Assessment of two different insulin regimens in children with type 1 diabetes: A longitudinal study

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Abstract

Aim: In type 1 diabetes, insulin therapy can be applied by either daily multiple dose injections with an insulin pen or subcutaneous continuous insulin infusion with an insulin pump. Numerous studies have investigated the superiority of both regimens over each other, and conflicting results have been reported. In this study, the periods when patients with type 1 diabetes were receiving subcutaneous continuous insulin infusion and multiple dose injections were compared in terms of clinical and metabolic outcomes.

Materials and Methods: Children with type 1 diabetes who were receiving multiple dose injections and later switched to subcutaneous continuous insulin infusion were included. Follow-up period was evaluated in two periods: during multiple dose injections and subcutaneous continuous insulin infusion. Physical and laboratory findings, blood sugar monitoring and food chart records were compared between these two periods.

Results: A total of 44 cases with a mean age of 10.6± 4.4 years were included. While a significant decrease was found in HbA1C values in the first year after the insertion of insulin pump, the values in the second year were similar to that in the pre-pump period. Mean body mass index was increased after switching to subcutaneous continuous insulin infusion. In the second year of the subcutaneous continuous insulin infusion, a significant decrease in hypoglycemic events was observed.

Conclusion: In terms of glycemic control, no difference was found between subcutaneous continuous insulin infusion and multiple dose injections in the long term suggesting that similar clinical results can be obtained with multiple dose injections therapy in cases who cannot afford an insulin pump. Considering that HbA1c levels tend to increase in the second year of subcutaneous continuous insulin infusion and similarly body mass index after switching to subcutaneous continuous insulin infusion, clinicians should be aware of the misuse of insulin pump, and patients' education should be revised regularly.

Introduction

Type 1 diabetes mellitus (T1D) is the most common chronic disease in children and adolescents, and it is estimated that there are a total of 1,110,100 children with T1D under the age of 20 years in the world (1). T1D incidence between the ages of 1 and 14 varies between 0.1- 57.6/100,000/years in different ethnic populations. In an incidence-prevalence study conducted in the northwest region of our country, T1D incidence was found as 10.8/100,000. It occurs as a result of autoimmune damage to pancreatic β-cells, and it is characterized by insulin deficiency and hyperglycemia (2).

The main objective of T1D is to provide glycemic control without causing hypoglycemia by mimicking physiological insulin secretion and to prevent metabolic complications. Today, insulin therapy can be applied by daily multiple dose injections (MDI) with an insulin pen or subcutaneous continuous insulin infusion (SCII) with an insulin pump. SCII provides a more successful blood sugar control by better mimicking daily insulin release (3), and it is also reported to improve the patients' quality of life (4). In addition, carbohydrate counting method, which is based on calculating the carbohydrate content of the meal and matching it with fast-acting insulin, provides flexibility in lifestyle, meal selection and timing. Better metabolic control is also associated with a decrease in the risk of long-term vascular complications. In many studies, it has been reported that SCII provides a better metabolic control than MDI therapy in adolescents with poor compliance to multiple dose injections and meal plan (5, 6). MDI therapy which includes long-acting insulin, does not make it possible to adjust instant changes (4, 7). While studies comparing the metabolic effects of MDI and SCII show a decrease in HbA1c levels with SCII (8, 9), there are also studies which show similar results on metabolic control

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in the long term (10, 11) .

In this study, the periods when patients with type 1 diabetes were receiving SCII and MDI therapy were compared in terms of clinical and metabolic outcomes.

Material and Methods

Forty-four children and adolescents with T1D who were receiving MDI and later switched to SCII therapy between 2013 and 2020 were included in this longitudinal study. Demographic data of the cases were obtained from patients' medical files; blood sugar monitoring and food chart records were kept by the patients. SCII therapy was initiated to the cases who had been followed up with a diagnosis of T1D for at least one year and who could use carbohydrate counting at the third level.

