Effectiveness of continuous subcutaneous insulin infusion pump therapy during five years of treatment on metabolic control in children and adolescents with Type 1 diabetes mellitus.

**RUNNING TITLE:** Comparison of long term CSII with MDI in young people with Type 1 diabetes mellitus

**AUTHORS:** Özlem Korkmaz, Günyay Demir, Hafize Çetin, İlkin Mecidov, Yasemin Atik Altınoğlu, Samim Özen, Şükran Darcan, Damla Göksen

**INSTITUTE(S):** Ege University Faculty of Medicine Department of Pediatric Endocrinology and Diabetes

**CORRESPONDING AUTHOR:** Prof. Damla Göksen, MD

**CORRESPONDING AUTHOR FULL POSTAL ADDRESS:** Ege University Faculty of Medicine, Department of Pediatric Endocrinology and Diabetes, Ege University, 35100 Bornova, İzmir, Turkey

**CORRESPONDING AUTHOR EMAIL ADDRESS:**

damla.goksen68@gmail.com

Word count: 4009

No funding sources

Nothing to declare

**Novelty Statement**

This data shows that with CSII treatment Type 1 diabetic children and adolescents can achieve better metabolic control than MDI treatment in long term.

**Ethic Committee Approval:** Yes

**Consent Form:** No

**What is already known on this topic**

With intensive insulin therapy Type 1 diabetic children achieves good metabolic control in children and adolescents.

**What this study adds**

This data shows that with CSII treatment Type 1 diabetic children and adolescents can achieve better metabolic control than MDI treatment in long term.
ABSTRACT

Aim: To compare continuous subcutaneous insulin infusion therapy (CSII) with multiple daily insulin therapy (MDI) on metabolic control in children and adolescents with type 1 diabetes mellitus (T1DM) over the long term.

Method: 52 T1DM patients treated with CSII and monitored for at least 1 year prior to and at least five years following CSII were included. 38 age and sex-matched MDI controls with a 5-year follow up were recruited.

Results: Mean age of the subjects, duration of diabetes and CSII therapy were 17.0±4.8 years, 10.7±2.8 years and 7.7±1.5 years respectively. Mean HbA1c in the year prior to CSII, during the first year of treatment and after 5 years of CSII were 7.3±1% (56 mmol/mol), 7.0±0.7% (53 mmol/mol) and 7.8±1.3% (62 mmol/mol) respectively. Initial and 5-year mean HbA1C levels of controls were 7.9±1.08% and 8.6±1.8%. Mean HbA1c values were significantly lower in those receiving CSII therapy throughout follow-up. Basal and total insulin doses were significantly lower in the CSII group at all times. HbA1c was compared between subjects by age (0-5, 6-11 and 12-18 years) with no significant difference between them.

Conclusion: Although CSII mean HbA1c values exceeded accepted good metabolic control limits after 5 years, CSII produces better HbA1c control at all times and in all age groups compared to MDI.

Keywords: Type 1 diabetes mellitus, continuous subcutaneous insulin infusion pump therapy, multiple daily insulin therapy, HbA1c

INTRODUCTION

Continuous subcutaneous insulin infusion therapy (CSII) has been used in the treatment of type 1 DM (T1DM) since the 1970’s and is increasingly used as an alternative to multiple daily insulin therapy (MDI) as pumps have become more widely available. Its effectiveness has been confirmed by meta-analyses of various observational and randomized controlled studies and in childhood and adolescence studies [1, 2]. The therapeutic goal in T1DM is to establish good and close-to-normal glycemic control, without hypoglycemic attacks, in order to protect against microvascular and macrovascular complications [3]. The International Society for Pediatric and Adolescent Diabetes (ISPAD), International Diabetes Federation (IDF) and the American Diabetes Association (ADA) cite a recommended HbA1c value of <7.5% in the pediatric age group.

CSII therapy is the most physiological insulin therapy currently available, more closely mimicking daily insulin release and is also reported to improve patients’ quality of life [4, 5]. Only a small percentage of patients achieve desired glycemic targets with MDI therapy [4, 6]. Although several studies have shown a decrease in HbA1c levels with CSII compared to MDI, the HbA1c levels recommended by the ISPAD/IDF/ADA have not been achieved in most studies. In some studies, however, no improvement was observed in HbA1c levels, or levels returned to pre-CSII values at the end of 3-4 years. The limitation of the majority of these studies is the short follow-up time (0.6-8.8 years). Long-term observation studies are therefore needed to determine the efficacy of CSII therapy [7, 8, 9].

