ORIGINAL ARTICLE

The Effectiveness and Durability of an Early Insulin Pump Therapy in Children and Adolescents with Type 1 Diabetes Mellitus

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Abstract

Background: This study evaluated the predictors of effectiveness and durability of insulin pump therapy in children and adolescents who have initiated continuous subcutaneous insulin infusion (CSII) within 2 years after the diagnosis of type 1 diabetes mellitus (T1DM).

Subjects and Methods: The charts of individuals with T1DM using insulin pumps who were treated at our center were reviewed, including subjects with age at onset of <22 years, interval between onset and insulin pump commencement (interval onset–commencement) of <2 years, use of pumps of >1 year, and use of glucose sensors for <4 weeks/year. The primary end point was the mean glycosylated hemoglobin (HbA1c) value (MHbA1c) throughout the follow-up.

Results: From 684 patients treated with insulin pumps, 119 met the inclusion criteria, and 113 were selected for statistical analysis (60 females; age at diabetes onset, 8.9 ± 5.6 years [mean $\pm$ SD]; follow-up, 4.0 ± 1.8 years; range, 1–8 years; baseline HbA1c, $9.3 \pm 1.8\%$). Only the interval onset–commencement was a linear predictor of the MHbA1c ($P=0.01$; $R^2=0.089$). A significant reduction of the mean yearly HbA1c from baseline throughout all the follow-up was observed ($P<0.001$). Categorizing the sample into four quartiles on the basis of an increasing interval onset–commencement resulted in levels of MHbA1c significantly lower in the first and second quartiles in comparison with the fourth quartile ($7.6 \pm 0.8\%$ and $7.8 \pm 1.0\%$, respectively, versus $8.5 \pm 0.8\%$; $P<0.001$ and $P=0.004$, respectively).

Conclusions: The present study suggests that early pump commencement in children and adolescents with T1DM provides lower and more durable HbA1c values than a late commencement. It is possible that an early pump commencement could prolong the honeymoon phase, but we cannot confirm or exclude this hypothesis because the lack of data about C-peptide levels during the follow-up.

Background

SEVERAL META-ANALYSES OF RANDOMIZED controlled trials of glycemic control comparing continuous subcutaneous insulin infusion (CSII) with multiple daily insulin injections (MDI) have established that the mean glycosylated hemoglobin (HbA1c) value (MHbA1c) is significantly lower with CSII (HbA1c reduction of approximately 0.1–0.8%), with some differences in relation to the age of the subjects treated.^{1–5} There is a substantial lack of data derived from randomized controlled trials of CSII versus MDI in children with a

follow-up of >12 months,^{6–9} but several observational studies have established that CSII use in children and adolescents is related to a significant and durable improvement of HbA1c levels.^{10–16} Some variables at pump commencement—age, gender, HbA1c, glucose variability, diabetes duration, and frequency of daily self-blood glucose monitoring—are related to a subsequent better glycemic control,^{2,3,17,18} but it is still controversial if starting CSII in patients with type 1 diabetes mellitus (T1DM) within 1 year of diagnosis results in better long-term glycemic control than starting it later.^{18–20} The purpose of this study is to evaluate the predictors of

effectiveness and durability of insulin pump therapy in children and adolescents who have initiated CSII within 2 years after the diagnosis of T1DM.

Subjects and Methods

This was an observational retrospective study, conducted at the Regional Reference Center for Diabetology and Insulin Pumps, located in the Hospital of Partinico, Palermo, Italy.

The following inclusion criteria were applied: patients treated with CSII, diagnosis of T1DM, age at onset of <22 years, interval between onset and insulin pump commencement (interval onset–commencement) of <2 years, use of CSII for >1 year, and use of continuous glucose monitoring for <4 weeks/year.

