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Original article

Initial Basal and Bolus Rates and Basal Rate Variability During Pump Treatment in Children and Adolescents

Short title: Basal Rate Varıability During Pump Treatment

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What is already known on this topic?
While recommendations for basal rate profiles in adolescents and adults have been published before at present there is no general consensus on how to start basal rate profiles in different age groups, and on which additional factors to consider. There are two different methods used in general. Total Basal Dose, (TBD) is divided by 24 to give the average basal rate per hour. Basal rates are increased or decreased according to fasting blood sugars. In the second method, basal insulin requirement is adjusted according to the requirement during the day.

What this study adds?
At the initiation of the insulin pump therapy, the basal rates should not be set equally during the day.
The basal rates should be initiated at a specific day rhythm for the age group.

ABSTRACT
Objective: Pump-treated children with type 1 diabetes have widely differing basal insulin infusion profiles for specific periods of the day. The pattern of basal insulin requirements depends on the timing and magnitude of cortisol and growth hormone secretion within each age group. In adolescents and young adults, a decreased insulin sensitivity is seen, particularly in the early morning (dawn phenomenon) and of lesser extent, in the late afternoon (dusk phenomenon). Different approaches exist for the inititation of basal rates however, there is a lack of evidence-based recommendation, especially in young children. Usually the basal rates are set equally throughout day and night or the day is divided into tertiles. The aim of our study was to analyze the change of the initial equally distributed basal insulin rates over time of standart insulin pump therapy.
Methods: A total of 154 children with T1D, aged between 0 and <21 yrs, from a single center were documented. Children with T1D were divided into five age groups, group 1; <5 yr (n = 36); group 2; 5 to 8 yrs (n =20); group 3; 8 to 15 yrs (n=74); group 4; 15 to18 yrs,(n = 19) group 5; >18 yrs, (n = 5). Distribution of hourly basal rates at the initiation of the pump and at the end of first year were evaluated.
Result: Median age and diabetes duration was 14.46 (min:1.91/max:26.15) and 7.89 (±3.8) yrs (min:1.16/max:17.15) respectively. Forty-four percent were male, 56% were female. Mean total insulin dose/kg at the initiation and 1 st year of pump therapy was 0.86±0.23 U/kg and 0.78±0.19 U/kg in all participants respectively and differs in each age group ($p<0.001$; $p<0.001$). Mean daily basal rate/ kg showed substantial differences between the five groups ($p<0.001$). Circadian distribution of basal insulin differed markedly among the five age groups.
Conclusions: At the initiation of the insulin pump therapy, circadian profiles by age group should be taken into account when initiating CSII therapy in pediatric patients to optimize basal rate faster and easier.

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Introduction:
Continuous Subcutaneous Insulin Infusion therapy (CSII) is an effective and flexible method of insulin delivery associated with improved glycemic control in children with diabetes [1]. CSII improves metabolic control and in addition offers more flexible and more precise insulin delivery than multiple daily insulin (MDI) therapy while increasing the quality of life of children and adolescents [2,3,4-8]. While recommendations for basal rate profiles in adolescents and adults have been published before at present there is no general consensus on how to start basal rate profiles in different age groups, and on which additional factors to consider. There are two different methods used in general. Total basal dose (TBD) is divided by 24 to give the average basal rate per hour. Basal rates are increased or decreased according to fasting blood glucose [9]. In the second method, basal insulin requirement is adjusted according to the requirement during the day as defined by Bachram et al [8,10].
The aim of our study was to analyze the change of the initial equally distributed basal insulin rates over time of standart insulin pump therapy.
Methods