The aim of this study was to assess the effect of CSII treatment on long-term metabolic control in children and adolescents diagnosed with T1DM and compare it to those treated with multiple daily insulin therapy (MDI).
MATERIALS AND METHODS

Type 1 diabetic patients aged between 2-18 years started on CSII therapy between January 2004 and December 2011 at a single centre and subsequently monitored for at least 5 years were included in the study. Demographic data of the patients, insulin doses, insulin/carbohydrate ratios, daily basal and bolus insulin (food and correction bolus) levels, frequency of capillary blood glucose monitoring, incidence of hypoglycemic attacks, episodes of diabetic ketoacidosis and HbA1c values were obtained retrospectively from file data recorded at every 3-monthly clinic visit. All patients were monitored by a team consisting of a pediatric endocrinology specialist, a diabetes nurse and a dietician. Anthropometric data were converted to standard deviation scores by using Turkish standard data [10]. BMI was calculated using the standard formula weight/height² (kg/m²). HbA1c was measured by turbidimetric inhibition immunoassay (Tina-quant HbA1c Gen. 3) (Normal range: 4.8-5.9%). Severe hypoglycemia was recorded as an event with symptoms consistent with hypoglycemia in which the patient required assistance from another person or resulted in seizure/coma [11]. Incidence rate of severe hypoglycemic episodes was calculated as number of episodes per 100 patient-years. All children were on Minimed Paradigm Insulin Pump (Minimed Medtronic; Northridge). CSII data for all cases were evaluated with pump data transferred to computer (CareLink® Pro Therapy Management Software, Minimed Medtronic; Northridge) at each visit. Patients aged between 2-18 years and treated with basal bolus regimen with MDI with both the same duration of diabetes and a monitoring period of at least 5 years were enrolled as the control group. CSII patients were classified in three different groups: preschoolers (≤6 years old) n:16, prepubertal (6 years to Tanner stage 2) n:18 and pubertal n:18. Patients who had at least Tanner 2 breast development or testicular volume ≥4 ml were included in the pubertal group [12]. CSII patients were also stratified according to well, moderate and poor metabolic control (% HbA1c: <7.5, 7.5-9 and > 9) (< 58, 58-75 and >75).

Before initiating CSII therapy, all patients and their families completed a training program. Patients refusing to complete informed voluntary consent forms, with diagnosed psychiatric disorders or a monitoring period of less than 5 years were excluded from the study. Ege University Medical Faculty Clinical Investigations Ethical committee approval was obtained for the study.

Statistical Analysis

Normal distribution of data was assessed using the Shapiro-Wilks test with p>0.05 indicating normal distribution. Chi square analysis was performed for categoric variables. Two-group HbA1c comparisons were performed using Mann-Whitney test. The Wilcoxon matched two samples test was used to determine variation over time in the groups. T test was used for comparisons between independent variables when comparing CSII and MDI groups. Analysis of variance was performed for recurring measurements in the analysis of groups determined on the basis of age groups. The Bonferroni test was used for multiple comparisons between times. Linear correlation between variables was evaluated using Pearson’s correlation analysis.

RESULTS

Demographic data

Ninety cases diagnosed with type 1 DM were included in the study. Fifty-two patients (57%) were on CSII therapy and 38 (43%) were on MDI. 48.1% were males and 51.9% were females in the CSII group. 44.7% were males and 55.3% were females in the MDI group. Mean age and duration of diabetes on CSII at the time of enrolment was 17.0±4.8 and 10.7±2.8 years respectively. Mean duration of CSII therapy was 7.7±1.5 years. Mean age of the subjects on MDI therapy was 17.6±3.5 years, and duration of diabetes was 10.1±3.9 years. There was no difference in terms of age of the subjects and duration of diabetes between the CSII and MDI groups.

Metabolic control
Mean HbA1c in the year prior to initiation of CSII was 7.3±1.0 % (56 mmol/mol) while mean HbA1c at the end of the first year of CSII was 7.0±0.7 % (53 mmol/mol). At the latter time point HbA1c levels were <7.5% (<58 mmol/mol) in 78.8% of cases. Mean HbA1c at the end of 5 years was 7.8±1.3% (62 mmol/mol). In the CSII group 19 patients (39%) still had a mean HbA1c <7.5% (<58 mmol/mol) at the end of the fifth year. Mean initial and 5-year HbA1c levels of cases on MDI therapy were 7.7±1.04% (61 mmol/mol) and 8.6±1.8% (70 mmol/mol) respectively and nine (23%) of the patients’ HbA1c were <7.5% (<58 mmol/mol) at the end of fifth year. Mean change in HbA1c at the end of 5 years in the CSII group was 0.5±1.5 compared with 0.6±1.9 in the MDI group and there was no significant difference between the groups with respect to change in HbA1c (Table 1). Mean HbA1c was significantly lower in the CSII group throughout the five year follow up (p<0.05; Figure 1). No correlation was found between HbA1c levels and age, sex, duration of diabetes, duration of CSII or insulin doses used.

There was no significant difference in HbA1c in the CSII group when sub-grouped according to age (Figure 2). HbA1c levels increased during follow-up in all age groups.

