

THE FOLLOW-UP RESULTS OF INSULIN PUMP USE IN TURKISH CHILDREN WITH TYPE I DIABETES MELLITUS

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ABSTRACT

Purpose: Although its use is increasing in children, there are no data about pump use in Turkish children with diabetes. The aim of this study was to investigate the outcome measures of insulin pump use in diabetic Turkish children.

Materials and Methods: Ten children (age; 14.7±2.6 years, pump therapy duration; 3-24 months) were prospectively studied. Main outcome measures were compared with those of the 12 months prior to pump therapy.

Results: Although statistically insignificant, HbA1c tended to be lower compared to the pre-pump period. Body mass index Z scores remained similar (0.45±0.76 vs. 0.54±0.53 kg/m², p>0.05). Insulin doses decreased (1.1±0.2 vs. 0.9±0.1 U/kg/day, p<0.01). Rates of certain episodes (event/patient-year) decreased: overall hyperglycemia; 244.0±84.5 vs. 90.6±38.9, Dawn phenomenon; 20.6±25.8 vs. 4.6±5.2, Somogyi phenomenon; 3.1±2.7 vs. 1.1±1.0, nocturnal hypoglycemia; 6.4±4.5 vs. 2.9±1.9, asymptomatic hypoglycemia; 21.3±13.4 vs. 8.8±6.7, symptomatic hypoglycemia; 3.7±2.2 vs. 1.6±1.3 (p values <0.05). Diabetic ketoacidosis rates were similar (0.24 vs. 0.30, p>0.05).

Conclusion: The consistency of the improvements in main outcome measures and their maintenance over time in our study suggest that pump therapy is safe and effective in diabetic Turkish children.

Key Words: Insulin Pump, Children, Type 1 Diabetes.

DİYABETLİ TÜRK ÇOCUKLARINDA İNSÜLİN POMPASI KULLANIMI İZLEM SONUÇLARI

ÖZ

Amaç: Çocuklarda kullanımı giderek yaygınlaşmasına rağmen, diyabetli Türk çocuklarında insülin pompası kullanımına dair yayınlanmış veri yoktur. Bu çalışmanın amacı diyabetli Türk çocuklarında insülin pompası kullanımının sonuçlarını araştırmaktır.

Gereç ve Yöntemler: Yaş ortalaması 14.7±2.6 yıl, pompa kullanım süresi 3-24 ay olan on diyabetik çocuğun verileri incelenmiş, ve pompa kullanımı öncesi bir senelik sürede elde edilen verilerle karşılaştırılmıştır.

Bulgular: İstatistiksel olarak anlamlı olmamakla birlikte, HbA1c düzeyi pompa öncesi döneme kıyasla azalma eğiliminde idi. Vücut kitle indeksi Z skorları benzerdi (Pompa öncesi ve sonrası sırasıyla; 0.45±0.76 ve 0.54±0.53 kg/m², p>0.05). Ortalama insülin dozu azalmıştı (Pompa öncesi ve sonrası sırasıyla; 1.1±0.2 ve 0.9±0.1 U/kg/gün, p<0.01). Bazı epizodların görülme sıklıkları (görülme sayısı/hasta yılı) azalmıştı: Pompa öncesi ve sonrası sırasıyla; tüm hipoglisemiler; 244.0±84.5 ve 90.6±38.9, şafak fenomeni; 20.6±25.8 ve 4.6±5.2, Somogyi fenomeni; 3.1±2.7 ve 1.1±1.0, nöktürnal hipoglisemi; 6.4±4.5 ve 2.9±1.9, asemptomatik hipoglisemi; 21.3±13.4 ve 8.8±6.7, semptomatik hipoglisemi; 3.7±2.2 ve 1.6±1.3 (p değerleri <0.05). Diyabetik ketoasidoz görülme sıklığı benzerdi (Pompa öncesi ve sonrası sırasıyla; 0.24 ve 0.30, p>0.05).

Sonuç: İzlemede değerlendirilen önemli parametrelerde istikrarlı düzelmeye sağlanmış olması, insülin pompası tedavisinin diyabetli Türk çocuklarında etkili ve güvenilir bir yöntem olduğunu göstermektedir.