A total of 154 (44% male) children with T1D, aged between 0 and 21 yrs, from a single center were documented. Participants were all on MDI therapy before CSII therapy and were counting carbohydrates. Rapid acting aspart insulin was used for insulin pumps. Total dose of insulin at the initiation of pump therapy was calculated according to patients' mean HbA1c of the last year and was reduced by 10% if > 64 mmol/mol (>8%) %, by 20 % if between 53-64 mmol/mol (7-8 %) and 30 % if < 53 mmol/mol (<7 %). Forty percent of the total insulin dose was calculated as the basal insulin dose. According to the department's recommendation; basal rates were equally distributed hourly at the initiation of therapy, and rates are changed based on premeal capillary blood glucose levels and when needed with a fasting test over a period of 6 to 8 hours. After initiation of CSII therapy, basal dose changes were done according to the needs of the children and adolescents. Children with T1D were evaluated in 3 months intervals, and data on HbA1c, weight, total basal and bolus insulin (IU/kg) doses were recorded. Participants were divided into five age groups according to insulin requirements and development. Group 1; <5 yr (n = 36); group 2; 5 to 8 yrs (n =20); group 3; 8 to 15 yrs (n=74); group 4; 15 to18 yrs,(n = 19) group 5; >18 yrs, (n = 5).

Ethics statement

Data collection was approved by the institutional review board Ege University and is in accordance with the Declaration of Helsinki (Approval number: 20-5.1T/29). The children with T1D and their parents signed a written informed agreement and consent form, respectively, when they were enrolled in the study.

Statistical Analysis

Analysis were carried out by using SPSS for windows 25.0, descriptive statistics are reported using mean ± SD for normally distributed variables, and median for skewed data. Groups are compared by independent samples t-test for normally distributed variables and the Mann-Whitney U test for skewed data. Trends across more than 2 groups were analyzed using linear polynomial contrasts (ANOVA). P value < 0.05 was considered statistically significant.

Results

Patient records of 154 (87 girl / 67 boy) T1D children and adolescents (age <21 years) between 2004 and March 2020 with a follow-up of >1 year on insulin pump therapy were evaluated. Children with T1D were divided into five age groups, group 1; <5 yr (n = 36); group 2; 5 to 8 yrs (n =20); group 3; 8 to 15 yrs (n=74); group 4; 15 to18 yrs,(n = 19) group 5; >18 yrs, (n = 5). Median age and diabetes duration of the study group was 14.46 yrs (min:1.91/ max:26.15) and 7.89 yrs (min:1.16/max:17.15) respectively. Basic characteristics of the five different age groups are presented in table 1. The mean total daily insulin dose increased from the youngest to the oldest age group until the end of puberty. At the initiation and 1st year of pump therapy insulin dose/kg were different in each age group (p<0.001; p<0.001) (Table 2). Also, the mean daily basal rate/ kg showed substantial differences between the five groups with the highest basal requirement in group 4 (Table 2) (p<0.001).

Median total insulin dose/kg at the initiation and 1 st year of pump therapy was 0.86±0.23 IU/kg and 0.78±0.19 IU/kg in all children with T1D respectively. The mean basal insulin requirement/ kg at the initiation and at the 1st year of therapy according to age groups are given in table 2.

The circadian distribution of basal insulin differed markedly among the five age groups (Figure 1). In adolescent group, basal insulin requirement was highest between 06:00 and 09:00 h and lowest between 10:00 and 13:00 h (p<0.001, n=74). Prepubertal children (0-5 age, 5-8 age) displayed a high peak between 22:00 and 01:00 h (p<0.001 and p:0.007 respectively) at the end of first year of therapy.While HbA1c was 7.5 (min:4,1- max:11,3) on the third month of pump therapy, it decreased to 7.1 (Min: 5,3-Max:11,4) at the end of the first year after circadian rythm was achieved (p:0.001).

