Continuous subcutaneous insulin infusion in preschool children with type 1 diabetes mellitus as initial treatment: Effect on glycemic control

Eren Er*, Aysun Ata, Ferda Evin, Yasemin Atik Altınok, Günay Demir, Samim Özen, Şükran Darcan, Damla Gökşen

Abstract

Background: Diabetes management and achieving good glycemic control are challenging in preschool period. Continuous subcutaneous insulin infusion (CSII) is the treatment of choice for managing type 1 diabetes mellitus (T1DM), especially in children under seven years of age.

Objective: To compare the glycemic control (HbA1c), anthropometric measurements, daily insulin requirement and basal and bolus insulin rates of the group using CSII as initial therapy with the group using multiple initial daily injection (MDI) treatment.

Method: Ten children with T1DM using CSII as a first-line therapy, who were followed up regularly for at least 1 year, and 10 children using MDI, who were similar in terms of age and gender with CSII group, were included in this retrospective study. Daily total insulin (U/kg), basal and bolus insulin rates, and HbA1c values of the children, obtained from medical records, were compared during the first year of the follow-up.

Results: The mean age of diagnosis of children with T1DM was 2.01 ± 1.28 years in the CSII group and 3.11 ± 1.49 years in the MDI group. While HbA1c values measured in the first year showed a significant decrease in both treatment groups, first year HbA1c was significantly lower in the CSII group compared to the MDI group (p=0.04). Mean total daily insulin requirement for first year was 0.61 ± 0.10 U/kg in the CSII group, and 0.82 ± 0.18 U/kg in MDI (p=0.007).

Conclusion: In children under the age of 5 with T1DM, using CSII as initial therapy provided better metabolic control with a lower daily insulin dose than MDI regimen even in the first year of the treatment. Studies with longer duration and more participants are needed.

Keywords: Diabetes technology, Diabetes in childhood, Insulin pump therapy, Metabolic control

Department of Pediatrics, Ege University, Izmir, Turkey

Corresponding author: *Eren Er,*
e-mail: drerener1984@gmail.com

Introduction

Almost 20 years ago, continuous subcutaneous insulin infusion (CSII) treatment swas used in children with type 1 diabetes mellitus (T1DM) as a last resort when adequate metabolic control could not be established, despite intensification of multiple daily subcutaneous insulin injections (MDI) regimens, or in children with type 1 diabetes with repeated episodes of severe hypoglycemia.[1] Technological improvements in the pumps and infusion sets have provided ease-of-use and comfort of CSII use. Numerous clinical studies have demonstrated safety and efficacy of CSII on short-term glycemic control evidenced by reduction in glycosylated hemoglobin (HbA1c) levels[2-4] reduced frequency of severe hypoglycemia[5-6] and improved quality of life in children and adolescents.[7-9] Insulin pumps are now widely accepted in many countries where their cost is reimbursed for children. Although, the use of insulin pumps as a first-line treatment at time of diagnosis was suggested in preschool diabetes[10], many clinicians are currently hesitant to start this treatment. We aimed to compare the glycemic control and anthropometric parameters of the group using CSII as initial therapy with the group using multiple initial daily injections (MDI) treatment in preschool children.

Methods

The study was conducted in accordance with the guideline of the Declaration of Helsinki. The study was approved by Ege University Faculty of Medicine, Ethics Committee (Number: 20-5.1T/37) and written informed consent was obtained from all participants or their parents/guardians.

Twenty (10 using CSII versus 10 using MDI) children with T1DM, who were diagnosed before the age of 5 years and followed up regularly for at least 1 year, were included in the study. The exclusion criteria included insufficient medical records and unwilling to participate in the study. In the group using CSII therapy, 6 children were on MiniMed® Paradigm® VEO and 4 children were on Medtronic Minimed 640 G® insulin pump regimen. The children using MDI treatment were on 4 subcutaneous daily injections with rapid and long-acting insulin analogs (insulin glargine) and were counting carbs. Ten children were on CSII as initial treatment, the recommended approach in the guidelines for preschool children.[10]