Minimed 754 Veo Insulin Pump (Minimed Medtronic; Northridge, USA) was used in 35 cases, while MiniMed 640G (Minimed Medtronic; Northridge, USA) was used in 7 cases. All cases who were using SCII had been receiving detemir (Levemir®) or glargine insulin (Lantus®) as basal, and lispro (Humalog, Lilly, Indianapolis, IN, USA) or aspart insulin (Novorapid, NovoNordisk, Baysvaerd, Denmark) as bolus insulin. Lispro or aspart insulin was used in the insulin pump.

Follow-up period was evaluated in two periods, during MDI and SCII therapy, to compare the clinical and metabolic data of the cases. The period with SCII was further divided into two periods: the first and second years of the therapy.

Glucose levels below 70 mg/dL were considered as hypoglycemia. Anthropometric measurements, blood pressure, hypoglycemia and ketosis episodes (episode/patient/year), daily total insulin (IU/kg/day), basal to bolus insulin ratio of the cases were determined. HbA1c levels, total, LDL, HDL cholesterol, triglyceride and urinary microalbumin levels were evaluated. An HbA1c level of <7% was determined as the optimal goal (12).

Nephropathy was assessed by screening annual urinary microalbumin level. Urinary albuminaria to creatinine ratio of >30 mg/g in males and >42 mg/g in females was considered as a marker of diabetic nephropathy. Peripheral neuropathy was evaluated with assessment of sensation, vibration and reflexes in the feet. Diabetic retinopathy was evaluated by an ophthalmologist through dilated pupils via bio-microscopy examination. Lipid profile and blood pressures were assessed as risk factors of macrovascular complications, as suggested by International Society for Pediatric and Adolescent Diabetes (13).

Declaration and the study were approved by the Istanbul University-Cerrahpasa ethics committee (number: E-83045809-604.01.02-69669)

Statistical Analyses

Statistical analyses were made by using Statistical Package for the Social Sciences (version 21.0; SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used to find out whether the data were normally distributed. In comparing more than two dependent groups, according to the distribution of the data, repeated-measures ANOVA or Friedman test are used .. In the comparison of dependent groups' data, Student's T test or Wilcoxon test was used. A p value of <0.05 was considered as statistically significant.

Results

A total of 44 cases, 19 males and 25 females, were included in the study. The mean age of the overall group was 10.6±4.4 years (1.5-17.9 years), and mean diabetes duration was 57.4± 37.7 months. The mean duration of MDI therapy was 40.5 ±33.3 months, and mean duration of using insulin infusion pump was 37.1± 13.2 months. The age of switching to insulin pump therapy was <5 years in 8 cases, 5-10 years in 15 cases and >10 years in 23 cases.

While the mean BMI of patients was 17.6±4.03 kg/m^2 in the MDI period , it was 19.6±3.06 kg/m^2 and 20.4±4.3 kg/m^2 in the first and second year of SSCI, respectively. Patients' mean body mass index standard deviation score (BMI SDS) was increased after switching to SCII treatment (p = 0.001). Mean basal and bolus insulin doses were similar during both treatment regimens (Table 1).

During the MDI therapy, HbA1c and mean blood glucose levels of 9 patients (21.4%) were within the optimal intervals whereas at the first year of the SCII therapy, HbA1c values and mean blood glucose levels of 15 (35.6%) cases were within the optimal intervals (HbA1c<7%; mean blood glucose level<150 mg/dL). Twelve cases (27.2%) were receiving SCII and continuous glucose measurement system (CGMS) simultaneously. While a significant decrease was found in HbA1C values in the first year after the insertion of insulin infusion pump, the values in the second year were similar to that in the pre-pump period (8.48%±1.49 vs 7.69%±1.23 vs. 8.3%±1.54 p<0.001, respectively). In post-hoc analysis, mean HbA1c level was found to be significantly lower in the 12th month of the SCII treatment compared with the pre-pump period (p<0.017), while it was found to be similar to pre-pump in the 24th month (p = 0.974). However, mean HbA1c level was found to be higher in the 24th month compared with the 12th month (p<0.017). Lipid profile was found to be similar between the two groups. The number of the patients with a decrease in HbA1c levels in the second year was 18, and the mean age of these patients was 7.95±1.2 years; while those with an increase was 3, and the mean age was 10.2±0.57 years (p = 0.81) (Table 2).