Discussion

CSII use in children, adolescents and especially preschool children is associated with improved glycemic control [6,8,11,12]. Other than achieving metabolic control, CSII has beneficial effects on psychosocial factors, physical performance, protection from long-term complications and hypoglycemia [13]. Insulin requirement at the time of pump initiation depends upon the insulin dose on MDI, the level of glycemic control and patient's current weight. According to Consensus statement from the European Society for Pediatric Endocrinology, in children with good glycemic control and a low frequency of hypoglycemia, the total dose may need to be reduced by 10–20%. In a patient who has been experiencing frequent hypoglycemia, the dose should be reduced by 20% [6]. According to Danne et al, in children with good glycemic control and low frequency of hypoglycemia, the total dose has to be reduced approximately by 10% if using soluble regular human insulin at pump. In case of frequent hypoglycemia, the dose should be reduced by 20% [14]. Alemzedah calculated his daily total dose as "Total dose = body weight X 0.74" in his research with 14 children with T1D [15]. In our institution total dose of insulin at the initiation of pump therapy is calculated according glycemic control to HbA1c of the patient and is reduced by 10% if above 64 mmol/mol (>8%), by 20% if between 53-64 mmol/mol (7-8%) and 30 % if below 53 mmol/mol (<7%). After calculating the basal dose as 40% of total insulin, we divided the total basal dose equally to 24 hr.

Studies show that total insulin dose decreases in the first year after CSII therapy. Esmaraldo et al showed a decrease from 0.89 to 0.73 UI/kg/day (p< 0.001) in total daily insulin (TDD) dose at the end of the first year of pump therapy [16]. Ahern did not show a decrease in TDD after 12 months of insulin pump use [3]. A randomized study by Doyle showed that after 16 weeks of therapy, the CSII group had a significant decrease in TDD [5]. In our research we showed a decrease from 0.86 to 0.78 UI/kg/day (p< 0.01) in TDD at the end of the first year of pump therapy.

In a cross-sectional international survey of CSII in 377 children and adolescents with T1DM, the TDD of insulin was lower in the younger age groups and increased with puberty [17]. In our study, the results were similar. The total insulin dose per kilogram was highest during adolescence.

CSII is the most physiological method of insulin delivery, simulating the pattern of insulin secretion with a continuous adjustable 'basal' delivery [18]. Guidelines for insulin dosing basal/bolus ratio, have been established for adults with T1D. However, these guidelines are not appropriate for children [6]. According to Danne et al, as during injection therapy, approximately 30–40%, rarely up to 50%, of the TDD accounts for the basal rate [14]. According to Hanas; approximately 40–50% of the daily insulin requirement should be the basal rate but some children with T1D may need up to 60% [19,20]. In our study, at the end of the first year, the mean basal rate of all cases was 38% and was similar to other studies.

In children basal insulin requirements are different in different age groups, especially in children younger than 7 years of age, as well as in children who are in different stages of puberty [21]. Klinkert et al. found that adolescents have the highest insulin doses, both as total and basal. Due to the balance of insulin and its counterregulatory hormones, mostly the action of growth hormone, insulin requirement raises throughout puberty [22]. According to consensus statement from the European Society for Pediatric Endocrinology, average total daily basal dose per body weight should be 0.2– 0.4 IU for toddlers, 0.4–0.6 IU for prepubertal children, and 0.8 –1.2 IU for adolescents (23). In our study, median total daily basal dose per body weight was 0.18 IU/kg for 0-5 age group, 0.39 IU/kg for prepubertal children, and 0.71 IU/kg for adolescents (p:0,00). The pattern of basal insulin requirements depends on the timing and magnitude of cortisol and growth hormone secretion within each age group [24]. According to the studies done up to now basal rate profiles should be programmed in hourly intervals, according to the patient's circadian variation in insulin sensitivity [6,8,14,19,24]. According to Scheiner et al, under twenty years of age, basal insulin requirement often begins peaking before midnight, maintains at a relatively high level throughout the night, drops through the morning hours, and gradually increases from noon to midnight [24]. Although no statistical difference was found in basal insulin requirement between age groups, many adolescents experienced a mid-day ''decrease'' rather than a significant ''increase'' in basal insulin requirement in this study. Twenty-four hour pattern of peaks and valleys was remarkably similar in the age group <10 yrs, as 11–20 age group. In the study of Nicolajsen, children with T1D between the ages of 3–9 years had higher basal rates late at night (10:00 pm–12:00 am), while the oldest age group had a slight increase in basal rates in the early morning (3:00 am–7:00 am)[18]. The reason for the reversed dawn phenomenon in the younger age group is unclear. An emptying of the gastric contents after falling asleep could be one explanation. Gastric emptying is slow during sleep, but rapid eye movement (REM) sleep is associated with faster gastric emptying. Children who take "afternoon naps" reach REM sleep faster after sleep onset than preadolescents who have discontinued their afternoon naps[25]. In two studies done in adolescents and young adults, decreased insulin sensitivity was seen, particularly in the early morning (dawn phenomenon) and of lesser extent, in the late afternoon (dusk phenomenon). This leads to a typical two-waved basal rate profile [14]. In other studies prepubertal children needed a higher basal rate late in the evening and it is common for the basal rate requirement to be higher earlier in the night (midnight to 3.00 a.m) than later on (3.00–7.00 a.m)[19]. The PedPump Study Group noted that younger children often need more basal insulin between 21.00 and 24.00 h [6]. In our study, the circadian distribution of the total basal rate shows characteristic profiles in the five age groups. Younger age groups had higher basal rates (10.00 pm–01.00 am), while the oldest age group had a slight increase in basal rates in the morning (6.00 am–9.00 am). Our study, like other studies, supports the high insulin requirement at early-night in the prepubertal period. We think that adjusting the hourly basal insulin doses according to the need instead of constant adjustment will provide faster blood glucose normalization in pediatric population. However, since there is no consensus on basal dose adjustment according to age groups, further studies are needed on this area.