In CSII group, six children were using CGMS (Continous Glucose Measuring System), while there were no children using this system in MDI group. Data on daily total insulin (U/kg) requirement, daily basal and bolus insulin rates, and HbA1c values, height, weight, BMI were retrospectively collected from children' medical records. In records of the participants, auxological

data calculations were made by an automatic calculator[11] according to Turkish standarts.[12] Hemoglobin A1c (HbA1c) levels, measured with turbidimetric inhibition immunoassay (Roche Cobas c513 analyzer using the Tina quant ® HbA1c Gen. 3 assay, Germany; reference range, 4.8%-5.9%), were obtained from the data of the children enrolled at each visit. The mean annual HbA1c level was calculated. Analyses were performed to compare annual mean HbA1c levels whether the child received either MDI or CSII treatment and on 2 subgroups according to the first-line treatment they received at time of diagnosis: MDI versus CSII. Statistical calculations of HbA1c values at the time of diagnosis were not included. The target HbA1c was determined as <7.5% that is recommended for preschool children.10 Data analysis was performed with statistical package (SPSS Inc., version 21.0, Chicago, IL, USA). Nonparametric Brunner and Langer model (F1-LD-F2) was used to test group effects by using a web-based software (R software, version 3.3.1, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org). Continuous variables are displayed as arithmetical means plus or minus SD; categorical variables are displayed as frequencies or percentages. Paired t tests were used to analyze changes in continuous variables with time. Differences between outcomes of subgroups were tested with the student t test (2-tailed) and repeated measures analysis of variance. The Mann-Whitney/Wilcoxon 2-sample test (Kruskal-Wallis test for 2 groups) was used when the analysis of variance test was not appropriate. A p level ≤ 0.05 determined statistical significance.

Results

The mean age of diagnosis of all patients was 2.56 ± 1.46 years (CSII group 2.01 ± 1.28 yrs, MDI group 3.11 ± 1.49 years) (p=0.096). Ketoacidosis at the time of admission was 70% in the CSII group and 60% in the MDI group. Mean duration of hospitalization was longer in CSII group than MDI group, 17.4 ± 6.5 and 10.6 ± 2.3 days respectively (p=0.009). At the time of diagnosis in the CSII and MDI groups, the mean SDS of the weight, height and BMI were -0.55 ± 0.98, -0.49 ± 0.78, -0.37 ± 0.97 and -0.65 ± 1.24, -0.27 ± 0.85, and -0.86 ± 1.59 respectively (Table 1). In both groups weight and BMI SDS increased significantly in the first year, but the difference was insignificant in terms of height SDS. The mean HbA1c at first year visit was 7.15% ± 0.58 in CSII group, and 8.03% ± 1.15 in MDI group (p=0.049), on the other hand, the mean of all the HbA1c values at the visits over a 12-months' period was statistically insignificant (7.20% ± 0.59 in CSII and 7.58% ± 0.93 in MDI group; p=0.280). At the end of the first year in the last visit, 80% of CSII patients reached target HbA1c level (≤ 7.5%) whereas 40% of MDI patients (p=0.06). There was no difference for insulin doses between the time of discharge and the first year in the group receiving CSII (0.60 ± 0.12 U/kg, 0.65 ± 0.09 U/kg respectively, p=0.271). The mean total daily insulin dose per kg are reported for both groups in Table 2. In the group receiving CSII, the mean daily basal dose/total daily insulin dose ratio was 34.34 ± 10.01% and in MDI it was 40.02 ± 12.80% (p=0.357). Episodes of severe hypoglycemia, ketoacidosis or other adverse events did not occurred during the follow-up period in both of the groups.

Table 1: *The weight, height, BMI SDS and HbA1c values at the time of diagnosis and first year of treatment*

	CSII (n:10)		**MDI (n:10)**		**nd**	**nd**
	At the time of diagnosis	**First year**	**p**	**At the time of diagnosis**	**First year**	**p**
Height SDS	-0.61 ± 0.72	-0.52 ± 0.48	0.380	-0.34 ± 0.73	0.07 ± 0.77	0.065
Weight SDS	-0.55 ± 0.98	0.46 ± 0.90	0.001	-0.65 ± 1.24	0.24 ± 0.91	0.001
BMI SDS	-0.37 ± 0.97	1.13 ± 0.90	0.001	-0.86 ± 1.59	0.25 ± 0.99	0.007
HbA1c (%)(diagnosis)	9.2 ± 1.31	7.15 ± 0.58	0.005	10.73 ± 1.63	8.03 ± 1.15	0.013
HbA1c (one-year mean)		7.20 ± 0.59			7.58 ± 0.93	0.280
CSII: Continuous subcutaneous insulin infusion, MDI: Multiple daily injection, BMI SDS: Body mass index standard deviation score						