Anahtar Kelimeler: İnsülin Pompası, Çocuk, Tip 1 Diyabet.

INTRODUCTION

Intensified insulin therapy has been the basis of diabetes management since the Diabetes Control and Complications Trial revealed that glycemic control is an important risk factor influencing the development of the complications of diabetes, even in adolescence.¹ There are two major ways of intensified therapy in type 1 diabetes mellitus (T1DM): multiple daily insulin injections by means of long acting insulin providing the basal insulin level and short or fast acting insulin doses providing postprandial glycemic control, and continuous subcutaneous insulin infusion (CSII) or pump therapy.

Since its first use in the 1970s, CSII has become an alternative therapy in T1DM.² The improvements in pump technology, together with the introduction of fast-acting analogs, resulted in it being the most physiological way to administer insulin.

Most of the data in the literature suggest that pump therapy offers improved glycemic control without increasing the risk of hypoglycemia, hyperglycemia/diabetic ketoacidosis (DKA), improved coverage of the Dawn phenomenon, increased flexibility in daily living, and improved coping with diabetes.³

In spite of its increasing use in children, the data in the literature are somewhat scarce about this age group. There are studies reporting the disadvantages and complications like increased cost, skin infection and allergy, unexplained hyperglycemia and/or ketoacidosis and hypoglycemia. This leads to pump therapy being reserved for those children in whom indications are strictly and carefully evaluated. In addition, every diabetes center should consider their patient's profiles and diabetes team's experience in order to decide whether or not to use this therapy privately in each child with T1DM.

CSII therapy in the routine care of Turkish children with T1DM has only been used very recently and there are no data so far concerning clinical and laboratory outcomes. This study reports for the first time the results of the use of CSII therapy in Turkish children with T1DM.

MATERIALS AND METHODS

Patients:

We have been using CSII as an alternative treatment of T1DM in the Pediatric Endocrinology Clinic at Gazi University since September 2003. Eleven patients who received insulin pump therapy until February 2006 were considered for this study, but 10 of them (3 girls and 7 boys) form the basis of this report; one did not follow the routine follow-up schedule and there were insufficient data. At the start of pump therapy, the mean age was 14.7±2.6 (range; 8.7-17.7, median 15.4) years and the mean duration of diabetes was

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5.9±5.0 (range; 1.1-16.0) years. Until the end of the study period, data were available for 3-24 (15.0±6.9) months of pump therapy; thus we obtained data of a total of 12.5 patient-years of pump experience.

The patients and/or their families needed to fulfill the generally accepted criteria for CSII initiation in our clinic: to be willing to use pump therapy as an alternative regimen, to be motivated and able to test blood glucose levels at least 4 times per day, to demonstrate an ability to comprehend the concepts of insulin pump mechanics, to have satisfactory record-keeping details, the ability to make appropriate insulin dose adjustments, and basic knowledge in counting carbohydrates. Additionally, in our unit, we usually reserve CSII for those who are followed up for at least one year and for those above 10 years of age, and all of our study population except for one patient (age 8.7 years) matched these criteria. All of them except for two had been using multiple daily injections as their therapy regimen for at least one year before pump therapy.

Indications for considering pump therapy were as follows: background retinopathy (one patient), poor metabolic control and/or frequent hypo-hyperglycemic episodes (three patients), and desire for a more flexible life-style (six patients).

Protocol for pump therapy:

The risks involved in pump use were discussed in detail with all patients and their families individually, and written informed consent was obtained.

In our unit, each patient who is a candidate for pump therapy is given routine education consisting of general guidelines about insulin pump mechanics, potential problems related to pump therapy (e.g., site infections, unexplained hyper- or hypoglycemia, air bubbles, kinked infusion sets, and dislodgement), and their prevention strategies. This is followed by an individual education session of about one hour that reviews general guidelines for diabetes management (e.g., carbohydrate counting and insulin adjustment). The patient is then hospitalized for the initiation of pump therapy.

