ORIGINAL PAPER

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Impact of Insulin Delivery Method on Hypoglycemia Incidence in Pediatric Type 1 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Insulin therapy of pediatric patients with type 1 diabetes mellitus (T1DM) is highly demanding due to their dynamic growth, development and different daily life activities. **Goal:** To determine the optimal insulin delivery method for the prevention of hypoglycemia recorded by continuous monitoring of glucose in patients with insulin pump and PEN. **Material and Methods:** The study included patients up to 18 years of age with diagnosed T1DM and treated with insulin pump and by insulin therapy with PEN at the Pediatric Clinic of the Clinical Center in Sarajevo. The study involved 149 patients, and lasted for 3 years. Patients were divided into two groups: group of patients on insulin pump therapy and group on insulin PEN. **Results:** There were 73 patients (49.6%) on insulin pump therapy and 79 patients (52.4%) on the insulin PEN therapy. There was no significant difference in the age between genders nor groups with different insulin application methods. There were no significant differences in the number of anamnestic hypoglycemia in patients with a different mode of insulin application (83.56% vs. 81.58%, p=0.114, F=2.533 < Fk=3.919). The number of hypoglycemia episodes in history is higher with the PEN therapy than in the insulin pump group. **Conclusion:** The number of anamnesis hypoglycemia as well as hypoglycemia from CGM records did not differ significantly in patients with IP and PEN therapy. The CGM record was significantly more valuable in the presentation of hypoglycemia compared to the history of hypoglycemia in all patients studied. Continuous monitoring of glycemia due to the ability to show glycemia variability and unrecognized hypoglycemia as well as predictive options for long-term metabolic control should be performed for all T1DM patients at least once a year.
Keywords: diabetes mellitus type 1, hypoglycemia, therapy.

1. INTRODUCTION

Diabetes mellitus TYPE 1 (T1DM) is the most common endocrine disorder of childhood whose incidence is growing annually worldwide by 3-4% and for children up to 7 years even to 7% (1, 2). The goal of complete diabetes therapy is to prevent the onset and progression of chronic micro-vascular complications: retinopathy, nephropathy and neuropathy, and chronic macrovascular complications, thus extending life span by increasing its quality (3, 4). Large variations in glycemia are, according to new findings, also a significant factor for the emergence and progression of chronic complications of T1DM. Glycemic variations exert their negative effect by activating oxidative stress and its products that adversely affect tissues (4).

All causes that lead to large variations in glycemia are simultaneously the cause of hypoglycemic episodes.

Hypoglycemia is defined by glycemia (BG) below 3.9 mmol/l. Repeat-ed severe hypoglycemia, especially in young children, can leave consequences in the form of permanent psychomotor developmental disorders. The significance of continuous glucose monitoring (CGM) for glycemia variability is huge. One of the most important features of CGM is the detection of hypoglycemia. The CGM record also helps in adequate correction of therapy, indicating periods of large fluctuations in glycemia.

Insulin therapy of pediatric patients with T1DM is very demanding due to their dynamic growth, development and daily life activities. The use of long-acting and fast-acting insulin analogues in the basal bolus therapy of pediatric patients of all ages significantly reduced the incidence of hypoglycemia and improved metabolic regulation of diabetes due to a more precise dosage of insulin for meals. However, the problem remains of a large number of injecting insulin and saturation of the application site, which on the

other side complicates regulation of diabetes and reduces the quality of life. The consequences of such insulin therapy are frequent hyperglycemia or severe hypoglycemic episodes followed by long periods of compensatory hyperglycemia (5). Therapy with T1DM Insulin Pump has been known for 20 years, and today it is technically a highly sophisticated device that allows continuous subcutaneous delivery of insulin as the most similar to its physiological secretion. Due to the long-term good regulation of diabetes in pediatric patients lasting for a lifetime, the use of insulin pumps in children and young people in the world is in remarkable expansion. Changes in basal flow as well as the desired number of bolus doses applied to a non-injected child allow for more adequate monitoring of variable daily insulin requirements, and thus more stable glycemic control (6, 7).

The long-term goal of T1DM in children therapy is their normal growth, development, good quality of life with the absence of acute (hypoglycemia and ketoacidosis) and chronic complications (3).

2. GOAL

Determine the optimal insulin delivery method for the prevention of hypoglycemia by continuous monitoring of glucose levels in patients on therapy by insulin pump and PEN.

