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INSULIN PUMP TREATMENT IN CHILDREN AGED 3.0 – 6.0 YEARS IN BULGARIA: SUSTAINING THE OPTIMAL CONTROL

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ABSTRACT

Insulin pump treatment in Bulgaria started in 2007. The results for the first 29 patients were satisfying but the following years showed deterioration in some patients. The country needed a team of educated nurses for pump treatment. The 6-months project aimed: To start pump treatment in 12 type 1 diabetes children, aged 3.0 to 6.0 years, attending a kindergarten /6 girls/ and to evaluate the change in the HbA1c, the proportion for basal/bolus dose and the ratio of insulin/body weight. To educate a team of diabetes nurses for the kindergarten

Organization:
Structured education for the parents
An informed consent signed by both parents
Anthropometry and HbA1c at the start and follow up
Sensor-augmented pump after the initial 3 months
Starting basal dose – 50% of the total daily dose /TDD/
Bolus wizard from the beginning
3 nurses from the University clinic for diabetes – Sofia gave duties daily in the kindergarten to educate the nurses in the kindergarten

Results:
Basal dose for 5 patients is 50%; in one - 52% and for six patients 40 - 45% of the TDD
Insulin/body weight ratio: 0.65±0.136IU/kg.
HbA1c decreased from 8.47 % /60.3 mmol/mol/ to 7.21% /51.33 mmol/mol/ /p<0.001/at the end of the first year and is sustained 3 years after: the latter is 7.3% without adverse events /DKA, severe hypoglycemia, injection site reactions/
All the parents and children are very satisfied with the continuous subcutaneous insulin infusion /CSII/ and with the exception of one family still continue it.

INTRODUCATION

In Bulgaria insulin pump treatment was introduced relatively late /in 2007/ compared to most of the other countries. For lack of reimbursement only about 100 children and adolescents aged 1 – 18 years are treated with insulin pumps. The initial results for the first 29 patients on pump treatment were inspiring: the average HbA1c for the treated group decreased significantly from 8.8 ±1.75% /62.6 ± 12.45 mmol/mol/ to 7.03±1.07%, /50.03 ± 7.62 mmol/mol/, p<0.001 after one year (Konstantinova, 2009). The following years showed that some of the patients and especially adolescents could not sustain the desired optimal control and one of the patients stopped the pump for recurrent diabetic ketoacidosis /DKA/. Besides the small experience of the team for the pump treatment, the impossibility to meet and control the patients regularly and adapt the treatment algorithms is thought to be a reason for the lack of sustain. Another finding was that if the bolus wizard is not started from the beginning /as we did initially with the first patients on pumps/, many of the pump patients do not appreciate its use after that, making the follow-up of the therapy less efficient. This showed the need for adequate control to upgrade the individual treatment plans and further educate the patients. A 6-months project was started.

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METHODS

Subjects: Twelve children /six girls/ aged 3.0 – 6.0 years with duration of type 1 diabetes from 3 months to 3.9 years, were started on insulin pump treatment. All of them attended the

kindergarten for children with diabetes in Sofia – Bulgaria. Only rapid insulin analogues and Medtronic Veo pumps were used. After the initial 3 months the project continued with sensor-augmented pumps for another 3 months. Blood glucose values were examined with Optium Xceed glucometer /Abbot Diabetes Care/. HbA1c was measured with NycoCard.

The objectives

- To start therapy with insulin pumps for 12 children aged 3 – 6 years attending a kindergarten and give the opportunity for better control in the lower-age patients
- To further educate a team of diabetes nurses in the kindergarten for pump treatment
- To evaluate:
  -change in the control through HbA1c value
  -optimal relation of the TDD to body weight in this age group
  - proportion for basal/bolus dose
  - adverse events – DKA, severe hypoglycemia and infusion site reactions

The project was approved by the Ethics Committee in the University Pediatric Hospital – Sofia and is in accordiance with the Declaration of Helsinki. An informed consent was signed by both parents.

Organization of the project

The parents and the nurses working in the kindergarten passed a structured education program for:

- The principles of the pump therapy
- The pump use including insertion of a pump set filled with 0.9% NaCl to one of the parents "using" the pump for one day;
- Carbohydrate /CHO/ counting;
- The principles and use of bolus wizard calculator
- Regular blood glucose measurements /8 – 10/ daily to be filled in the logbook of the patient;
- For the period of sensor-augmented pump – at least 2 measurements a day for calibration
- Measuring blood ketones /ß-hydroxybutyrate/ if blood glucose exceeds 13.0 mmol/l. and changing the set if there is no improvement after a correction bolus for 1 hour;

Anthropometry

Height and weight were measured at the start, at the end of the project and one year after the end of the project. Body mass index was calculated and compared to (Cole *et al*., 2000). HbA1c /NycoCard/ was evaluated at the start and every 3 months after that, range 4 – 6%.