Patients discontinued all long-acting insulin and took regular insulin four times a day for at least 24 h in order to determine daily insulin dosage. Insulin pump therapy was then started as an inpatient procedure using either Dana Diabcare 2^R or Medtronic Minimed 507^R insulin pumps. The CSII dose using a fast-acting analogue (lispro or aspart insulin) was calculated to be 10%-20% less than the daily insulin need, with about 40%-50% of this given as the basal dose. Blood glucose monitoring was performed eight times a day (pre- and post-meals, bedtime, and at 03:00 am) and the patient was discharged after acceptable blood glucose values were maintained. At discharge, patients were given the cell and home phone numbers of the entire diabetes team and instructed to contact them for any, even minor, problem. The patient was seen within a week after discharge, and then followed up according to the routine diabetes schedule (every 3 months). Patients measure glucose levels and record them at least four times a day after the first appointment.

Outcome measures:

In our clinic, every patient (whether using pump therapy or not) is seen every 3 months. Each visit includes a review of blood glucose records (each patient has a standardized diary), episodes of hypo- and hyperglycemia, insulin doses, basic educational up-grading, and adjustment of the insulin regimen together with measurements of body mass index (BMI) [weight (kg)/height (m)²] and HbA1c. A standard clinic visit form is available for each patient.

Data were collected retrospectively for 12 months before the initiation of the insulin pump therapy (the control period) and prospectively for as long as the patient remained on the therapy, or until the end of the study period. Daily blood glucose measurements for at least four times a day were available for each patient before and after the start of pump therapy.

BMI Z-scores were calculated using data available for Turkish children.⁴

The relevant outcome measures to assess insulin pump therapy included BMI-Z score, insulin dose [expressed as the total daily dose (TDD)/kg], episodes of hypoglycemia (blood glucose <60 mg/dl)⁵⁻⁸ and hyperglycemia (blood glucose >180 mg/dl)⁵, DKA (defined as pH<7.30 and plasma ketone >3 mmol/L),⁹ and HbA1c (%). Hypoglycemia was classified as "asymptomatic" or "symptomatic" according to the presence of hypoglycemia-related symptoms. Fasting morning hyperglycemia was defined as "Somogyi Phenomenon" and "Dawn Phenomenon" respectively depending on whether it was preceded by hypoglycemia or not. Episodes are expressed as events/one patient-year.

HbA1c was assessed by cation-exchange high-performance liquid chromatography. The upper limit for the non-diabetic range is 6.5% in our laboratory. Prepump HbA1c was defined as the mean of all HbA1c measurements for that child for up to 1 year before the start of pump treatment. The first HbA1c level was not included in the calculation if it covered the prediagnosis period (one patient).

Statistical Analyses:

All data are reported as mean±SD. Statistics were analysed using SPSS for Windows (version 12). Between-group comparisons were performed using Wilcoxon's rank-sum test. All statistical tests were two-tailed and used a 5% level of significance (p<0.05).

RESULTS

Table I shows the mean HbA1c values of the patients still being followed up at each 3-month interval and the mean of HbA1c values of each individual group for the one year prior to the commencement of pump therapy. At each follow-up interval, the current and cumulative post-pump mean HbA1c values tended to be decreased compared to the pre-pump period, but the differences did not reach statistical significance.