3. MATERIAL AND METHODS

Patients aged up to 18 years who were diagnosed with T1DM and who were treated by an insulin pump or insulin therapy at the Pediatric Clinic of the University Clinical Center in Sarajevo were included in the study. The study involved 149 patients, and lasted for 3 years. Patients who were diagnosed with T1DM at least 1 year before the study and who received insulin via an insulin pump or PEN were included in the study.

The study did not include patients who changed diabetes therapy in a period of 6 months prior to the onset of the study, and patients who did not undergo controls for more than 6 months or were hospitalized at the Clinic. The study was conducted as prospective clinical-analytical study and lasted one year. Patients were divided into two groups: group of patients on insulin pump therapy and group on insulin PEN therapy. Groups are homogeneous by age and gender.

In statistical data processing, the Student's t test and the Fisher exact test for two independent samples for N are less than 80 were used. Also, was calculated the Pearson correlation coefficient. The value of p <0.05 will be considered significant.

4. RESULTS

There were 73 patients (49.6%) on the insulin pump therapy and 79 patients (52.4%) on the insulin PEN therapy. There was no significant difference in the age and gender of patients within the groups with different insulin application. There were no significant differences in the number of anamnestic hypoglycemia in patients with a different mode of insulin application (83.56% vs. 81.58%, p=0.114, F=2.533 <Fk=3.919).

	MEAN	
Hipo-anamnestic	IP	PEN
0	2.75	3.685
1	2.85	3.265
2	3.408	3.956
3	3.94	3.966
4	3.37	4.187

Table 1. Distribution of mean glycemia (CGM) by number of anamnestic hypoglycemia in patients treated with insulin pump and PEN

Table 1 shows the distribution of the number of anamnestic hypoglycemia to mean glycemic values in patients treated with insulin pump and PEN. At all values of SD Glycemia (CGM), the number of anamnesis hypoglycemia is higher on the PEN than on the insulin pump. Tables 2 and 3 show the correlation of anamnestic number of hypoglycemia and mean glycemia (CGM) in patients with insulin pump and PEN therapy. Correlation is at the level of significance of 0.05. An increase in the number of hypoglycemia in hypoglycemia increases with mean. This finding is valid both in patients treated with insulin pump and treated with PEN. In the case of further increase, the number of hypo-anamnesis in the group on pump shows a slight decrease in mean, while with a PEN slight increase in mean.

Insulin pump	
	Hypo- anamnesis
Mean	0.766*

Table 2. Correlation of number of anamnestic hypoglycemia and mean glycemia (CGM) in patients with insulin pump therapy. *Correlation coefficient r=0.766. *Correlation significant at p<0.05 level

Insulin PEN	
	Hypo- anamnesis
Mean	0.762*

Table 3. Correlation of anamnestic number of hypoglycemia and mean glycemia (CGM) in patients with PEN therapy. * Correlation coefficient r =0.762. * Correlation significant at p<0.05 level

There was no significant difference (87.67% vs. 82.89, p=0.647, F=0.209 <Fk=3.916) in the number of CGM hypoglycemia in patients with a different insulin application mode.

Table 4 present the distribution of mean glycemia (CGM) in relation to the number of hypoglycemia (CGM). For patients with insulin pump therapy, the highest mean glycemia was recorded in patients with 10 CGM hypoglycemia, and in patients with PEN therapy, the highest mean corresponds to the incidence of 5 hypoglycemia on the CGM record.

Table 4 shows the distribution of mean glycemia (CGM) relative to the number of hypoglycemia episodes (CGM). For patients on insulin pump therapy, the highest mean glycemia occurs in patients with 10 CGM hypoglycemia, and in patients with PEN therapy, the highest mean corresponds to the incidence of 5 hypoglycemia on the CGM record.

Correlation between the number of hypoglycemia CGM and the mean glycemia (CGM) in patients on in-

Hypo-CGMS	Mean glycaemia (CGM)	
	IP	PEN
0	2.62	3.26
1	2.76	2.52
2	3.37	4.09
3	3.05	4.21
4	3.49	3.77
5	3.06	4.79
6	3.07	3.88
7	-	3.4
8	3.48	3.46
9	3.6	-
10	4.1	2.6

Table 4. Distribution of mean glycemia (CGM) in relation to the number of hypoglycemia (CGM)

sulin pump and PEN therapy is significant at the level of 0.05 for patients on insulin pump therapy.