Starting the pump

The project started in June 2011 and the team initiated the pump treatment of 2 children for a session. There were 2 sessions a week and all the 12 children were started on pumps for 3 weeks. For the initiation of the pumps the total daily dose was reduced with 20% and divided in 2 equal parts for the basal and bolus dose (Danne and Kordonouri, 2010). The basal dose was distributed using at least 4 different basal rates according to the physiological circadian profiles of the insulin sensitivity for the age (Buckingham *et al*., 2013). The bolus wizard was initiated from the beginning with the initial insulin sensitivity /IS/ calculated by dividing 100 mmol/l with the TDD. The initial Carbohydrate ratio /CHO/ was calculated by dividing 200/300 gr. CHO to the TDD. The logbooks were filled in from the parents while the patients were at home and from the diabetes nurses on duty for the hours spent in the kindergarten. One of the team of 4 diabetes nurses had 4-hours duties in the kindergarten to:

- Evaluate the blood glucose levels and fill in the logbooks
- Measure CHO for the meals
- Enter the data in the pumps and precise the boluses
- Further educate the 2 nurses, who work in the kindergarten and continue controlling the therapy with the pumps for the rest of the day.
- The nurses had constant telephone contact with the physician

Follow up of the treatment

The team regularly adjusted /weekly for the first month and monthly for the next 3 months and at 3-months intervals after that/ the basal dose and the bolus wizard parameters.

RESULTS

Table 1 shows the results for the examined 12 patients at the beginning and during the 3-years follow-up. The last evaluations were done March-April 2014. One of the families did not continue the pump treatment after the end of the project and HbA1c shows the mean value for the 11 patients who are still on pump treatment /Table 1./. The initial HbA1c for the whole group was 8.46±0.66% /60.26±4.7 mmol/mol./ At the end of the project after 6 months though lower, the mean value of HbA1c was not significantly different: 7.66±0.41% /54.5± 2.92/ /$p>0.1$ compared to the initial value. Fortunately there was further improvement over the next 9 – 12 months after the end of the project and the mean value showed HbA1c 7.30±0.89% /51.9±6.33/, $p<0.001$/. Eight of the patients improved their control gradually and met the ISPAD criteria for optimal control of HbA1c below 7.5% /53.39mmol/mol/ while 3 of them are with excellent levels of HbA1c below 7% /49.83 mmol/mol/.

The three patients who could not succeed in lowering the HbA1c value below 7.5% and remained with a value of 8.1 – 8.0% were those with the highest level before starting the pump – above 9% /64 mmol/mol.//fig.1/. The last examined HbA1c 3 years after the start of the project is sustained to 7.30±0.72 /51.9±6.33/, $p<0.001$, significantly lower compared to that before the pump treatment. The ratio of the TDD to body weight showed decreased daily insulin dose/kg.b.w. compared to that before the start of the pump. BMI- z scores for all the patients is in the normal range, and neither thinness nor overweight or obesity are found for now. We have not registered any changes in the infusion sites also. There was no severe hypoglycemia during the whole evaluation period.

Table 1. HbA1c, % Basal insulin dose and Units of TDD Insulin/kg.b.w. in the group of children on pump therapy

	Initial N=12	3 months N=12	6months N=12	1year N=11	3 years N=11
HbA1c%	8.46±0.66	8.10±0.44	7.66±0.41	7.30±0.89	7.30±0.72
mmol/mol	60.26±4.7	57.7±3.13	54.5±2.92	51.9±6.33	51.9±5.13
%Basal	48±1.6			47.2±4.1	46.0±5.52
Units TDD/kg.b.w.	0.84±0.19			0.61±0.17	0.74±0.06

