lack of data, and three were excluded because of pregnancy. In total, 247 patients were included in this analysis: 126 in the CSII group and the 121 in iMDI group. Table 1 shows that there were no significant differences between the two groups in baseline characteristics except body mass index, which was significantly higher in the CSII group than the iMDI group ($P=0.021$). Mean (±SD) follow-up was comparable in the iMDI group and the CSII group (48 ± 26 vs. 39 ± 26 months, $P=0.08$). HbA1c and weight data were available for up to 60 months in both groups.

Table 1. Baseline Characteristics of the Study Sample, According to Treatment: Continuous Subcutaneous Insulin Infusion and Intensive Multiple Daily Insulin Injections Program

	CSII (n = *126*)	*iMDI* (n = *121*)	P *value*
Age (years)	44 ± 13	47 ± 13	0.069
Male	57 (46%)	59 (49%)	0.620
Diabetes duration (years)	18 ± 12	20 ± 11	0.297
HbA1c (%)	8.0 ± 1.0	7.8 ± 1.0	0.215
Weight (kg)	77.7 ± 12.3	75.7 ± 13.7	0.231
BMI (kg/m^2)	26.9 ± 3.7	25.7 ± 3.8	0.021

Data are mean ± SD values or *n* (%).
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1c; iMDI, intensive multiply daily insulin injections.

Patient numbers declined over time. However, loss to follow-up was not an important cause of this. Because the date of the baseline visits varied, there were significant numbers of patients who had only been in the study for relatively short follow-up periods by the end of the observation period. Over the 5 years the numbers of patients not reaching study time points because of later baseline visit dates were none, 12, 45, 68, and 80 in the CSII group and none, 10, 22, 35, and 37 in the iMDI group at 1, 2, 3, 4, and 5 years, respectively. The numbers genuinely lost to follow-up were none, five, five, eight, and nine in the CSII group and none, six, 10, 19, and 24 in the iMDI group at 1, 2, 3, 4, and 5 years, respectively. Patient demographics for those with less than 2 years of follow-up were not significantly different from those of the total cohort for CSII and iMDI.

HbA1c

HbA1c was significantly lower than baseline in the CSII group in every time period up to 36 months (Fig. 1). The peak HbA1c reduction was 0.64% at 6 months, and this declined progressively over time. To account for the possibility that earlier pump starts may have been associated with smaller HbA1c change over time, we assessed the effect of pump starts before and after 2008, the median start date, on HbA1c. The pattern of HbA1c change was similar in those with early and later pump starts, with a progressive decline in HbA1c change over time. Beyond 36 months there was a nonsignificant HbA1c reduction in the CSII group compared with baseline. In the iMDI group there was a significant reduction