No correlation of HbA1c values of pre-pump, the first year and second year periods with duration of diabetes and age of diagnosis was found. The frequency of severe hypoglycemia decreased significantly in the second year after the pump was inserted (36% vs 13% p = 0.001).

No difference was found between the two periods in terms of diabetic ketoacidosis (DKA) and macro and micro complications (Table 3).

Discussion

In the present study 44 T1D cases were evaluated longitudinally, and metabolic effects were compared between the MDI and SCII period. Although a better metabolic control and a significant decrease in HbA1c was achieved in the first year after switching to SCII therapy, the results in the second year were similar to that in the MDI period.

While a decrease in HbA1c values has been shown with pump therapy in several studies (9, 14–16) , there are also studies showing no significant change (16). On the other hand, in line with our results, there are also studies which reported an increase over time after an initial decrease (8, 17, 18). The contradiction in the results can be attributed to the differences in the

Table 1. Comparison of anthropometric and clinical data between multiple dose injections therapy and subcutaneous continuous insulin infusion therapy

	MDI period	SCII period	P value
BMI (kg/m²)	17.6±4.03	1. year 19.6±3.06	0.001*
		2. year 20.4±4.3	0.015*
Mean Daily basal insulin dose (unit / day)	16.6±10.9	14.9±8.9	0.564*
Mean daily bolus insulin dose (unit/ day)	21.6±16.5	18.7±14.1	0.224*
Mean blood pressure systolic/diastolic (mmHg)	94±5/62±3.2	90±7.1/65±4.2	0.554*

MDI: Multiple dose injections ; SCII Subcutaneous continuous insulin infusion;

BMI Body mass index; * p-value results from paired samples T-test.

Table 2. Comparison of biochemical data between multiple dose injections therapy and subcutaneous continuous insulin infusion therapy

	MDI period	SCII period	P value (p<0.05)
Mean HbA1c MDI vs first year of SCII (%)	8.48±1.49	7.69±1.23	<0.001**
Mean HbA1c MDI vs second year of SCII (%)	8.48±1.49	8.3±1.54	0.874**
Mean HbA1c of first vs second year of SCII (%)	7.69±1.23	8.3±1.54	<0.001**
Triglyceride (mg/dL)	80.3 (min:35 max:236)	76.9 (min:41max:180)	0.530*
Total cholesterol (mg/dL)	162.3 (min:82 max:299)	163.09 (min:89 max:229)	0.117*
LDL cholesterol (mg/dL)	75.2 (min:52 max:173)	96.4 (min:61 max:148)	0.277*
HDL cholesterol (mg/dL)	62.2 (min:18 max:93)	67.04 (min:34 max:92)	0.219*

LDL Low-density lipoprotein, HDL High-density lipoprotein; * p-value results from related samples T-Test. ;

** p-value results from the Friedman test.

Table 3. Comparison of complication ratio between multiple dose injections therapy and subcutaneous continuous insulin infusion therapy

	MDI period	SCII period	P value (p<0.05)
The frequency of severe hypoglycemia (%)	%36	First year: %28	0.252**
		Second year: %13	0.01**
Diabetic ketosis (episode / patient /year)	2	2	
Microal-buminuria (spot urine)	12.9±5.1	10.1±8.3	0.732*

MDI multiple dose injections ; SCII subcutaneous continuous insulin infusion * p-value results from paired sample T-test ** p-value results from the Wilcoxon test

study designs. As some studies investigated metabolic control before and after SCII therapy in the same patient group (13,), there also exist some studies comparing separate patient groups using SCII or MDI treatment (8, 19).