Chart reviews were conducted by two investigators who collected gender, date of birth, date of onset of diabetes, date of pump commencement, body mass index and HbA1c level (baseline HbA1c) at pump commencement, and HbA1c level at each visit during the follow-up. HbA1c assays were performed through high-performance liquid chromatography and standardized according to the Diabetes Control and Complications Trial method. The subjects included in the study were followed up as outpatients (frequency of appointments, two or more times per year). HbA1c values obtained at each follow-up visit were used to calculate the yearly MHbA1c. If a patient missed an appointment, the HbA1c value was taken as the average of the HbA1c measurements before and after the appointment. The interval onset–commencement was obtained by subtracting the date of insulin pump commencement from the date of diabetes onset and was expressed in days. The primary end point was the MHbA1c throughout all the follow-up, calculated by dividing the yearly MHbA1c for the number of years observed. Secondary outcomes were yearly MHbA1c, year by year, throughout all the follow-up.

The study was approved by the local ethics committee and was performed in agreement with the Declaration of Helsinki.

All the subjects studied (or their parents, if the subjects were not adults) gave a written informed consent to the treatment of their personal data, in agreement with Italian law.

Statistics were analyzed using mainly KyPlot version 2.0 beta 15 software.

In the first step of statistical evaluation, we performed a regression analysis using the MHbA1c as the dependent variable; age at T1DM onset, age at pump commencement, interval onset–commencement, duration of follow-up, body mass index at pump initiation, and baseline HbA1c were considered as independent variables. The analysis of variance (ANOVA) for repeated measures was performed to compare, in the whole sample, the baseline HbA1c and the yearly MHbA1c throughout the years; a *t* test for independent samples was also used to compare the baseline HbA1c with the yearly MHbA1c values.

In the second step, the patients studied were divided into four quartiles, based on the interval onset–commencement. The interquartile MHbA1c differences and baseline differences of continuous variables were compared using the *t* test for independent samples, whereas the categorical variables were compared using the χ^2 test. The ANOVA for repeated measures was performed to compare the HbA1c values of the quartiles, from the baseline throughout the follow-up, and a

TABLE 1. BASELINE CLINICAL AND METABOLIC PARAMETERS OF ALL THE PATIENTS INCLUDED IN THE STUDY (SECOND COLUMN FROM THE LEFT), OF THE PATIENTS SUBDIVIDED INTO FOUR QUARTILES ON THE BASIS OF THE DURATION OF DIABETES AT PUMP COMMENCEMENT (THIRD–SIXTH COLUMNS FROM THE LEFT), AND INTERQUARTILE DIFFERENCES (FIRST COLUMN FROM THE RIGHT)

	All (n = 113)	First quartile (n = 29)	Second quartile (n = 28)	Third quartile (n = 28)	Fourth quartile (n = 28)	Interquartile differences
Female/male ratio	60/53	16/13	12/16	19/9	12/16	NS
Age (years) at onset	8.9 ± 5.6 (0.2–21.8)	8.1 ± 5.5 (0.7–19.5)	8.6 ± 5.6 (1.0–20.9)	8.7 ± 6.0 (0.2–20.7)	10.2 ± 5.4 (0.9–21.8)	NS
Age (years) at pump implant	9.6 ± 5. (0.8–23.3)	8.2 ± 5.5 (0.8–19.7)	8.9 ± 5.6 (1.4–21.4)	9.5 ± 6.0 (1.1–21.5)	11.8 ± 5.4 (2.2–23.2)	<i>P</i> = 0.017 ^a
Duration of diabetes at pump commencement (days)	252.7 ± 217.5 (1–726)	34.1 ± 19.4 (1–61)	118.9 ± 40.0 (62–181)	287.6 ± 64.4 (182–400)	578.0 ± 96.5 (425–726)	ND
BMI (kg/m ²)	18.5 ± 3.1 (13.0–28.1)	18.1 ± 2.9 (14.6–26.0)	18.1 ± 2.8 (14.0–24.7)	17.3 ± 4.1 (14.6–26.0)	18.6 ± 2.6 (13.0–22.9)	NS
Baseline HbA1c (%)	9.3 ± 1.8 (6.4–14.8)	9.8 ± 1.7 (7.5–14.3)	9.0 ± 1.8 (6.4–12.6)	9.0 ± 1.6 (6.8–12.4)	9.4 ± 2.1 (6.4–14.8)	NS
Follow-up (years)	4.0 ± 1.8 (1.0–8.0)	4.5 ± 1.8 (1.0–7.0)	3.6 ± 1.5 (1.0–7.0)	4.1 ± 2.0 (1.0–8.0)	4.1 ± 1.8 (1.0–8.0)	NS

Data are mean ± SD values (range).