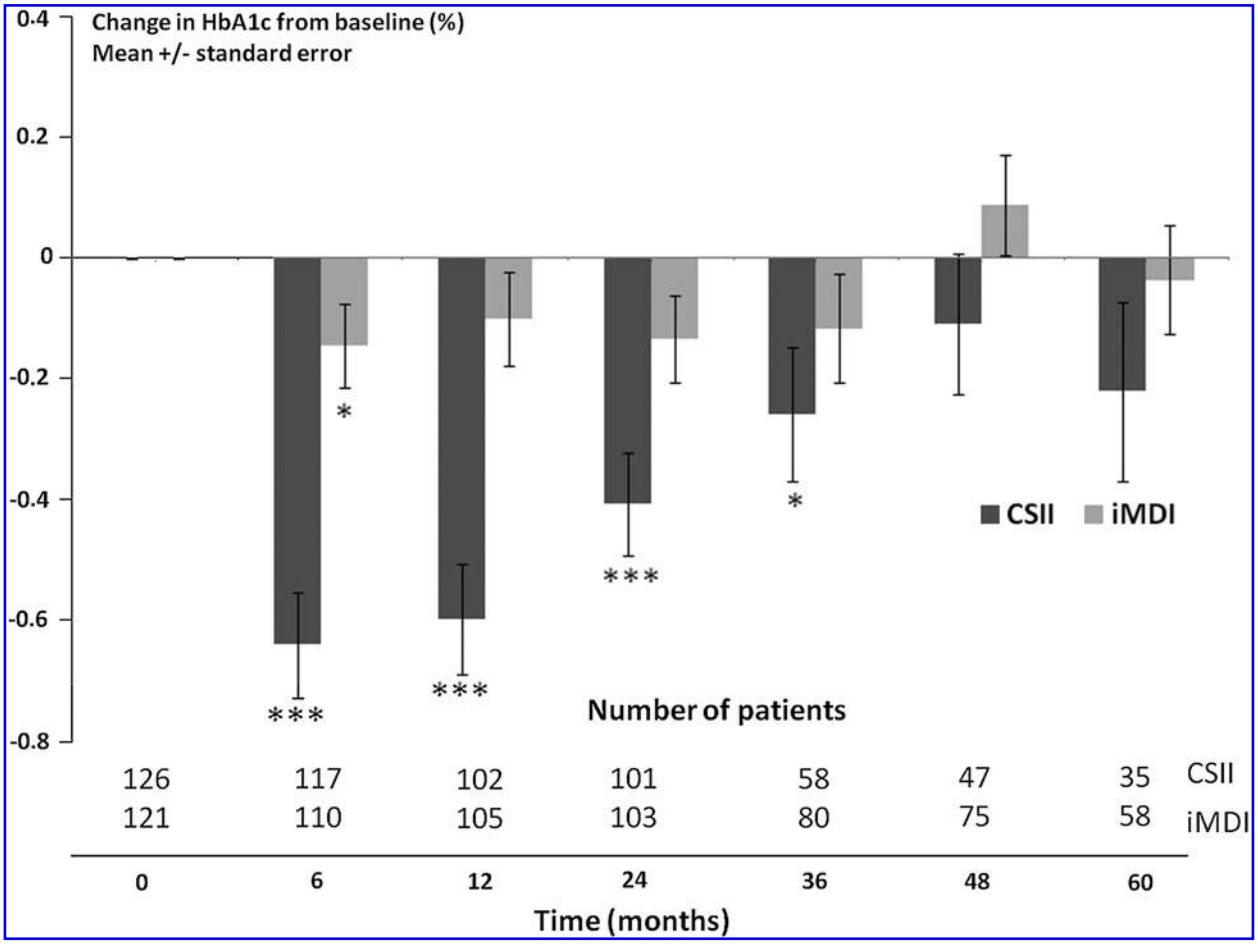

FIG. 1. Mean difference in hemoglobin A1c (HbA1c) from baseline (%) at each time point. Patients receiving continuous subcutaneous insulin infusion (CSII) are represented by black bars; patients receiving intensive multiple daily insulin injection (iMDI) therapy are represented by gray bars. Data are mean ± SEM values. *$P < 0.05$, ***$P < 0.001$.

in HbA1C from baseline at 6 months of only 0.15%. Small, nonsignificant decreases in HbA1c from baseline were seen until 36 months. Adjusted for baseline HbA1c, the difference between CSII and iMDI treatment was significant up to 24 months.

Weight and body mass index

Body mass index was significantly higher in CSII compared with iMDI at baseline (Table 1). There was no significant weight or body mass index change from baseline in either group over time.

Blood glucose data from meter downloads

Glucose meter download data at both baseline and 6 months were available for only 60 CSII and 59 iMDI patients. The reasons for missing data were predominantly meters being unavailable at clinic appointments or technical difficulties with downloads. There were no significant differences at baseline or follow-up in any measured parameter between those with and without meter downloads at 6 months in the CSII or iMDI groups. In the CSII group, mean blood glucose, SD of glucose level, and percentage of readings in the hyperglycemia range were all significantly decreased at 6 months compared with baseline. The percentage of readings in the hypoglycemia range was no different at 6 months compared with baseline. In the iMDI group there was no significant difference at 6 months in any glycemic parameter compared with baseline (Table 2). Comparing the two treatment groups, there were significant differences in treatment effects between CSII and iMDI for average glucose ($P=0.02$), SD glucose ($P=0.001$), and percentage readings in the hyperglycemia range ($P=0.008$). There was no significant between-group difference for percentage of readings in the hypoglycemia range or for the number of glucose tests performed. There were no significant differences between pre- and post-hypoglycemia when the total number of hypoglycemic readings were analyzed (data not shown), with median of seven pre- and nine post-hypoglycemia in the CSII group and five pre- and nine post-hypoglycemia in the iMDI group.

