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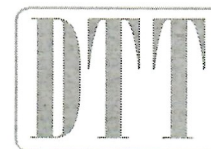Jay S. Skyler, MD, MACP
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ORIGINAL ARTICLE

Type 1 Diabetes and Long-Term Continuous Subcutaneous Insulin Infusion Therapy: A 10-Year Experience from Macedonia

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Abstract

Background: Subcutaneous insulin infusion (CSII) therapy is a challenge for both patients and healthcare providers. The long-term CSII use is scarce. The aim of this study is to describe the impact of CSII therapy for 10 years of use at our center.

Methods: This single-center retrospective study includes 162 type 1 diabetes patients using CSII for >3 years during October 2004 until October 2014. Data were collected through the electronic medical record system cross-sectional analysis (telephone, e-mail, or social media), and CSII reports generated by Carelink Therapy Management Software (Medtronic, Northridge, CA).

Results: Patients were analyzed in three age groups: 12–18, 19–24, and >25 years. All patients were treated with CSII for >3 years. Total daily dose of insulin was >0.9 U/(kg·day) in age group 12–18 years old, which was significantly higher than other two age groups ($P < 0.05$). Basal ratio was lower in younger age (<40%) and showed trend of increasing with age and longer diabetes duration (up to 44%). Younger patients used bolus wizard on regular basis (>75%), which was significantly higher than other age groups ($P < 0.05$). More than 50% of patients achieved glycated hemoglobin (HbA1c) <7.0% and >70% of patients achieved HbA1c <7.5%. HbA1c level significantly changed from baseline in all groups ($P < 0.05$).

Conclusion: Our study shows improved glucose control in long-term CSII users. A reduction of HbA1c level by −1.1% was maintained during the study period.

Keywords: Continuous subcutaneous insulin infusion, Type 1 diabetes, Long-term therapy.

Introduction

THE INCIDENCE AND prevalence of type 1 diabetes (T1D) is increasing worldwide[1] with special regard to the European region and developed countries.[2–4] Treatment goals of T1D include achieving near-normal glucose levels with minimizing the risk of hypoglycemia and preventing or delaying diabetes complications.[5]

Continuous subcutaneous insulin infusion (CSII) is an established model for mimicking physiological insulin, which can assist in achieving and maintaining these goals. Multiple daily injection (MDI) barriers such as dose adjustments by unit, less flexibility, and insulin stacking can be minimized using CSII. Multiple trials have shown that CSII therapy can improve diabetes management in T1D patients by improving glucose control and better quality

of life with less hypoglycemic events.[6–8] It can decrease glycemic variability, dawn phenomenon, and improve glycemic control.[7,9,10] Several retrospective studies have shown the long-term benefit of improvement in hemoglobin A1c (HbA1c),[11,12] wherein this therapy appears to be safe and effective in T1D regardless of age.[13]

The use of CSII in Macedonia as out-of-pocket policy began in 2002. The first 1-year experience[14] showed improved glucose control among uncontrolled T1D patients decreasing HbA1c to 7.4%. Our experience and several publications in CSII, continuous glucose monitoring (CGM) and sensor-augmented pump (SAP)[15,16] was used to influence on the Health Care Authorities to start a program for reimbursement of CSII and disposals. Our center treated >97% of T1D patients on CSII (October 2014), which can be a representative model for Macedonia.

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TABLE 1. DEMOGRAPHIC CHARACTERISTICS

Group	I	II	III
Age group, years	12–18	19–25	>25
Age, years	14.7±2.8	22.2±2.1	30.4±5.2
N	53	49	60
Male	25	26	24
Female	28	23	36
BMI, kg/m^2	21.4±2.8	23.1±4.3	24.7±2.6
Diabetes duration, years	8.1±3.3	13.2±3.9	15.2±4.9
HbA1c at CSII, %	8.4±3.4	8.1±2.6	8.2±1.9

CSII, subcutaneous insulin infusion; HbA1c, hemoglobin A1c.