^aFirst quartile versus fourth quartile, by *t* test for unpaired data.

BMI, body mass index; HbA1c, glycosylated hemoglobin; ND, not determined; NS, not significant.

FIG. 1. Linear relationship between the mean glycosylated hemoglobin (MHbA1c) throughout all the follow-up and the interval diabetes onset–pump commencement (expressed as days).

t test for independent samples was also used to compare, within each quartile, the baseline HbA1c with the yearly MHbA1c values. ANOVAs and *t* tests were limited until the year whose smallest group showed a number of patients (*n*) of >10. All tests were two-tailed. When continuous variables showed a skewed distribution, the data were logarithmically transformed. Values of *P* < 0.05 were considered significant. When the trend analysis showed more than one significant trend, only the *P* values of the simpler trend (linear simpler than quadratic; quadratic simpler than cubic) are described. Data are expressed as mean ± SD values, unless otherwise specified.

Results

In total, 684 patients attending the Regional Reference Center for Diabetology and Insulin Pumps from January 2005 to September 2013 used insulin pump therapy. One hundred nineteen patients met the inclusion criteria; six patients were excluded because they discontinued CSII within the first year after pump initiation. Therefore, the statistical analysis included 113 patients. Baseline clinical and metabolic parameters of all the patients included in the study are showed in Table 1. Fourteen patients reverted back to MDI 2–6 years after pump commencement.

The regression analysis showed that only the interval onset–commencement was a linear predictor of the MHbA1c (*P* = 0.001; coefficient of the coefficient of determination $R^2 = 0.089$) (Fig. 1). The regression equation that expressed the linear relationship between the MHbA1c and the interval onset–commencement was as follows: MHbA1c (expressed as a percentage) = $7.6025 + (0.001366 \times \text{interval onset–commencement})$ (expressed as days). The other clinical and metabolic parameters were not useful as predictors: age at onset, *P* = 0.747; age at pump commencement, *P* = 0.521; baseline HbA1c, *P* = 0.527; follow-up duration, *P* = 0.922; and body mass index at commencement, *P* = 0.455.

The ANOVA for repeated measures, limited to the 30 patients who completed the sixth year of follow-up, showed a significant reduction of the yearly MHbA1c from baseline (*P* < 0.001; *F* = 10.86), with a significant quadratic trend

(*P* < 0.001). The yearly MHbA1c, from the first until the sixth year, was significantly lower than baseline HbA1c (by *t* test for unpaired samples: baseline HbA1c vs. yearly MHbA1c at the first, second, third, and fourth year, *P* < 0.0001; baseline HbA1c vs. yearly MHbA1c at the fifth year, *P* = 0.0004; baseline HbA1c vs. yearly MHbA1c at the sixth year, *P* = 0.001); the seventh and eighth years were not considered for statistical analysis because the number of patients was ≤ 10 (Fig. 2).

The four quartiles, obtained dividing the patients on the basis of the interval onset–commencement, showed the baseline clinical and metabolic parameters illustrated in Table 1: at pump initiation, the patients of the first quartile were significantly younger than the patients of the fourth quartile (8.2 ± 5.5 SD vs. 11.8 ± 5.4 years of age [mean ± SD]; *P* = 0.017). After the follow-up, the MHbA1c levels of the first and second quartiles were significantly lower than the MHbA1c of the fourth quartile ($7.6 \pm 0.8\%$ and $7.8 \pm 1.0\%$, respectively, vs. $8.5 \pm 0.8\%$; *P* < 0.001 and *P* = 0.004, respectively) (Fig. 3). The comparison of the HbA1c values within the quartiles, from the baseline HbA1c throughout the follow-up (yearly MHbA1c values) showed significant within-subjects effects in the first, second, and third quartiles (by ANOVA for repeated measures: *P* < 0.001, *P* = 0.009, and *P* < 0.001, respectively), with significant results of the trend analysis (first quartile, linear trend, *P* = 0.0069; second quartile, cubic trend, *P* = 0.006; third quartile, quadratic trend, *P* < 0.0001). Significant between-subjects effects were found comparing only the first with the fourth quartile (test of between-subjects effects,