Table 2: *The mean total daily insulin dose per kg of body weight of children using CSII and MDI*

Insulin dose (U/kg)	**CSII (n:10)**	**MDI (n:10)**	**p**
At the time of diagnosis	0.47 ± 0.14	0.79 ± 0.29	0.01
3. month	0.57 ± 0.15	0.64 ± 0.14	0.32
6. month	0.60 ± 0.1	0.80 ± 0.15	0.003
9. month	0.65 ± 0.09	0.76 ± 0.14	0.06
12. month	0.65 ± 0.09	0.82 ± 0.18	0.01
CSII: Continuous subcutaneous insulin infusion, MDI: Multiple daily injection			

Discussion

After the development of CSII and continuous glucose monitoring systems (CGM), a breakthrough in diabetes treatment was achieved. Although confusing results about CSII effectiveness and safety were published in the first years, the studies about positive effects of pump therapy have increased. Although one of the feared consequences of pump therapy was the increase in diabetic ketoacidosis and severe hypoglycemia, population based cohort studies and meta-analysis concluded that among young individuals with type 1 DM, CSII therapy, compared with MDI therapy, was associated with lower risk of diabetic ketoacidosis, severe hypoglycemia and increased quality of life.[13-18] In recent years, clinical trials investigating CSII in preschool-aged children with type 1 DM have been numerous and CSII therapy is the preferred method of insulin administration for young children (aged <7 years) and its usage is increasing.[10] To date, only few trials have examined the efficacy of CSII in pediatric patients who are new onset type 1 DM.[19-21] Initiating CSII treatment at diagnosis is time consuming. Diabetes and coping with it should be explained on diagnosis, and on the other hand, use of the technological tools and carbohydrate counting is added on which they may have not even heard before. In addition to teaching about the new diagnosis; pump mechanics and also CGM training will make this process more difficult but not impossible because it is the preferred method for pediatric patients. Several observational or cohort studies have shown CSII to be one of the strongest predictors of low HbA1c levels.[7] Many clinicians are currently hesitant to start this treatment at the time of diagnosis, but our study revealed that insulin pump therapy provides a more stable insulin regimen and better glycemic control.

In a study of type 1 DM patients, throughout the 7 years of follow-up, CSII therapy provided a sustained improvement in glycemic control, and reductions of severe hypoglycemia compared with a matched cohort using injections.[22] In our study training of CSII added mean 6.8 days more hospitalization but with excellent HbA1c results, reaching 80% of patients to target HbA1c.

CSII patients in this study had relatively low daily amounts of insulin which continued 12 months after diagnosis, lower than the MDI group. This may indicate no deterioration in the endogenous insulin production over 12 months of follow-up but we didn't measure C-peptide secretion during the first year. In a study by Ramchandani et al., in 28 pediatric patients treated with CSII from the time of diagnosis, measured C-peptide levels were stable in first 12 months claiming that CSII treatment may prolong honeymoon.19 Sensor-augmented pump therapy starting from the diagnosis of type 1 diabetes can be associated with less decline in fasting C-peptide particularly in older children, although regular sensor use is a prerequisite for improved glycaemic control.[23]

Intensive insulin treatment and unhealthy life style may be the causative agent for obesity in the years after diagnosis.[24] Results of The Diabetes Control and Complications Trial Research Group (DCCT) showed that intensive glycemic control leads to increase body weight.[25] All of our patients' BMI and weight SDS parameters increased in the first year as expected, but it is necessary to monitor whether this increase continues or not.

In randomized parallel group studies of children and adolescents with new onset type 1 DM, patients in the CSII treatment group showed a greater treatment satisfaction when compared with MDI treatment in 24 months.[26] In our study quality of life did not appear to be adversely affected, but this was not quantitatively measured, however, all subjects expressed satisfaction with CSII and no child refused CSII when this option was given at the time of diagnosis and that no child chose to discontinue.

This study had some limitations. First, some statistical analysis could not be made due to the small sample size. Furthermore, the metabolic control parameters such as time in range, CV, time above/below target can be obtained objectively in children using continuous glucose monitoring system. Since only 6 children used CGMS, HbA1c was evaluated as the only glycemic control parameter, which is regularly evaluated in each child. Possible selection bias due to one tertiary center was also another limitation.