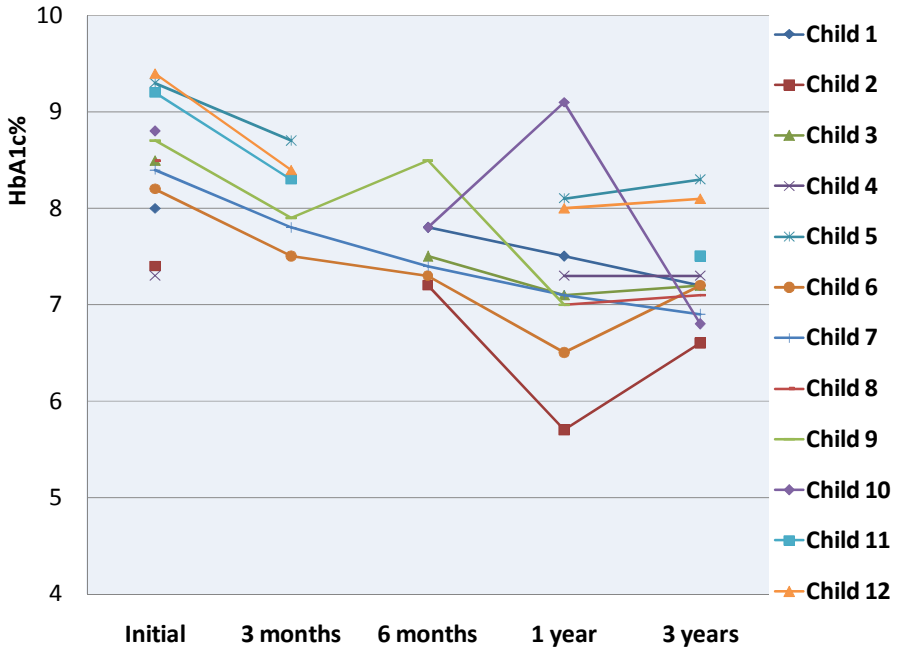

Fig.1. Individual levels of HbA1c in the patients after the start of the pump treatment

During the time of the project two patients were hospitalized for acute gastrointestinal diseases for rehydration therapy. No one had ketonuria or elevation of ß-hydroxybutyrate above 0.6 mmol/l. The estimation of the ratio of basal to bolus daily insulin dose showed: Five of the patients have 50% basal dose; only in one of the patients the basal dose exceeds 50% - the actual basal dose is 52% of the TDD. The rest six patients need basal insulin dose between 40 – 45%. No one of the patients in our group could be controlled with a basal dose below 40% of the total daily dose. The average insulin dose per kg. body weight for the group at the last evaluation of HbA1c is 0.74±0.006 IU/kg. b.w. The education of the two diabetes nurses in the kindergarten was successful and all the patients who are below the age of 6 years are still in the kindergarten.

DISCUSSION

Type 1 diabetes is a serious chronic disease and the prognosis and quality of life depend on the long term glycemic control. The results from DCCT 20 years ago changed thoroughly the concept for the insulin regimes and intensive insulin treatment with multiple daily insulin injections is the treatment of choice for all the children and adolescents with type 1 diabetes immediately after the diagnosis. The goals for the insulin therapy are not only to achieve lower level of HbA1c, but also less time spent below or above the target glucose levels, to improve the quality of life of the whole family and possibly to preserve the residual C-peptide secretion, thought to decrease the incidence of the late complications of diabetes (Danne and Kordonouri, 2010; Buckingham *et al*., 2013; Kordonouri *et al*., 2012 and Steffens *et al*., 2003). Parents and children are educated to be as precise as possible in calculating the insulin doses for the boluses. This is really a continuous struggle to achieve the desired glucose levels. Failure to obtain the optimal control causes lower health related quality of life HRQOL in the patients and parents (Frøisland *et al*., 2013). Fear from hypoglycemia especially during the sleeping hours is another reason for constant discomfort for the families and worsening of the control (Streisand *et al*., 2005 and Patton, 2011).

Insulin pump therapy and especially the closed –loop system bionic pancreas is very promising to overcome most of the issues with insulin therapy (Weinzimer *et al*., 2008; Steil *et al*., 2005; Hovorka *et al*., 2010; Ellery *et al*., 2012; Dauber *et al*., 2013; Russel *et al*., 2012; Phillip *et al*., 2013; Battelino *et al*., 2012 and Kovatchev *et al*., 2013). But before the artificial pancreas becomes a standard therapy for most of the patients, therapy with an insulin pump and especially a sensor-augmented pump SAP is mostly appreciated. The advantage of the SAP on the preservation of the B-cell function is confirmed, especially if SAP is started from the diagnosis of the disease (Kordonouri *et al*., 2012). Besides the positive data concerning the overall control, the risk for hypoglycemia, the area under the curve AUC for both below and over the targets,

connected to the number of glucose measurements or usage of sensors and the number of boluses, there are controversial statements about the benefits of the pump treatment compared to the multiple daily injections MDI (Battelino *et al*., 2012; Misso *et al*., 2010; Slover *et al*., 2012; Ayoola *et al*., 2013; Pickup and Sutton, 2008 and Kumar *et al*., 2013). But the recently published paper showing the improvement of the metabolic control of the whole pediatric cohort of patients with diabetes in Slovenia during the last 12 years in parallel with the increased pump usage is extremely indicative of the pump priorities. This paper confirms not only the advantages of the pump treatment, but the significant role of the well organized multidisciplinary diabetic team (Dovc *et al*., 2013). The results from the German-Austrian large cohort of type 1 diabetes children and adolescents with high percent of pump therapy also show achievement of optimal control especially in the younger age below 12 years (Bachran *et al*., 2012 and Ludwig-Seibold *et al*., 2012). Our results though based on a little number of patients confirm the possibility of the CSII to improve and sustain the metabolic control of the patients.