	IP		PEN	
	Hypo anamnesis	Hypo CGMS	Hypo anamnesis	Hypo CGMS
Rank	4	10	4	10
X	1.438	3.45	1.618	3.118
S	0.985	2.386	1.188	2.443
Sx	0.115	0.279	0.136	0.28
Median	1	3	2	3
Min.	0	0	0	0
Max.	4	10	4	10
p	5.92×10^{-10}		3.60×10^{-06}	
F test	F=44.39>Fk=3.905		F=23.15>Fk=3.905	

Table 5. Comparison of anamnestic and hypoglycemia numbers from a CGM record in patients on insulin pump and pencil therapy.

In Table 5, is made parallel comparison of the number of anamnestic and CGM hypoglycemia in patients on insulin pump and PEN therapy. There is a statistically significant difference in the number of number of recorded glycemia from anamnesis and the CGM record, both in patients receiving insulin pump therapy and in PEN therapy patients.

5. DISCUSSION

Anamnesis confirmed hypoglycemia had 83.56% of patients on insulin pump therapy, and 81.58% of patients on PEN therapy. The number of hypoglycemia did not differ significantly between the different insulin application groups (p=0.114). On average, by anamnestic data patients in both groups had two hypoglycemia with the same rank (1-4).

Hypoglycemic episodes with blood glucose levels below 3.9 mmol/l verified on the CGM record had 87.67% of IP patients and 82.89% of PEN therapy patients. The number of hypoglycemia on the CGM record did not differ significantly between the groups with different insulin application (p=0.647). On average, patients with IP therapy had 4, and 3 hypoglycemia on PEN, with the same rank (1-6).

During the continuous monitoring of glycemia, we did not identify any severe hypoglycemia episodes.

The hypoglycemia that we recorded through the CGM records are according to the nomenclature of the ADA hypoglycemic working group: documented symptomatic hypoglycemia (8).

The largest number of comparative therapeutic studies for IP and PEN provide data on the reduction of incidence of severe hypoglycemia in IP patients (9-11).

However, Kilpatric ES believes that only 80% of episodes of severe hypoglycemia are reported and that less than 50% of all T1DM patients have one episode of severe hypoglycemia per year, which is 27% of patients on intensive insulin therapy and 10% on conventional insulin therapy (12).

Data from the DCCT study indicate that severe hypoglycemia occurs in only 1/3 of T1DM patients, and only 5% of patients reported to have hypoglycemia, or half of all episodes (13).

Jeitler K in a meta-analytical study on 23 comparative IP therapy studies found a comparable number of mild hypoglycemia in these therapy groups, for patients on IP average 1.9 per week compared to 1.7 mild hypoglycemia per week in patients with basal-bolus therapy applied by a PEN (10).

The introduction of modern therapeutic agents such as insulin analogs and IP has contributed to improved metabolic control of T1DM, or HbA1c is lower by 0.4-0.6%, but there is no evidence of increased incidence of hypoglycemia (14).

IP therapy according to Pickup JC and Suton AJ is recommended to reduce the incidence of severe hypoglycemia in T1DM patients, but the comparability of hypoglycemia frequency in general, in patients with IP and PEN is unclear (15).

According to Fatourechi MM and colleagues, IP patients have slightly lower HbA1c (-0.2%) compared to those treated with PEN, but without significant difference in the incidence of severe and night-time hypoglycemia. Adolescents had somewhat less hypoglycemia in general, but the children included in these studies had significantly more episodes of hypoglycemia (16).

The reason for the higher number of hypoglycemia on the CGM record compared to the anamnestic data lay in better detection of asymptomatic night-time hypoglycemia, as a result of the research by Chetty VT and associates (17).

Battelino T and associates point to the therapeutic role of REAL-time CGM in T1DM patients who had a CGM sensor within 6 months, every second week for 5 days. The number and duration of all hypoglycemic episodes decreased, and at the end of the study ADA targets were achieved in regard to HbA1c (18).

Tanenberg RT and colleagues reported a total of 1.9±1.6 and 2.3±2.3 hypoglycemia per week in patients randomized in study according to their CGM and capillary BG measurements (19).