Conclusion

This study reports short-term metabolic control in patients with type 1 DM who was diagnosed <5 years, depending on whether initial treatment was with MDI versus CSII. Our results show that the use of CSII as a first-line treatment in young children is feasible in clinical practice and it will be a viable option in many countries, especially for very young children.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

References

1. V Sulmont. Metabolic control in children with diabetes mellitus who are younger than 6 years at diagnosis: Continuous subcutaneous ınsulin ınfusion as a first line treatment? The J Pediatrics. 2010; 157(1):103–107.

2. LP Plotnick, LM Clark FL, Brancati, et al. Safety and effectiveness of ınsulin pump therapy in children and adolescents with type 1 diabetes. Diabetes Care.2003;26(4):1142–1146.

3. J Colquitt, C Green, M Sidhu, et al. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. Health Technol Assess.2004;43(8).

4. M Mavinkurve, A Quinn, CS O'Gorman. Continuous subcutaneous insulin infusion therapy for Type 1 diabetes mellitus in children. Ir J Med Sci. 2016;185(2):335–340.

5. RM Bergenstal. Threshold based ınsulin-pump ınterruption for reduction of hypoglycemia. N Engl J Med. 2013;369(3):224–232.

6. P Pozzilli, T Battelino, T Danne, et al. Continuous subcutaneous insulin infusion in diabetes: Patient populations, safety, efficacy, and pharmacoeconomics: CSII Safety, Efficacy: Comprehensive Review. Diabetes Metab Res Rev.2016;32(1):21–39.

7. K Jeitler. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: Systematic review and meta-analysis. Diabetologia. 2008;51(6):941–951.

8. P Benedikt Júlíusson, M Graue, T Wentzel-Larsen, et al. The impact of continuous subcutaneous insulin infusion on health-related quality of life in children and adolescents with type 1 diabetes. Acta Paediatrica.2006; 95(11): 1481–1487.

9. B Rosner, A Roman-Urrestarazu. Health-related quality of life in paediatric patients with Type 1 diabetes mellitus using insulin infusion systems. A systematic review and meta-analysis. PLoS ONE.2019;14(6):0217655.

10. F Sundberg. Managing diabetes in preschool children. Pediatr Diabetes.2017;18(7):499–517.

11. K Demir. New features for child metrics: Further growth references and blood pressure calculations. J Clin Res Pediatr Endocrinol.2020;12(2):125–129.

12. Neyzi. Reference values for weight, height, head circumference, and body mass ındex in Turkish Children. Jcrpe.2015;7(4):280–293.

13. J Blair. Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people at diagnosis of type 1 diabetes: the SCIPI RCT. Health Technol Assess.2018;22(42):1–112.

14. JL Sherr. ISPAD clinical practice consensus guidelines 2018: Diabetes technologies. Pediatr Diabetes.2018; 19:302–325.

15. B Karges. Association of ınsulin pump therapy vs ınsulin ınjection therapy with severe hypoglycemia, Ketoacidosis, and Glycemic Control Among Children, Adolescents, and Young Adults With Type 1 Diabetes. JAMA.2017;318(14):1358.

16. JI Wolfsdorf. ISPAD clinical practice consensus guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes.2018;19:155–177.

17. ML Misso, KJ Egberts, M Page, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews.2010.

18. E Müller-Godeffroy, S Treichel VM. Wagner and on behalf of the German Working Group for Paediatric Pump Therapy, Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus-a large-scale multicentre pilot study. Diabetic Medicine. 2009; 26(5):493–501.

19. N Ramchandani. Insulin Pump Therapy from the Time of Diagnosis of Type 1 Diabetes. Diabetes Technology & Therapeutics.2006;8(6):663–670.

20. M Berghaeuser. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. Pediatric Diabetes.2008;9(6):590–595.

21. A Szypowska, M Lipka, M Błazik, et al. Insulin requirement in preschoolers treated with insulin pumps at the onset of type 1 diabetes mellitus. Acta Paediatrica.2009;98(3):527–530.

22. SR Johnson, MN Cooper, TW Jones, et al. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case–control study. Diabetologia.2013; 56(11):2392–2400.

23. Kordonouri. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. Diabetologia.2010;53(12):2487–2495.

24. P Calella, F Gallè, G Fornelli, et al. Type 1 diabetes and body composition in youth: A systematic review. Diabetes Metab Res Rev.2020;36(1).

25. DM Nathan and for the DCCT/EDIC Research Group, The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. Dia Care.2014; 37, (1):9–16.

26. L Skogsberg, H Fors, R Hanas, et al. Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. Pediatric Diabetes.2008;9(5):472–479.