Diabetes Ther (2018) 9:2091–2098
https://doi.org/10.1007/s13300-018-0510-5

ORIGINAL RESEARCH

Continuous Subcutaneous Insulin Infusion Characteristics in Type 1 Diabetes Children and Adolescents in Qatar

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Received: July 26, 2018 / Published online: September 15, 2018

ABSTRACT

Aim: To describe continuous subcutaneous insulin infusion (CSII) characteristics in type 1 diabetes mellitus (T1DM) children and adolescents using a standardized protocol in routine clinical settings in Qatar.

Methods: A total of 138 T1DM patients (62 males; 76 females; mean age 9.8 ± 3.4 years) with a mean diabetes duration of 2.4 ± 1.9 years initiated CSII (MiniMed® Veo®™ and MiniMed® 640 G insulin pumps; Medtronic, Northridge, CA, USA) in 2016 and 2017. CSII characteristics and glycated hemoglobin (HbA1c) were evaluated 1 year after treatment initiation.

Results: At 1 year after treatment initiation, the insulin dose had significantly increased (from 0.59 ± 0.23 to 0.74 ± 0.26 U/kg body weight per 24; $P < 0.05$), and the HbA1c level had significantly decreased (from 9.7 ± 1.3 to 8.1 ± 0.6%; $P < 0.05$). More than 92% of patients used the Bolus Wizard feature of the insulin pump at the following settings: insulin-to-carbohydrate ratio 19.2 ± 9.3 g; insulin sensitivity factor 131 ± 68 mg/dl; target range 91 ± 9.3–135 ± 14.2 mg/dl; active insulin time 3.8 ± 0.8 h.

Conclusion: Our results show that CSII may significantly improve glucose control in T1D children and adolescents who use a standardized protocol. A reduction of HbA1c by − 1.6% was achieved at 1 year after CSII initiation. These results need to be confirmed in a study with a longer duration.

Keywords: CSII; Glucose control; Type 1 diabetes

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic condition that is generally diagnosed in children and adolescents. Its incidence and prevalence is increasing worldwide [1, 2]. The general goals of the treatment of T1D are to maintain blood glucose levels as normal as possible through intensive insulin therapy, to reduce the frequency of hypoglycemia, to prevent serious long-term complications, and to improve the quality of life [3, 4].

Continuous subcutaneous insulin infusion (CSII), as one of the treatment options for T1DM, can improve glucose control [5, 6] with fewer hypoglycemic events [7, 8], decrease glycemic variability, and improve the quality of life

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of the patient. Scientific and technological developments in CSII and continuous glucose monitoring (CGM) with such functions as alarms for high and low glucose levels, predictive low glucose suspend (PLGS), and low glucose suspend (LGS) have resulted in a substantial increase in the use of insulin pumps worldwide [9–11]. Suspending basal insulin delivery in response to sensor-detected low glucose levels is an established strategy to reduce the severity and duration of hypoglycemic events [12–14], and suspending basal insulin delivery in response to predicted hypoglycemia (PLGS) has been tested in studies using various configurations of pumps, sensors, induction protocols, and algorithms [15, 16].

Over the past three decades, major social and economic changes have transformed many of the countries in the Middle East. Qatar has undergone rapid economic growth and urbanization associated with reduced infant mortality and increasing life expectancy [17]. Healthcare authorities have made diabetes prevention and treatment a national priority. Insulin pumps and glucose sensors are reimbursed at different levels: full reimbursement for Qatari Nationals; partial reimbursement for insurance holders; and charity support for patients from lower socio-economic groups. Sidra Medicine in Doha is a private institution that provides government services and is the only center in Qatar that provides treatment for children with T1DM below 18 years of age. More than 900 children with diabetes have been treated at our institution.

The objective of this study was to describe CSII characteristics in T1D children using a standardized protocol in routine clinical settings in Qatar.

METHODS

This retrospective and cross-sectional study was conducted by the Pediatric Endocrine Division, Sidra Medicine, Doha, Qatar. The study enrolled all T1D children and adolescents who started using an insulin pump (MiniMed® 640 G or MiniMed® Veo™; Medtronic, Northridge, CA, USA) in 2016 and 2017.

In this study, for the patient to be started on CSII he/she had to meet one of the following criteria: inadequate glycemic control with multiple daily insulin injections (MDI); recurrent hyperglycemia; dawn phenomenon; recurrent severe hypoglycemia; frequent diabetic ketoacidosis (DKA), erratic blood glucose; lifestyle flexibility. Patients were excluded from the study if T1DM was not firmly established; the duration of T1DM was < 3 months; CSII use was transitory (< 3 months).