The objective of this retrospective and cross-sectional study of cohort of patients with T1D treated by CSII is to describe insulin pump characteristics and long-term effects on glucose control in real-life conditions.

Methods

This single-center retrospective and cross-sectional study was conducted by the Center for Insulin Pump and Sensor at University Clinic of Endocrinology in Skopje. The study enrolled patients with T1D using CSII for >3 years during October 2004 until October 2014. Our Center uses Medtronic Minimed insulin pumps (Medtronic 722 and 754; Medtronic, Northridge, CA), where previous models (Medtronic 508 and 711) were upgraded accordingly (pump malfunction, no pump disposals available, or upgrade after 5 years of use).

Patients were excluded from the study if CSII use was transitory or for <3 years and diagnosis of T1D was not firmly established. According to our standards of care, CSII treatment was initiated during a 5-day out-patient group education program (2–3 patients) with previous carbohydrate-counting sessions.

CSII therapy was usually started with 10%–20% reduction in total daily dose (TDD) of MDI, basal/bolus distribution 40/60, four to five basal rates, and insulin-to-carbohydrate ratio (ICHR) formula of 300–450/TDD and insulin sensitivity factor (ISF) formula of 90–110/TDD (mmol/L). We s glucose target range from 5.0 to 7.2 mmol/L, with two IS (nighttime is usually 10%–20% higher than the daytime).

Baseline data at CSII initiation were collected through th electronic medical record system used at our center: sex, ag weight, diabetes duration, and initial and current HbA1 levels.

The cross-sectional analysis was conducted from Januar 2016 to December 2016 by telephone, e-mail, or social med (Facebook and Viber) to collect actual data, including th recent HbA1c level, weight, insulin daily dose, basal rati and bolus wizard use. Collected data were analyzed togethe with CSII reports generated by Carelink Therapy Manage ment Software (Medtronic).

Statistical analysis was performed with SAS version 12. for Windows (SAS Institute, Cary, NC). Quantitative var ables are expressed as the mean±standard deviation. Num ber of basal rates, ICHR, and ISF are expressed as the media (interquartile range). The HbA1c variation from baseline wa analyzed using the paired Student's t-test. Comparisons be tween HbA1c levels according to CSII duration and betwee age groups (12–18, 19–24, and >25 years) were performe using a Student's t-test. A P value <0.05 was considered t denote significance.

Results

Among 189 CSII-treated patients during the 10-year perio 162 patients met criteria for analysis (as shown in Figure 1 Patients were distributed according to age (12–18, 19–24, an >25 years) to meet different habits, lifestyle, and real cond tions. Demographic characteristics of this population are d scribed in Table 1. Indication for CSII was high HbA1c (58% dawn phenomenon (21%), glucose excursions (12%), hyp glycemia (5%), and patient preference (4%). Diabetes duratio was longer in adults than in adolescents.

All patients were treated with CSII for >3 years. TDD wa >0.85 U/(kg·day) in age group 12–18 years (Table 2), whic was significantly higher than that in the other two age grou ($P < 0.05$). Basal ratio was lower in younger age (<40%) an showed a trend of increasing with age and longer diabete