Distribution of mean glycemia in IP patients and PEN according to the number of their anamnesis hypoglycemia was performed in order to place the number of

anamnestic hypoglycemia and mean in the relationship. The number of anamnestic hypoglycemia with an exception of mean for patients with only one anamnestic hypoglycemia is increased with mean increase in PEN group. The mean glycemia is over 4 mmol/l in patients with 4 anamnestic hypoglycemia while the highest mean glycemia in IP patients is with 3 hypoglycemia. The correlation between the number of anamnestic hypoglycemia and the mean glycemia (CGM) suggests a high level of significance below 0.05 in both PEN and IP patients. The coefficient of correlation r=0.7 allows assumption of high probability to estimate the level of glycemic variability from the number of anamnestic hypoglycemia.

Unlike Kovatchev B which reports a correlation of 0.15-0.16 between mean glycemia and hypoglycemia, our correlation is highly significant at the level of 0.05. The predictive value for hyperglycemia was 0.58-0.56 (20).

De Vries JH in a comparative study of poorly regulated T1DM patients on IP therapy and PEN with mean glycemia measured by capillary BG self-control of 4.57±1.66 mmol/l for IP and 4.85±1.7 mmol/l for PEN reported about 2.13±2.05 mild hypoglycemia in IP patients and 1.97±1.53 on PEN therapy (21).

The correlation of HbA1c, or medium glycemia from HbA1c, and mean glycemia is very significant for the prediction of hypoglycemic episodes. According to Kilpatric ES, each increase in mean by 1 mmol/l increases by 1.09 times the risk for the first hypoglycemic episode, and the increase of 1.12 lead to the increases risk for hypoglycemia by five times. Every lowering of mean glycemia from HbA1c by 1 mmol/l imply a constant risk of 1.02-1.03 times for repeated hypoglycemic incidents.

Therefore, patients, regardless of the manner in which insulin is applied, with the deterioration of T1DM regulation, or increasing HbA1c, should also have a higher incidence of hypoglycemia.

Kaufman FR by CGM system recorded a glycemia lower than 2.2 mmol/l in 27% nights and glycemia below 2.7 mmol/l in 35% monitoring nights in pediatric patients with T1DM. The incidence of night-time hypoglycemia was similar for patients on IP therapy and PEN (22).

Correlation of the number of hypoglycemia registered with the CGM system and the mean glycemia for patients on IP and PEN showed a mainly linear increase relative to the increase of CGM hypoglycemia. Patients with the highest mean on IP therapy of 4.1 mmol/l have the highest number of CGM registered hypoglycemia (23). Correlation of these parameters for IP group is significant at level of 0.05 with the coefficient of correlation r=0.764. Predictive significance of high mean values for hypoglycemic episodes in IP therapy is great when using CGM monitoring.

However, in patients treated with an PEN, mean increases according to the number of hypoglycemia CGM up to 5 episodes and then with the increase in the number of hypoglycemic episodes decrease to the initial level.

Comparison of the number of hypoglycemia registered in the anamnesis and CGM system for patients on IP as well as for patients on PEN therapy provided data on the high significance of the difference in these measurements.

From the establishment of the CGM system, there is a controversy on the accuracy of the measured glycemic values, especially the sensitivity and specificity of the hypoglycemic registration machine.

Although this technology cannot completely replace the standard capillary blood glucose measurement, characteristics of the results that contribute to improved metabolic control and decreased variability in T1DM patients are the best confirmation of the accuracy of results, especially if combined as a REAL-time insulin system.

The accuracy of the CGM system used in children with T1DM was confirmed by DirectNet already in 2003 (24).

Presentation of glycemia variability, postprandial peak hyperglycemia, and unidentified hypoglycemia are some of the events that CGM shows and contributes to their elimination (25, 26).

6. CONCLUSION

The number of anamnesis hypoglycemia as well as hypoglycemia from the CGM record did not differ significantly in patients on IP and PEN therapy. The CGM record was significantly more valuable in the presentation of hypoglycemia compared to the history of hypoglycemia in all patients studied. Continuous monitoring of glycemia due to its ability to show glycemia variability and unrecognized hypoglycemia as well as predictive options for long-term metabolic control should be performed for all T1DM patients at least once a year. Further research in this field should be focused on the determination of biochemical markers of oxidative stress, and the linking of insulin pump "download" parameters with T1DM metabolic regulation and glycemia variability in order to find the best patterns of IP use for our patients.

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REFERENCES

1. Stipancic G, La Grasta Sabolic L, Malenica M, et al. Incidence and trends of childhood Type 1 diabetes in Croatia from 1995 to 2003. Diabetes Res Clin Pract. 2008; 80(1): 122-7.