Carbohydrate counting education sessions were delivered to all patients by a registered dietitian to ensure accurate carbohydrate counting before CSII initiation.

According to our standards of care, diabetes educators initiated CSII treatment during a 5-day (12 h) out-patient group education program (2–3 patients per group). A structured plan was delivered with written literature to support learning. The group education program started with CGM initiation, followed by a daily program on technical skills (pump button pushing, calibration, use of the Bolus Wizard feature, and infusion set change, alerts and alarms, etc.) and theoretical issues (sick day, exercise, hypoglycemia and hyperglycemia management, troubleshooting, etc.). The glucose sensor in the Veo™ insulin pump was used according to patient affordability.

A standardized protocol for CSII initiation was used for all patients. CSII therapy was usually started with a 0–20% reduction in total daily dose (TDD) of MDI, basal/bolus distribution 40/60%, and five basal rates (timings individualized for patient age and daily routine). An insulin-to-carbohydrate ratio (ICHR) formula of 300–450/TDD and insulin sensitivity factor (ISF) formula of 1800/TDD (mg/dl) were targeted. The glucose target range was set to the range 80–130 mg/dl using two ICHR (breakfast time usually 10–20% lower than daytime) and two ISF formulae (nighttime usually 10–20% higher than the daytime). We developed a computerized program that calculates the initial CSII settings according TDD, patient age and weight, and daily routine activity. The physician initiated the CSII based on standardized protocol and a 7-day CGM profile (if any) obtained 1 week before.

Baseline data at CSII initiation and cross-sectional analysis were collected through the electronic medical record system (Cerner Millennium, North Kansas City, USA) and included sex, age, weight, diabetes duration, initial and follow-up HbA1c level. Collected data were analyzed together with CSII reports generated by Carelink Therapy Management Software (Medtronic) upon CSII initiation and 1 year later.

Statistical analysis was performed using SAS software version 12.5 for Windows (SAS Institute, Cary, NC, USA). Quantitative variables are expressed as the mean ± standard deviation. Number of basal rates, ICHR, and ISF were expressed as the median with the interquartile range. HbA1c variation from baseline was analyzed using the paired Student *t* test. A *P* value of < 0.05 was considered to denote significance.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research ethics committee (Sidra Medicine, Qatar) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed and assent consent was obtained from the patient and his/her caregiver.

RESULTS

Among the 161 children who started CSII, 138 patients met the criteria for analysis (as shown in Fig. 1). Demographic characteristics of the study population are presented in Table 1. Indications for initiation of CSII therapy were: high HbA1c (57%), dawn phenomenon (21%), glucose excursions (14%), hypoglycemia (1%), and patient preference (7%).

Of the 138 patients, 89 were started on the MiniMed® 640 G insulin pump, 11 were started on the MiniMed® Veo™ insulin pump with sensor, and 38 patients were started on the MiniMed® Veo™ insulin pump without sensor. The total daily insulin (TDI) dose had significantly increased ($P < 0.05$) by the end of the study. The majority of patients (> 92%) used the Bolus Wizard feature of the insulin pump on a regular basis. The Bolus Wizard settings showed two ICHR (67% of the patients), where the morning ICHR was 18% lower than the other one; two ISF (85% of the patients), where the evening ISF was 23% higher than the other one; active insulin time of 4 h (86%) and 3 h (14%); one target range in all patients. Five basal rates were found in 92% of patients and four basal rates were found in 8% of the patients. The LGS on the MiniMed® Veo™ insulin pump was set at 78 ± 11 mg/dl and showed 0.3 ± 0.2 events per patient per day. The PLGS on the MiniMed®

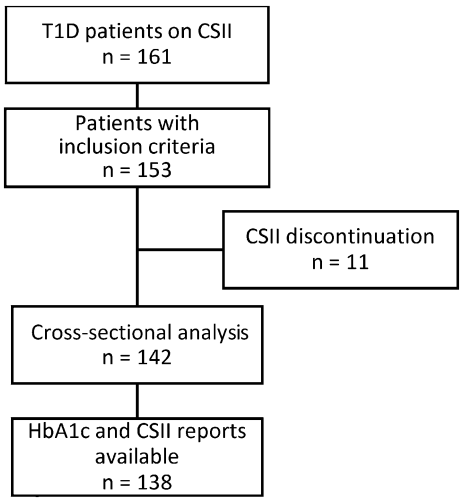

Fig. 1 Flow chart of patient entry. *CSII* Continuous subcutaneous insulin infusion, *HbA1c* glycated hemoglobin, *T1D* type 1 diabetes mellitus