At the end of the fifth year of CSII therapy HbA1c of the patients in the well controlled group increased to 7.6±0.8 % (60 mmol/mol) from 6.8±0.6 % (51 mmol/mol). The group with the moderate control decreased HbA1c levels during the first year but HbA1c increased by the end of the fifth year. In the poor metabolic control group, although HbA1c decreased in the first year, at the end of the fifth year it had again increased but in no patient did it exceed pre-treatment HbA1c levels (Table 2).

**Insulin Dosage**

Children using MDI therapy used lower total daily insulin doses compared to those treated with CSII at the beginning of therapy (MDI: 0.96±0.21 U/kg/d; CSII: 1.2±0.35 U/kg/d respectively). Daily insulin dose decreased to 0.83±0.21 U/kg/d at the end of one year of CSII. No time-dependent changes in daily insulin dose were observed between the two groups during the subsequent years (Figure 3).

Basal insulin dose in the first year of treatment was 0.36±0.14 U/kg/d in the CSII group vs 0.48±0.19 U/kg/d in the MDI group. No time-dependent change was found in basal insulin throughout follow up in the two groups. Basal insulin dose were significantly lower in the CSII group compared to the MDI group at all of the time periods (p<0.05; Figure 3). When cases were assessed in terms of age within the CSII group, the basal insulin doses used by subjects aged over 12 was higher than that in the other age groups.

Bolus insulin used in the first year of treatment was 0.46±0.25 U/kg/d in the CSII group and 0.47±0.17 U/kg/d in the MDI group. No statistically significant difference was found between the groups at 5-year follow period (Figure 3). Neither was there a difference in terms of bolus insulin doses found between age groups.

**Anthropometric Data**

BMI SDS at start of therapy was 0.39±0.95 SD in the CSII group and 0.39±0.85 SD in the MDI group. At the end of 5 years it was 0.49±1.01 SD in the CSII group and 0.34±0.87 SD in the MDI group. At the beginning of the study, there were three obese cases, but this increased to five at the end of the study period (two CSII, three MDI). Although BMI SDS in the CSII group increased in the first and second years, there was no statistically significant difference between the groups at 5-year follow up (Figure 4).

**Adverse Events**

Diabetic ketoacidosis was observed in one of the CSII cases (0.31/100-patient-years) and four of the patients on MDI treatment (2.1/100-patient-years) during monitoring, while severe hypoglycemia was seen in two patients in the CSII group (0.62/100-patient-years) and in one case in the MDI group (1.9/100-patient-years).
DISCUSSION

CSII is a safe and effective therapeutic technique in children and adolescents diagnosed with type 1 DM. There has been a significant increase in its application in the last 10 years, although there are still differences in rates of use between countries [13]. Various studies have shown that CSII improves glycemic control and increases patients’ quality of life, without increasing the incidence of hypo or hyperglycemic episodes [14-16]. However, target HbA1c levels of <7.5%, based on ADA/IDF/ISPAD recommendations, have not been achieved in the majority of these studies. Although there have been several studies about the effectiveness of CSII, a short monitoring period has been a limitation in most of these studies [4]. In one study over a 2 year follow up period, HbA1c levels, despite improving in the first 6 months tended to increase over the subsequent 18-month period in pump patients. At longer term follow-up of up to 5 years, the initial decrease in HbA1c was described as a temporary improvement, while an increase in HbA1c levels was observed in later periods [17]. A meta-analysis of results of various randomized, controlled studies have shown that a decrease in HbA1c levels of 0-0.9% has been achieved with CSII when the duration of intervention ranged from 6 to 12 months [18]. At the end of the first year in this study there was a significant decrease in HbA1c with 78.8% of the patients <7.5% (58 mmol/mol). Although mean HbA1c levels were lower in the patients receiving CSII during follow up, mean HbA1c increased to 7.8±1.3% (62 mmol/mol) at the end of the fifth year from 7.3±1.0% (56 mmol/mol) before CSII initiation. The increase in HbA1c in our patients after the first year could be due to increasing age, duration of diabetes or due to decreased compliance of the patients. One multi-center study reported lower HbA1c levels in all age groups in a group receiving CSII compared to MDI patients [13]. Another study from Denmark showed lower HbA1c levels at all years in the CSII group, followed up for more than 5 years, in keeping with our findings [19]. In the Danish study, although a marked improvement was observed in HbA1c levels in the first year of CSII, HbA1c levels tended to increase in subsequent years with the best metabolic control established one year after CSII initiation. We found exactly the same pattern of metabolic control in our study group. The lower mean HbA1c in the CSII group throughout the five year maybe due to short duration of CSII treatment which is a relatively recent treatment modality compared to MDI treatment. At the end of fifth year of therapy, HbA1c of the patients in well and moderately controlled groups increased. In the poorly controlled group HbA1c decreased in the first year similarly to the other groups but the rate of increase after the first year was slower than the other groups. A long term aim should be to develop new approaches to prevent the impairment of metabolic control over the long-term which mirrors the short term improvement seen in metabolic control in first year of therapy. Repetition of periodic diabetes education and planning of practices that increase motivation, such as motivational interviewing, should be recommended.