FIG. 2. Glycosylated hemoglobin (HbA1c) at commencement and mean yearly HbA1c throughout the follow-up (first, second, third, fourth, fifth, sixth, seventh, and eighth years). The bars express the SD; the horizontal lines on the bars express the mean values. All HbA1c values are expressed as percentages. The analysis of variance for repeated measures, limited to the 30 patients who completed the sixth year of follow-up, showed a significant reduction of the HbA1c level from baseline (*P* < 0.001; *F* = 10.86). The comparisons between HbA1c at baseline and the mean yearly HbA1c, from the first until the sixth year (by *t* test for independent samples) are also shown; comparisons at the seventh and eighth years were not determined (n.d.) because the number of patients was ≤ 10.

FIG. 3. Comparison of the mean glycosylated hemoglobin (MHbA1c) throughout all the follow-up of four quartiles obtained dividing the sample on the basis of the interval diabetes onset–pump commencement. The bars express the SD; the horizontal lines on the bars express the mean values. Only those comparisons with significant results (by *t* test for independent samples, $P < 0.05$) are shown here.

$P = 0.023$, $F = 5.63$; test of within-subjects effects, $P < 0.001$, $F = 13.36$) and the second with the fourth quartile (test of between-subjects effects, $P = 0.045$, $F = 4.37$; test of within-subjects effects, $P = 0.001$, $F = 5.15$) (Fig. 4). Comparison of the baseline HbA1c with the yearly MHbA1c values, within each quartile (by *t* test for independent samples), showed that the yearly MHbA1c was significantly reduced at the first, second, third, and fourth years of follow-up, in both the first and second quartiles; in the third and fourth quartiles, yearly MHbA1c was significantly reduced in the first, second, and third years and in the first and second years of follow-up, respectively. The yearly MHbA1c values from the fifth until the eighth year were not considered for statistical analysis within and between the quartiles because the number of patients was ≤ 10 .

Discussion

The present study shows, in children and adolescents with T1DM treated with insulin pumps, a significant reduction of HbA1c level from the pump commencement until the sixth year of follow-up.

The magnitude of the reduction is 0.9%, a figure higher than the 0.17–0.25% obtained by the meta-analyses of crossover trials^{4,5}; the reduction obtained in the present study is also higher than the figures of 0.2–0.7% reported by many different observational studies.^{10–14} Moreover, the latter studies show a follow-up ranging from 1 to 5 years,^{10–14} which is shorter than in the present work. Nevertheless, an observational study with a follow-up duration of 7 years reported, in an Italian cohort (and with the use of advanced pump features), only a stabilization of HbA1c level at the end of the follow-up.¹⁵ Moreover, our study shows that the HbA1c reduction trend in the whole sample was significant throughout the follow-up, in agreement with similar observational studies.^{15,16} Of note is that the results of the present

study were obtained with a sample of subjects who made negligible use of continuous glucose monitoring. In fact, at our center we prefer to spare, when possible, the cost of a glucose sensor to address a consistent part of the yearly budget to purchasing and maintaining a greater number of insulin pumps; the main reason for this policy is to improve the accessibility of insulin pumps for children and adolescents with lower socioeconomic status, who would be otherwise unable to access to CSII.²¹

However, the most relevant finding of our study is that the interval onset–commencement is a linear predictor of MHbA1c throughout the follow-up: the shorter the interval, the lower the HbA1c level. Our results are in partial agreement with a previous observational study from Pinhas-Hamiel et al.,¹⁹ who demonstrated that lower HbA1c levels during a long-term follow-up (up to 7 years) are related to an interval onset–commencement of ≤ 1 year, but also other predictors, not useful in our model, were found: a baseline HbA1c level of $\leq 7.5\%$ and a younger age at pump initiation. Another observational study from Shalitin et al.¹⁸ showed that a shorter diabetes duration is, together with other predictors, related to the achievement of the target HbA1c level. Conversely, in a subsequent study, Shalitin et al.²⁰ found that starting pump therapy at an early disease stage did not improve the glycemic control over time when compared with starting later. The results of the latter studies are not fully comparable with our work, mainly because the younger age at diagnosis and/or at pump initiation and the shorter interval for diabetes onset–pump commencement.