Conclusion: At the initiation of the insulin pump therapy, the basal rates should not be set equally during the day but should be initiated at a specific day rhythm for the age group. Our results indicate that it is simply not reasonable to expect basal insulin needs to be met by a flat rate of insulin delivery for 24 hr.

Limitations of the study:

This study may be conducted as a multicenter study to increase the number of children with T1D in order to drive a better conclusion and to compare two groups of participants (children with T1D with the same basal all the time vs children with T1D with a circadian basal) with a crossover design.

Conflict of Interest: No conflict of interest

Financial Disclosure: No financial disclosure

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Table 1. Patient characteristics and daily insulin requirement by age group (mean ± SD, percentage)

	0-5 age (n=36)	5-8 age (n=20)	8-15 age (n=74)	15-18 age (n=19)	>18 age (n=5)
Age (yr)	7.62±3.68	11.63±3.10	16.20±3.56	20.98±3.17	23.38±2.20
Boys (%)	42	50	43	37	60
DM duration (yr)	5.61±3.64	7.18±3.37	8.62±3.70	9.85±3.47	9.21±2.00
Basal Insulin (%)	36.47±9.08	38.75±7.67	38.45±8.58	42.89±14.59	38.40±7.95
Basal Insulin(IU/kg/d)	0.25±0.07	0.30±0.08	0.34±0.09	0.32±0.11	0.24±0.06
TID (IU/day)	12.12±4.70	24.46±6.96	44.73±18.76	46.33±12.94	44.69±11.64
TID (IU/kg/d)	0.69±0.14	0.81±0.12	0.89±0.19	0.76±0.16	0.63±0.08

DM: Diabetes Mellitus
TID: Total Daily Insulin

Table 2. According to five age groups. The median basal insulin requirement per kilogram of body weight.

yrs/n	pump initiation BI (U/kg/d)		first year BI (U/kg/d)		p
	Median	Max/Min	Median	Max/Min	
0-5 / 36	0.22	0.04/0.72	0.26	0.10/0.43	0.019
5-8 / 20	0.30	0.18/0.57	0.30	0.12/0.52	0.794
8-15 / 74	0.30	0.09/0.87	0.33	0.17/0.66	0.019
15-18 /19	0.32	0.12/0.50	0.34	0.10/0.53	0.334
>18 / 5	0.25	0.13/0.26	0.22	0.18/0.36	0.500
P*	<0.001		<0.001		

P: Initial and first year basal rates in the same age group
P*:Basal rates among age groups
BI: Basal Insulin

Figure 1. The mean circadian distribution of the total basal rate showed different profiles in the 5 age groups