When metabolic control was analyzed according to age groups no significant difference was observed throughout the 5 year follow up period in all the age groups in our study. In a study by Johnson et al, with respect to different age groups, the older age groups (6–12 years and >12 years) had the most dramatic initial improvement of glycaemic control compared with the <6-year age group upon commencement of insulin pump therapy, with HbA1c decreasing by 0.6 to 0.8% within 3 months [20]. Over the following 5 years, each age group on CSII showed an improvement compared with non-CSII counterparts. However, the initial HbA1c was lowest in the <6-year-old group, followed by the 6 to 12 year olds and then the >12 year olds. The mean HbA1c of the <6-year-old pump cohort remained below 7.5% (58 mmol/mol) from 6 months through the first 5 years of follow-up.

An increase was found in BMI SDS in the first and second years of CSII in our study. This might be attributed to patients initially adopting a more flexible dietary model with CSII. However at the end of 5-year follow-up, no significant difference was seen between the CSII and MDI groups in terms of mean BMI SDS. There was no relation between BMI SDS and poor metabolic control. The SWEET study group reported similar BMI SDS in CSII and MDI patients. Significant increase in BMI SDS was found in the 6-12 age group when compared with the MDI treatment group, but when linear regression analysis was performed on the basis of duration of diabetes, no significant variation was observed between the two treatment groups [13]. Johnson et al. also reported a similar change in BMI.
SDS in CSII and MDI groups [20]. No difference was found in change in BMI SDS during follow-up in terms of the age groups in our study (p=0.885). There was also no correlation between HbA1c and BMI SDS. The impact of CSII treatment on BMI is different in every study as shown by our study and other studies. Longer follow up periods are needed to draw a conclusion on BMI in children and adolescents on pump therapy.

Total daily insulin doses recommended by IDF/ISPAD in prepubertal and pubertal children are 0.7-1U/kg/d and 1-2U/kg/d respectively. A potentially greater insulin requirement has been reported due to insulin resistance in puberty [21]. In our study, total insulin dose used before initiation of CSII was significantly higher than the total dose used after CSII therapy commencement and the MDI group’s total daily insulin dose was higher than the CSII group throughout follow up. In the SWEET study, CSII patients used lower-dose insulin compared to subjects on MDI [13]. Similarly, Pickup et al. also observed a lower daily insulin dose in the CSII group [1]. When patients in our study were analyzed according to age groups, daily and basal insulin doses were higher in subjects over 12 years, possibly reflecting early puberty insulin requirement increases or to a flexible lifestyle change with CSII or a combination of the two factors. Studies have reported that lower HbA1c levels are associated with a higher basal insulin levels [22]. However, no relation between HbA1c and basal insulin doses was observed in our study. Conversely as a single center study, all the patients were monitored with the same treatment protocol which is a strength in terms of standardization of laboratory results, measurement techniques, patient counseling and team approach to management.

In conclusion, although HbA1c values were not within recommended metabolic control limits with either treatment modality at the end of the five years follow up, CSII produces better metabolic control compared to MDI over the long-term.

References


Table 2: Comparison of metabolic control during the five year follow-up in the CSII group in terms of well, moderate and poor metabolic control prior to pump therapy initiation.

<table>
<thead>
<tr>
<th>Metabolic Control At the beginning of the study</th>
<th>At the beginning</th>
<th>1st year</th>
<th>5th year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good &lt;7.5 (n=37)</td>
<td>6.8±0.6*</td>
<td>6.9±0.7**</td>
<td>7.6±0.8</td>
</tr>
<tr>
<td>Medium 7.5-9 (n=9)</td>
<td>7.7±0.2</td>
<td>6.9±0.8</td>
<td>8.7±2.0</td>
</tr>
<tr>
<td>Poor &gt;9 (n=6)</td>
<td>9.6±0.5*</td>
<td>7.6±0.8***</td>
<td>8.2±1.4</td>
</tr>
</tbody>
</table>

* p<0.05 between initiation of pump and 5th years

**p<0.05 between 1st and 5th years
***p<0.05 between initiation of pump and 1st years

**Figure 1:** Comparison of the mean HbA1c values between the two treatment groups during the five year follow-up period.

**Figure 2:** Mean HbA1c levels in the CSII patients by age group during the five year follow-up period.
Figure 3: Comparison of the daily insulin dose between the two treatment groups during the five year follow-up period.

Figure 4: Body Mass Index SDS values during the five year follow-up period.