To further test the long-term predictive value of the interval diabetes onset–pump commencement, we categorized the whole sample into four quartiles: the subjects who initiated the pump therapy ≤ 61 days (first quartile) or 62–181 days (second quartile) after the onset showed a MHbA1c throughout the follow-up that was lower by 0.9% and 0.7%, respectively, than the subjects who initiated pump therapy after ≥ 485 days (fourth quartile). Similarly, the yearly MHbA1c values during the follow-up were lower, year by year, comparing first and second with fourth quartile. Again, the first and second quartiles maintained, for more years than the third and fourth quartiles, significantly decreased values of yearly MHbA1c from baseline. Summarizing these findings, the achievement and maintenance of low HbA1c values is better obtained when the insulin pumps are initiated earlier (≤ 181 days) after the onset of diabetes.

The Diabetes Control and Complications Trial showed that an early intensive insulin therapy resulted in a longer retention of residual endogenous insulin secretion, lower HbA1c levels, and a reduced risk of diabetes complications than conventional therapy.^{22,23} Some subsequent intervention studies, but with a short follow-up duration (≤ 24 months), showed that an early pump commencement has a favorable effect on residual β -cell function and glycemic control^{24,25} and that using a sensor-augmented pump led to similar results.^{26,27} It is possible that the better glycemic control observed in our study in the first and second quartiles is related to a better preservation of residual β -cell function; in other words, an early pump commencement could prolong the honeymoon phase. However, we cannot confirm or exclude this hypothesis because of the lack of data about C-peptide levels during the follow-up.

Different scientific societies have produced clinical recommendations containing the indications on CSII treatment

FIG. 4. Glycosylated hemoglobin (HbA1c) at pump commencement baseline and mean yearly HbA1c of four quartiles obtained dividing the sample on the basis of the interval diabetes onset–pump commencement. The bars express the SD; the horizontal lines on the bars express the mean values. All the HbA1c values are expressed as percentages. Also shown are the comparisons between HbA1c at baseline and the mean yearly HbA1c, from the first until the fourth year (by *t* test for independent samples); the fifth through eighth years were not considered for statistical analysis because the number of patients was small. By analysis of variance for repeated measures, within-subjects effects: * $P < 0.001$, ** $P = 0.009$, *** $P < 0.001$. ^For first versus fourth quartile, by analysis of variance for repeated measures: between-subjects effects, $P = 0.023$, $F = 5.63$; within-subjects effects, $P < 0.001$, $F = 13.36$. ^^For second versus fourth quartile, by analysis of variance for repeated measures: between-subjects effects, $P = 0.045$, $F = 4.37$; within-subjects effects, $P = 0.001$, $F = 5.15$.

in individuals with T1DM. These indications are mainly based on high HbA1c levels at baseline: the United Kingdom National Institute for Health and Clinical Excellence recommends insulin pump therapy when individuals >12 years old show HbA1c levels persistently $\geq 8.5\%$ ²⁸; the Société Francophone du Diabète uses a threshold of 7.5% for both adults and children²⁹; and the American Association of Clinical Endocrinologists³⁰ and another consensus from five scientific societies³¹ recommends CSII for subjects who do not reach glycemic goals, without an explicit HbA1c value.

The robust evidence that supports all these recommendations is centered on the CSII-lowering effect on HbA1c levels in comparison with MDI,^{28–31} and this effect is strongly and inversely related to the baseline HbA1c value.^{2,3} However, the Diabetes Control and Complications Trial and the subsequent Epidemiology of Diabetes Interventions and Complications Study demonstrated that the most relevant factor

that predicts the reduction of the complications of diabetes mellitus is the ability of the therapy to achieve and maintain an HbA1c value at below or around 7%, and not the effect of therapy on the absolute reduction of HbA1c values.^{32,33}

The present observational study suggests that an early pump commencement in children and adolescents with T1DM provides lower and more durable HbA1c values than a late commencement, independent of other factors, such as baseline HbA1c, age at diagnosis, or age at commencement. The applications of new technologies to diabetes management could produce interesting results,³⁴ but further studies are needed to confirm the relevance of an early commencement of insulin pumps on long-term outcomes in individuals with T1DM.

Author Disclosure Statement

No competing financial interests exist.

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