In a recent meta-analysis conducted by Halid Benkhandra et al. (14) (25 studies including 1,456 adults with a mean age of 40.4 years and 543 children with a mean age of 8.3 years), a significant decrease was found in HbA1c in children and adults treated with SCII compared with MDI. In a study conducted by Blair et al. (19) in 2019, 144 cases using SCII and 149 cases using MDI were evaluated with a randomized controlled design, and no significant difference was found in HbA1c between both groups in their one-year follow-up. This result was attributed to selection of the patients with high HbA1c at the time of switching to SCII therapy by the authors. When the patients using SCII were evaluated longitudinally, a moderate increase in HbA1c after an initial decrease was shown, which is similar to our results and was explained by the onset of puberty, decrease in motivation of SCII therapy and decrease in frequency of hospital visits over time. In a multi-centered cohort analysis of three years, Jakish (8) showed the superiority of SCII therapy over MDI only in the first year, and the difference in HbA1c did not continue in the following years. In a study from Kuwait, 5-year data of 326 patients using SCII were compared with 326 patients using MDI. This study revealed that lower HbA1c levels were obtained especially in the first year, and a better metabolic control during the whole study in the patients using SCII treatment (10). A better metabolic control in the patients using SCII may not be a surprising result when considered that the government's criteria for providing financial and social support for insulin pump are

extremely strict (e. g., ability to self-monitor the blood sugar level at least four times a day, to comply with dietary plans and insulin regimens and successful carbohydrate counting). In our study, the increase in HbA1c level in the second year of SCII treatment may be due to losing motivation or misuse of flexible dose insulin administration with carbohydrate count. In studies which show improvement in HbA1c, it is noteworthy that follow-up was shorter and the cases using SCII were selected from the well-controlled ones (8). In this study, patients using SCII were not selected based on their metabolic control but their economic status and patients' request for more flexibility. A significant recovery in the first 6 months may be due to a closer communication between the family and healthcare teams during this process and more careful behavior while trying to adapt to a new technology.

SCII has been reported to cause weight gain, and this situation has been supported by many studies (10, 21–27), which may be due to the opportunity to eat without extra injections. Alderisio et al. (2019) assessed 10-year results of patients with T1D treated with SCII and MDI retrospectively and found an increase in BMI in both groups including the ones with good metabolic control and low HbA1c levels, which was associated with increased insulin use (27). Insulin is known to cause a significant increase in skeletal muscle mass in both genders, visceral tissue fat in men and decrease in subcutaneous fat tissue in women due to its anabolic effects (28). Increase in BMI after SCII treatment may be thought to be due to increased muscle mass; however, studies evaluating body composition are needed. On the other hand, there are also studies which show that mean BMI SDS decrease gradually (29, 30) or remain unchanged (14, 15, 31, 32).

Insulin pump therapy improves glycemic control without increasing hypoglycemic events. In our study, in the second year of the SCII treatment, a significant decrease in hypoglycemic events was observed, in line with a large number of previous studies (16, 26, 33). In a study conducted by Karges et al. (11) with 30,579 cases (14,119 SCII, 16,460 MDI), the patients who received SCII treatment were found to have a lower risk of severe hypoglycemia and DKA. In the meta-analysis conducted by Khalid Benkhandra et al. (9) in 2017, no significant difference was found in terms of overall hypoglycemic events, while a decrease was shown in the incidence of nocturnal hypoglycemia with SCII therapy. The decrease in the frequency of severe hypoglycemic events can be attributed to that SCII is more physiological, and it provides possibility of basal dose adjustment based on activity, sleep and eating models.

No significant difference was found regarding DKA rates (events /100 patients-years) between MDI and SCII periods. There are numerous studies supporting this result (34, 35): In a study by Steindel et al. (36), while ketoacidosis frequency decreased, HbA1c level remained the same. On the contrary, Shalitin et al. (37) reported an increase in DKA episodes from 0.03 to 0.07 incidents/100 patients-year, which was attributed to be due to the technical errors interrupting insulin delivery and delay in the patients' or caregivers' response.

Limitations

The strength of this study is that patients had a longer follow-up period compared with previous studies. Its limitations are that the study was conducted with a small number of cases, and glycemic variability was not evaluated. In addition, more informative data could be obtained with bioimpedance method.

Conclusion

Although a better metabolic control and a significant decrease in HbA1c was achieved in the first year after switching to SCII therapy, no difference was found between SCII and MDI in the long term suggesting that similar clinical results can be obtained with MDI therapy in cases who cannot afford the SCII therapy.

Considering that HbA1c levels tend to increase in the second year of SCII and similarly BMI after switching to SCII, clinicians should be aware of the misuse of insulin pump, and patients' education should be revised regularly.

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