TABLE 2. FOLLOW-UP CHARACTERISTICS

Group	I	II	III	P
Age, years	12–18	19–25	>25	
CSII duration, years	4.8±1.8	5.4±2.3	6.7±3.1	N.S.
HbA1c, %	7.2±0.8	7.0±0.7	6.9±0.8	N.S.
% of patients achieving Hba1c <7.0%	50.2	54.5	68.4	N.S.
% of patients achieving Hba1c <7.5%	78.6	74.3	72.3	N.S.
Diabetic ketoacidosis, per patients/year	0.05±0.3	0.02±0.1	0.02±0.2	I vs. II; I vs. III $P<0.0$
Severe hypoglycemia, per patients/year	0.01±0.2	0.01±0.2	0.01±0.3	N.S.
TDD, U/(kg·day)	0.89±2.4	0.78±1.3	0.74±0.9	I vs. II; I vs. III $P<0.0$
Basal ratio	38.2±10.2	41.5±9.8	44.6±8.4	N.S.
Basal rates, median, IQR	5 (4–5)	4 (4–5)	4 (3–5)	N.S.
Bolus wizard use,%	78.2	63.5	53.5	I vs. II; I vs. III $P<0.0$
ICHR, median, IQR	10 (8–13)	10 (9–12)	10 (9–12)	N.S.
ISF, median, IQR	2.1 (2.5–3.1)	2.3 (2.0–2.5)	2.2 (1.8–2.5)	N.S.
Active insulin time, hours	4	4	4	N.S.

Values are expressed as mean±standard deviation unless otherwise indicated.
ICHR, insulin-to-carbohydrate ratio; IQR, interquartile range; ISF, insulin sensitivity factor; N.S., not significant; TDD, total daily dos
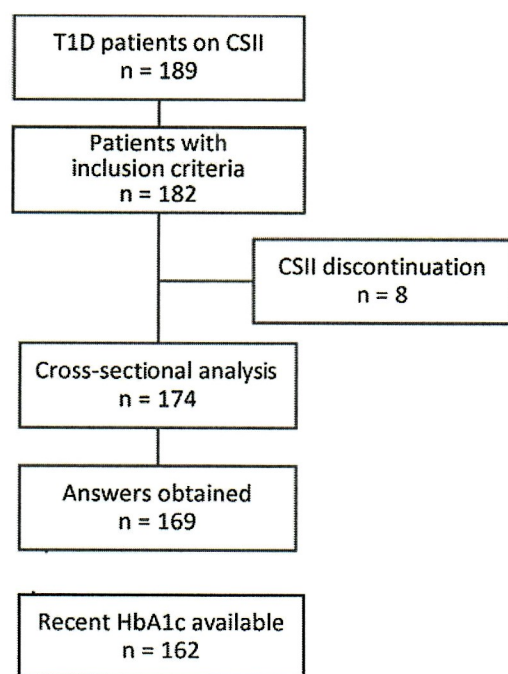
FIG. 1. Flowchart. CSII, subcutaneous insulin infusion; T1D, type 1 diabetes.

duration (44%). No significant difference was found in number of basal rates in all groups. Younger patients used bolus wizard on a regular basis (>75%), which was significantly higher than other age groups ($P < 0.05$). There was no significant difference in ICHR, ISF, and active insulin between groups. More than 50% of patients achieved HbA1c <7.0% and >70% of patients achieved HbA1c <7.5%.

HbA1c level significantly changed from baseline in all groups ($P < 0.05$). No significant difference between groups was found. Highest reduction of HbA1c levels by −1.3% was found in patients with CSII duration from 3 to 6 years (Fig. 2).

Weight was significantly increased in patients with CSII duration >3 years (<3 years, 59.4 ± 10.2 kg; 3–6 years, 64.6 ± 9.2 kg; >6 years, 63.7 ± 8.7 kg)
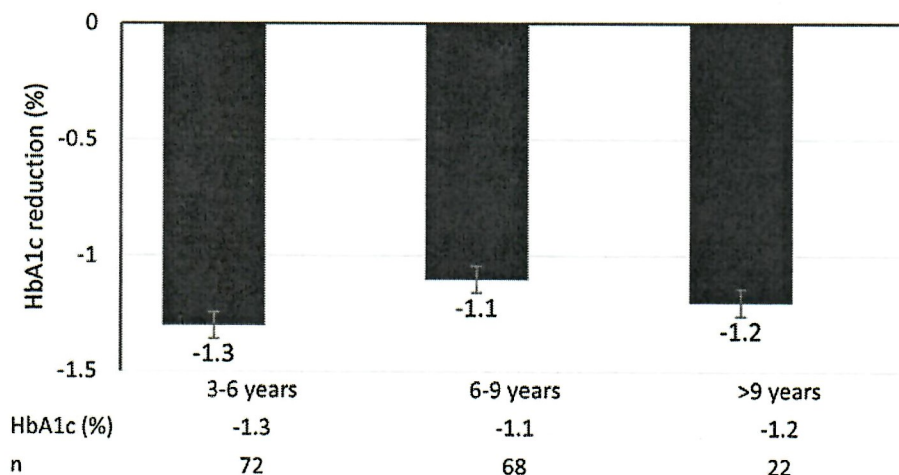
Discussion