Discussion

This study demonstrates the long-term glycemic benefits of CSII treatment in patients with type 1 diabetes previously treated with basal bolus treatment using analog insulins. These benefits include improvement in HbA1c without an increase in hypoglycemia or body weight and reduced glycemic variability. For CSII this is consistent with many clinical trials and meta-analyses. However, these previous studies are mostly based on short-term data, and there are few long-term data currently published. For CSII, HbA1c reduction was greatest at 6 months following pump initiation and declined thereafter up to 5 years. This decline in therapeutic benefit has been shown in other studies and suggests a "wearing off" effect of this technology. Previous studies are mainly from pediatric groups with up to 3 years of observation. Jakisch et al.[11] demonstated an initial HbA1c difference between CSII and MDI in the first year only compared with MDI, with apparent wearing off of the benefits thereafter. In another pediatric group a similar wearing off in HbA1c benefit was seen after 12 months compared with 6 months, with no benefit seen with a flexible MDI intervention.[12] Possible reasons for this reduced efficacy over time may include decreased compliance or loss of skill. Based on our results there appears to be an argument for re-education at 12 months post-pump initiation.

In contrast, we demonstrated a small glycemic benefit of an iMDI program at 6 months only in a cohort of patients that was well matched with the CSII group. For flexible intensive insulin programs, most data come from the DAFNE program. One long-term follow-up study[13] showed that after 7 years there was a persistent HbA1c improvement over time compared with a reference group. An Australian audit of DAFNE participants also showed a significant HbA1c reduction over 12 months in a DAFNE follow-up study[14] and similar findings in a United Kingdom randomized clinical trial.[15] Differences between our study and the DAFNE follow-up publications may be explained by possible differences between the programs, with our program being 2½ h over 5 weeks in contrast with DAFNE, which was over 5 consecutive full days, from

Table 2. Blood Glucose Levels from Blood Glucose Meter Downloads at Baseline and at 6 Months, Measured over a 1-Month Period, According to Treatment: Continuous Subcutaneous Insulin Infusion and Intensive Multiple Daily Insulin Injections Program

	Blood glucose reading			
	Baseline	*6 months*	*Difference*	P *value*
CSII ($n=60$)				
Mean glucose (mmol/L)	10.6 (9.2, 11.3)	9.3 (8.4, 10.9)	–0.8 (–2.2, 0.2)	0.0001
SD glucose (mmol/L)	4.8 (4.4, 5.4)	4.2 (3.6, 5.0)	–0.6 (–1.1, 0.10)	0.0001
Number of glucose readings	119 (63, 154)	129 (89, 173)	28 (–28, 68)	0.03
Hyperglycemia (%)	63 (54, 74)	58 (49, 67)	–6 (–14, 2)	0.004
Hypoglycemia episodes (%)	6 (3, 12)	7.4 (4.1, 12.5)	0 (–3, 4)	0.8
iMDI ($n=59$)				
Mean glucose (mmol/L)	9.2 (8.3, 10.7)	9.6 (8.1, 11.1)	0.1 (–0.8, 1.1)	0.7
SD glucose (mmol/L)	4.5 (3.8, 4.9)	4.6 (3.8, 5.3)	0.2 (–0.5, 0.5)	0.7
Number of glucose readings	65 (41, 107)	89 (49, 116)	16 (–20, 49)	0.05
Hyperglycemia (%)	55 (46, 69)	58 (44, 69)	–1 (–9, 10)	0.8
Hypoglycemia episodes (%)	9 (4, 16)	11 (6, 14)	0 (–6, 6)	0.7

Data are medians (quartile 1, quartile 3).
CSII, continuous subcutaneous insulin infusion; iMDI, intensive multiple daily insulin injections.