Table 1 Demographic characteristics of patients

Demographic characteristics	Values
Age (years)	9.8 ± 3.4
Total number of patients	138
Male (*N*)	62
Female (*N*)	76
Diabetes duration (years)	2.4 ± 1.9
HbA1c at CSII (%)	9.7 ± 1.3
HbA1c (mmol/mol)	83 ± 14

Values in table are presented as the mean ± standard deviation (SD) unless indicated otherwise
HbA1c Glycated hemoglobin

640 G was set at 63 ± 8 mg/dl and showed 2.1 ± 0.9 events with a duration of 94 ± 26 min per patient per day.

The HbA1c level significantly decreased by − 0.9% (− 9.8 mmol/mol) by the end of the first 6 months of CSII and by an additional − 0.8% (− 8.7 mmol/mol) by the end of the study (see Table 2). The reduction in HbA1c level at the end of the study differed according to the model insulin pump used: − 1.9% (− 17.5 mmol/mol) according to the MiniMed® 640 G; − 1.7% (− 18.6 mmol/mol) according to the MiniMed® Veo™ with sensor; − 1.5% (− 16.4 mmol/mol) according to the MiniMed® Veo™ without sensor (see Fig. 2). At the end of the study, a significant difference in HbA1c level was found between patients using the MiniMed® 640 G model and those using the MiniMed® Veo™ model without sensor.

There was no significant difference in the Bolus Wizard setting between 6 and 12 months (see Table 2). There was also no significant difference in patient weight and total carbohydrate intake per day at the end of the study.

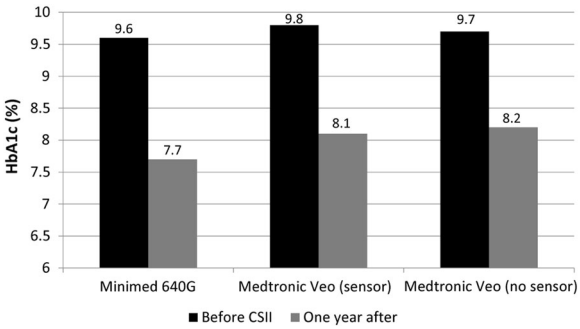

Fig. 2 Reduction in HbA1c level according to CSII insulin pump model used

DISCUSSION

In this study, we described CSII characteristics and glucose control of a cohort of children and adolescents with T1D who were started on an

Table 2 Follow-up characteristics of patients at 6 and 12 months

Follow-up characteristics	Before CSII	6 months after CSII	12 months after CSII	*P*
HbA1c (%)	9.7 ± 1.3	8.9 ± 0.8	8.1 ± 0.6	< 0.05*
HbA1c (mmol/mol)	83 ± 14	74 ± 9	65 ± 6	< 0.05*
Diabetic ketoacidosis (per patient per year)	0.06 ± 0.3	0.02 ± 0.1	0.02 ± 0.1	< 0.05**
Severe hypoglycemia (per patient per year)	0.01 ± 0.2	0.01 ± 0.2	0.01 ± 0.2	NS
TDI (U/kg per day)	0.59 ± 0.23	0.74 ± 0.26	0.78 ± 0.21	< 0.05**
Basal ratio	48.8 ± 9.2	42.3 ± 10.5	44.7 ± 9.8	< 0.05**
ICHR	25 (18–30)	20 (18–25)	20 (18–25)	< 0.05**
ISF	140 (120–170)	130 (110–150)	130 (110–150)	NS
Target range (mg/dl)	120	91 ± 9.3 to 121 ± 14.2	89 ± 8.4 to 124 ± 12.8	NA
Active insulin time (h)	–	3.8 ± 0.8	3.6 ± 0.9	NA

Values in table are presented as the mean ± SD or the median with the interquartile range in parenthesis, as appropriate
*Significant difference ($P < 0.05$) between characteristic before CSII initiation and at both 6 and 12 months after CSII initiation. **Significant difference ($P < 0.05$) between characteristic before CSII initiation and at 6 months after CSII initiation only
CSII Continuous subcutaneous insulin infusion, *TDI* total daily insulin, *ICHR* insulin-to-carbohydrate ratio, *NS* not significant, *NA* data not available

insulin pump with or without sensor. The design of our study included data collection on CSII utilization and reports obtained by CSII downloads. At the end of the study we found that there had been a significant improvement in glucose control using CSII.