In this study, we described insulin pump characteristic and long-term effects on glucose control of a cohort of patients with T1D treated with CSII for several years. The design of our study included data collection on CSII utilization and reports obtained by CSII downloads. The CSII duration in our study is >4 years in all age groups, which can be a representative model for long-term analysis.

In this study, CSII efficacy and safety could not be analyzed due to retrospective design, lack of a control group, and missing data. Previous meta-analyses of prospective studies reported reduction in HbA1c levels of −0.2% to −0.7%[17,18] and retrospective studies showed decreased HbA1c levels by −0.5% to −1.3%,[13,19,20] both with CSII in comparison with MDI. In contrast, our finding shows sustained reduction of HbA1c levels by −1.1% with CSII utilization after 6 years. In our study >70% of patients achieved and maintained HbA1c <7.5%. Possible explanation of improved glucose control is high degree of educational support for Flexible Insulin Therapy (FIT) at the moment of CSII initiation, re-education sessions on a yearly basis, and social media use between patients and healthcare providers. Around 74% of our CSII patients use social media to gain diabetes knowledge and information and interact in their daily insulin adjustments.[21,22]

We did not find significant difference in basal ratio (38%–45%) and number of basal rates (4–5), which are comparable with other studies.[23,24] The average of four basal rates in adults can be explained with our standards of care of CSII initiation at the age of adolescent in this group.

Several authors found an improvement in glucose control when using the bolus wizard function,[25–27] where the use of this feature is from 50% to 100%. Another study reports that 60% of all patients are using advanced functions continuously.[28] Our results support this finding, where 78% of adolescents and >50% of adults use the bolus wizard feature. More focus should be made during education session in adults to stress the importance of this feature. ICHR and ISF in all age groups are calculated and used by a well-established calculation formula.[29]

Concerning safety issues, we found an incidence of 0.0 events per patient/year for severe hypoglycemia, which i

FIG. 2. HbA1c variation from baseline to recent value (during analysis) according to CSII treatment duration (mean ± standard deviation). HbA1c, hemoglobin A1c.

particularly low. Low rate of hypoglycemia was also reported by other authors,[30] where CSII therapy achieves and maintains its efficacy mainly in terms of reducing severe hypoglycemia.[31] We also found a very low rate of hospitalization for diabetic ketoacidosis (DKA), which can be explained by improved glucose control, frequent visit, motivation, and education in patients. The incidence of DKA with CSII utilization is controversial, with an increase in studies performed before 1995 and conflicting results in subsequent studies.[19,32] DKA can be reduced and avoided with proper education to functional insulin therapy and good diabetes care.[33]

Our study presents several limitations including the lack of a comparative group of MDI, existence of missing data, and single-center study for possible missed data for self-reported severe hypoglycemia. However, the strengths of our study are its large sample population, its long length of follow-up, and its real-life conditions.

Conclusion

In this study, we showed improved glucose control in long-term CSII users, where safety and efficacy were maintained for several years of pump utilization. A reduction of HbA1c levels by −1.1% was maintained during the study period.

Acknowledgments

Author Disclosure Statement

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MACEDONIAN EXPERIENCE IN CSII OVER 10 YEARS OF USE

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