9 a.m. to 5 p.m. However, the principles of our iMDI program are based on DAFNE with a comparable amount of education time.

Patient selection may have played an important role. It is notable that the mean HbA1c in the DAFNE studies was higher, ranging from 8.2% to 9.3% prior to intervention.[14–16] This compares with 7.8% in our cohort. The previously published DAFNE cohorts may have had a high percentage of patients initially using a less intensive insulin regimen and old insulins. This may be an important difference compared with our iMDI group who were all on MDI with analog insulins prior to the study.

As it is difficult to separate effects of education from the effects of the technology, some groups have suggested that CSII produces beneficial effects through the education associated with the pump rather than the pump technology. Based on the difference between outcomes in the iMDI and CSII groups, our study would suggest that the education, which was similar in both groups, may be more effective in combination with the pump technology. It is important to note that education is a critical factor in insulin pump commencement and that there may have been significant differences in frequency of follow-up between the CSII and iMDI groups. There is evidence from other studies to suggest that the frequency of patient review has a strong correlation to glycemic outcomes in the management of diabetes.

In type 1 diabetes, HbA1c is frequently inversely correlated to hypoglycemia rates (Diabetes Control and Complications Trial).[17] Results of blood glucose meter downloads in our study showed no change in hypoglycemia, with lower mean glucose levels and reduced glycemic variability in the CSII group compared with baseline. This is consistent with many other trials using continuous glucose monitoring system technology[18] and meta-analyses[3] looking at hypoglycemia rates in CSII therapy. This study supports evidence from clinical trials suggesting that glycemic variability is an important limiting factor in the management of type 1 diabetes and that CSII improves outcomes by reducing blood glucose fluctuation.

Limitations

This was a retrospective study in two patient groups, and limited comparisons can be made between the groups. Although patient characteristics were well matched, it is possible that patients undergoing CSII and their treating health professionals may have had a greater level of initial enthusiasm regarding a new treatment approach. Despite these limitations, these data represent real-world clinical experience, particularly as a large, long-term randomized pump trial is not likely, given the enormous costs involved.

Blood glucose meter downloads were used to analyze glucose variability and hypoglycemia. Data were only available in approximately half of the cohort, and the reasons for this were not recorded. Furthermore, data were only available for a 6-month period. It is possible that the more poorly compliant patients were selected out of this glucose monitoring; however, comparison of those who had meter results with those who did not showed no significant difference in age, diabetes duration, and initial or 6-month HbA1c. Meter downloads rely on patient testing, and there were differences in frequency between the two patient groups. This again makes the comparison between groups difficult. However, the changes before and after CSII were highly significant and associated with only a small increase in the frequency of testing. There was no change in any blood glucose parameter in the iMDI group despite a small increase in the frequency of monitoring. Although there was no significant difference in the percentage of hypoglycemia in the two treatment groups, it should be noted that there was a slightly higher percentage of hypoglycemia with fewer glucose downloads per day in the iMDI group, and we could hypothesize that more hypoglycemia may have been missed in the iMDI group. Severe hypoglycemia and ketoacidosis were not assessed in this study but are important outcomes.

Conclusions

This retrospective study shows that insulin pump therapy in adults is associated with improved long-term glycemic control over a period of up to 3 years in patients with type 1 diabetes, previously on MDI. HbA1c improvement declined over time, suggesting the need for patient re-education or training approximately 12 months after pump commencement. The improvement in blood glucose levels was associated with reduced glycemic variability with no change in hypoglycemia. More long-term data, particularly in adults, are needed to confirm our findings, which suggest that the pump technology is an important factor over and above the education received. In comparison, a flexible MDI training program improved glycemic control to a much smaller degree, at 6 months only, in a comparator patient group previously on MDI. Further long-term analyses of DAFNE-style programs are needed with well-defined comparator groups.

Author Disclosure Statement

No competing financial interests exist.

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