More than 70% of our patients started using the sensor-augmented pump system. The preferred insulin pump was the MiniMed® 640 G with PLGS (> 60% of patients). Those patients who could not afford the MiniMed® 640 G with PLGS were started on the MiniMed® Veo™, with the disposals being covered by the patients or charities. However, > 20% of patients on the MiniMed® Veo™ insulin pump used the CGM on continuous basis. Our long-term plan is to achieve CSII utilization among 60% of patients with T1DM with a HbA1c level of < 7.5%.

In our study, CSII efficacy and safety could not be analyzed due to the lack of a control group and missing data. While CSII treatment is well established and has been shown to decrease the HbA1c level compared to MDI [18–20], a recent study does not support a policy of providing an insulin pump to a patient with poor glycemic control until that patient's level of engagement in self-management has been determined [21]. Our findings show an average reduction of HbA1c levels of − 1.6% at 1 year after of CSII initiation, with a reduction of − 1.9% achieved in patients using the MiniMed® 640 G model. One possible explanation for this improved glucose control is the structured approach that has been implemented at our institution during the pre-CSII process (improved carbohydrate counting and improved patient knowledge of diabetes), standardized protocol in CSII initiation, CGM use, and close follow-up visits (average of six visits per year).

Regarding the PLGS feature to prevent hypoglycemia (MiniMed® 640 G), we found 2.1 ± 0.9 events with a duration of 94 ± 26 min per patient per day, which is lower than the 2.9–3.1 events per patient per day reported by other authors [22–24]. A possible explanation for this difference is the lower settings of PLGS in our study (average 63 mg/dl) compared with those reported in other studies (average 70 mg/dl).

The basal ratio of 44% and five basal rates in our study are comparable with those reported in other studies [21, 25]. Our standardized protocol is designed to initiate CSII with five basal rates, with possible fine tuning in the following period.

Advanced CSII features [26] and the Bolus Wizard function [27, 28] can improve glucose control, with patient use of these features reported to vary from 50 to 100%. Our results are similar to these findings, with 92% of the patients in our study using the Bolus Wizard function on a regular basis. Instructions on the use of the Bolus Wizard function are a part of our group CSII education program, where we stress the importance of using this feature. ICHR and ISF in all age groups are calculated using this function and applied using well-established calculation formulae [29].

We found an incidence for severe hypoglycemia of 0.01 events per patient per year, which is particularly low. A low rate of hypoglycemia has also been reported by other authors [30], but it has been shown that the use of the PLGS feature can significantly reduce the risk for hypoglycemia in T1D children without increasing HbA1c levels [22, 23]. The low rate of DKA in our study can be explained by the improved glucose control, frequent visits, patient motivation, and patient education. DKA evaluation in CSII patients is controversial, with studies performed before 1995 showing increasing levels of DKA and subsequent studies reporting conflicting results [31, 32]. Such conflicts can be avoided with structured program of diabetes education.

The limitations of our study include its retrospective nature, lack of a comparative group of MDI, 1-year follow-up, and missing data on the insulin pump upload to Carelink Therapy Management software. However, the strength of our study is the number of patients and significant decrease in HbA1c level.

CONCLUSION

In this study we showed improved glucose control in T1D children and adolescents initiated on CSII using a standardized protocol. An average reduction in HbA1c level by − 1.6%

(17.5 mmol/mol) was achieved in 1 year using different insulin pump models. A HbA1c level of 7.7% (61 mmol/mol) was achieved in patients using the sensor-augmented pump with PLGS at the end of the study. A study with a longer duration is needed to confirm the results.

ACKNOWLEDGEMENTS

We would like to thank the patients and patients' families for participating in the study.

Funding. No funding or sponsorship was received for this study or publication of this article. The article processing charges were funded by the institution.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Goran Petrovski conceived and designed the study, performed the data acquisition, statistical analysis, and interpretation of data, drafted the manuscript, and carried out the clinical revision of the manuscript. Fawziya Al Khalaf interpreted the data, drafted the manuscript, and carried out the clinical revision of the manuscript. Khalid Hussain, Judith Campbell, and Ahmed El Awwa carried out the clinical revision of manuscript.

Disclosures. Goran Petrovski, Fawziya Al Khalaf, Khalid Hussain, Judith Campbell, and Ahmed El Awwa declare that they have nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research ethics committee (Sidra Medicine, Qatar) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed and assent consent was obtained from the patient and his/her caregiver.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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