The age below six years is special for the fact that the control is constant and reliable, done from a parent or a caregiver, which makes it more predictable compared to the adolescents, on the one hand. But on the other hand some of these little children are so difficult to be controlled for the lability of their glucose metabolism, based on the unpredictable appetite, physical activity and especially the typical for the age frequent infections. This makes the CSII very suitable for the little patients. The improved metabolic control impacts the physical development of the child. The BMI shown appropriate for the age and sex confirms the possibility of the pump to infuse the most physiologically distributed and calculated dose during the day and night. The fact that the TDD is reduced with about 17 – 20% since the start of the pump compared to that while on MDI, is favoring the patients on pumps (Nicolajsen *et al*., 2012). They are not supposed to be overinsulinized – a frequent event when on MDI, causing overweight and increased risk for hypoglycemia. The rate of overweight and obesity is found to increase among children with type 1 diabetes and is in parallel with an enhanced risk for metabolic syndrome (Vliet *et al*., 2010).

The data showing the deleterious effect of either hypoglycemia or hyperglycemia on the structure and function of the developing brain is striking and emphasizes the need for the precision of the insulin dose (Arbelaez *et al*., 2013). The insulin pump gives better opportunity for that and the closed-loop is promising to further decrease the glucose variability and time spent below or above the targets (Hovorka *et al*., 2010 and Phillip *et al*., 2013). Our results for the total insulin dose/kg/d /0.74±0.06 IU/kg/d/ are in line with that found from Bachran *et al*. for 837 German-Austrian patients aged below 6 years on pumps /0.71± 0.27 U/kg/d/ and for the C-peptide negative patients in a study of 90 children on CSII / 0.65 ±0.3 IU/kg/d/ (Bachran e tal., 2012 and Pankowska *et al*., 2008). We assume that this dose is much more physiological compared to the usual for this age when on MDI, nearing 0.8 – 1.0U/kg/d. Our data for the basal insulin dose which ranges 40 – 50% of the TDD is also compatible with other studies (Bachran e tal., 2012; Pankowska *et al*., 2008; Shehadeh *et al*., 2004 and Klinkert *et al*., 2008).

The basal needs in children and adolescents show to be different compared to the adults for whom the basal dose may be around 30% of the TDD (King, 2010 and Kuroda *et al*., 2011). Our study is unique for it was based on co-education of the parents and the nurses in the kindergarten, both not aware of the pump treatment before the project. It also shows the usefulness of the bolus-wizard and its reliability to control a group of 10 – 12 children with diabetes in a kindergarten setting. All the patients participated in all the activities of the everyday program of the setting, both educational and physical activities with the relevant adaptations for the basal bolus infusion made from the nurse. The absence of any acute complication during the time spent both in the kindergarten and at home is another achievement of the insulin pump therapy for this young age. Our experience with pump therapy is still insufficient and probably the low number of pump patients is the reason that we have not registered any changes in the injection sites of our patients. No one of these patients has any associated autoimmune diseases and this could be another explanation.

The limitation of the study is the low number of the patients which is connected with the low number of patients with diabetes on therapy with CSII in the country. But the sustained control more than three years after the end of the project is inspiring for both the parents and the diabetes team. The economic study comparing insulin pump therapy with MDI is also in favor of the CSII therapy concerning its cost-effectiveness for the degree of the improvement of the metabolic control (Petkova *et al*., 2013 and Petkova *et al*., 2013). Our previous experience with the pump therapy is that once the parents/patients become familiar with the principles of the treatment and especially after the initial improvement of the control, the original curiosity falls and the patients/parents enter in a specific channel of control, satisfying their lives as there are less hypoglycemic events and more precised boluses. In fact some of them do not achieve the best possible /with pump treatment/ control. Unfortunately the growing children need constant adaptation of the treatment plan according to the changing insulin needs. This can be done only if the contact between the patient and the team is continuous with data downloaded and analyzed. The probable reason for the "disappointment" in the pump treatment could be the lack of appropriate adaptation, continuous education and motivation of the patients and their families.

Conclusion

The analysis of 12 patients aged 3 – 6 years, started with CSII in a setting of a kindergarten, show its safety, reliability and sustaining of the improved control. Continuous adaptation of the pump parameters in parallel with further education are the absolute conditions needed for success of the pump treatment.

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