2. Soltesz G, Patterson CC, Dahlquist G. EURODIAB Study Group. Worldwide childhood type 1 diabetes incidence-what can we learn from epidemiology? Pediatr. Diabetes. 2007; 8 (Suppl 6): S6-S14.

3. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005; 28(1): 186-212.

4. De Beaufort CE, Swift PG, Skinner CT, et al. Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood. Diabetes. Diabetes Care. 2007; 30: 2245-50.

5. Bangstad HJ, Danne T, Deeb LC, et al. International Society for Pediatric and Adolescent Diabetes (ISPAD). Insulin treatment. ISPAD clinical practice consensus guidelines 2006-2007. Pediatr. Diabetes. 2007; 8(2): 88-102.

6. Danne T, Battelino T, Jarosz-Chobot P, et al. Establishing glycaemic control with continuous subcutaneous insulin infu-

sion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. Diabetologia. 2008; 51(9): 1594-1601.

7. Skyler JS, Ponder S, Kruger DF, et al. Is There a Place for Insulin Pump Therapy in Your Practice? Clinical Diabetes. 2007; 25: 50-6.

8. American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes. Diabetes Care. 2005; 28: 1245-9.

9. Jakisch BI ,Wagner VM, Heidtmann B, et al. Comparison of continuous subcutaneous insulin infusion (CS II) and multiple dose (MDI) in paediatric Type 1 diabetes; multicentre match-opair cohort analysis over 3 years. Diabet Med. 2008; 25(1); 80-5.

10. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008; 51(6): 941-51.

11. Colino Alcol E, Lopez Capape M, Alvarez Gomez MA, et al. Continuous subcutaneous insulin infusion in pediatric patients with type 1 diabetes mellitus. An Pediatr (Barc). 2006; 64(1): 21-7.

12. Kilpatrick ES, Rigby AS, Goode K, et al. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycemia in type 1 diabetes. Diabetologia. 2007; 50: 2553-61.

13. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial Diabetes. 1997; 46: 271-86.

14. Heller SR. Minimizing Hypoglycemia While Maintaining Glycemic Control in Diabetes. Diabetes. 2008; 57(12): 3177-83.

15. Pickup JC, Sutton AJ. Severe hypoglycemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008; 25: 765-74.

16. Fatourechi MM, Kudva YC, Murad MH, et al. Hypoglycemia with Intensive Insulin Therapy: A Systematic Review and Meta-Analyses of Randomized Trials of Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections J Clin Endocrinol Metab. 2009; 94(3): 729-40.

17. Chetty VT, Almulla A, Odueyungbo A, et al. The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: a systematic review. Diabetes Res Clin Pract. 2008 ; 81(1): 79-87.

18. Battelino T, Phillip M, Bratina N, et al. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011; 34: 795-800.

19. Tanenberg RT, Bode B, Lane W, et al. Use of Continuous Glucose Monitoring System to Guide Therapy in Patients With Insulin-Treated Diabetes: A Randomized Controlled Trial. Mayo Clin Proc. 2004; 79(12): 1521-6.

20. Kovatchev B, Otto E, Cox DJ, et al. Evaluation of a New Measure of Blood Glucose Variability in Diabetes. Diabetes Care. 2006; 29: 2433-8.

21. DeVries JH, Snoek FJ, Kostense PJ, et al. Dutch Insulin Pump Study Group. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care. 2002; 25(11): 2074-80.

22. Kaufman FR, Austin J, Neinstein A, et al. J. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. J. Pediatr. 2002; 141(5): 623-30.

23. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295: 1681-7.

24. Diabetes Research in Children Network (DirecNet) Study Group .The accuracy of the CGMS in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet) accuracy study. Diabetes Technol Ther. 2003; 5: 781-9.

25. Deters MA, Läer S, Hasanbegovic S, et al. Diabetes Stewardship - Pharmaceutical care of adolescents with type 1 diabetes mellitus provided by community pharmacists. Med Monatsschr Pharm. 2016 Nov; 39(11): 477-82.

26. Obarcanin E, Krüger M, Müller P, et al. Pharmaceutical Care of Adolescents with Type 1 Diabetes Mellitus: A Randomized Controlled Trial. Int J Clin Pharm. Int J Clin Pharm. 2015 Oct; 37(5): 790-8.