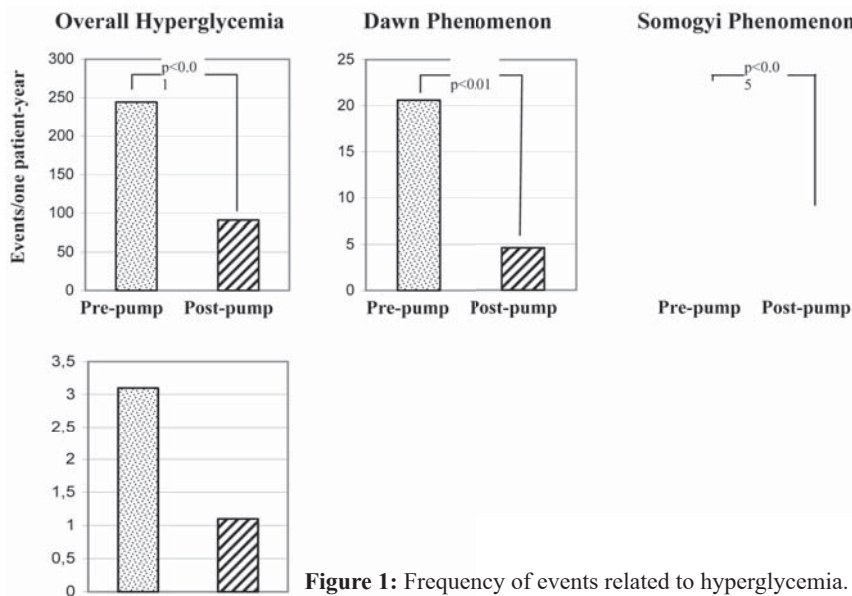
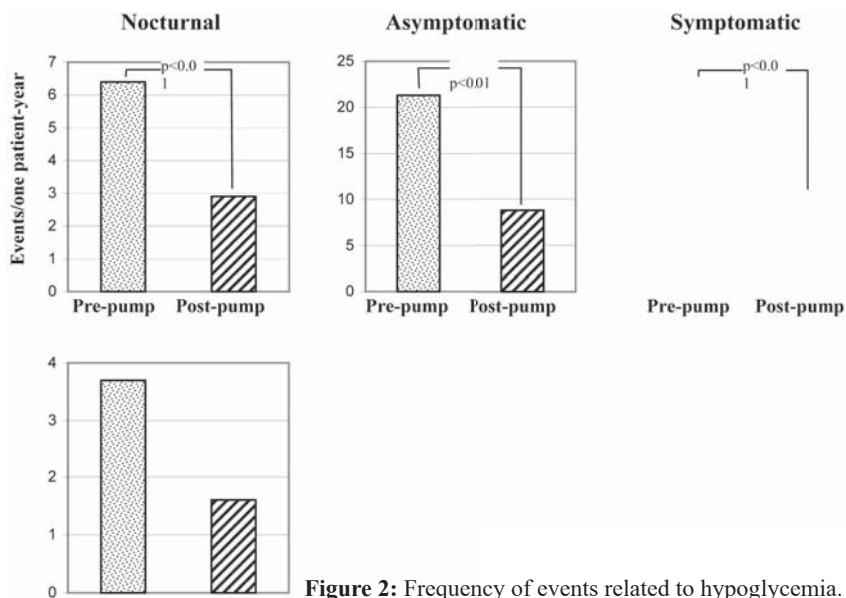
BMI-Z scores did not change significantly after starting

Table I: The pre-pump period (1 year), the current and the cumulative post-pump mean HbA1c values at each follow-up period*.

Months→	3 (n=10)	6 (n=9)	9 (n=9)	12 (n=7)	15 (n=5)	18 (n=5)	21 (n=4)	24 (n=1)
Pre-pump	8.4±1.8	8.1±1.5	8.1±1.5	8.2±1.6	8.7±1.7	8.7±1.7	8.3±1.7	10.5±2.4
Current	8.0±1.6	7.5±1.4	7.2±1.3	7.7±1.8	7.9±1.7	8.4±2.4	7.6±1.4	9.0
Post-pump	8.0±1.6	7.6±1.3	7.5±1.3	7.7±1.5	8.0±1.5	8.1±1.7	7.5±1.2	9.0
p[†]	NS	NS	NS	NS	NS	NS	NS	NS

*: Values refer to the group of patients evaluated at each interval.

†: Comparison of the pre-pump vs. current and pre-pump vs. cumulative post-pump values. NS: Not significant

**Figure 1:** Frequency of events related to hyperglycemia.**Figure 2:** Frequency of events related to hypoglycemia.

pump therapy (pre-pump; 0.45±0.76 vs. post-pump; 0.54±0.53 kg/m² respectively, p>0.05). At baseline, subjects were receiving 1.1±0.2 U/kg/day of insulin dose, which decreased significantly after pump therapy (0.9±0.1 U/kg/day, p<0.01). The frequency (event/patient-year) of total hyperglycemic episodes (pre-pump vs. post-pump; 244.0±84.5 vs. 90.6±38.9), Dawn

phenomenon (20.6±25.8 vs. 4.6±5.2), documented Somogyi phenomenon (3.1±2.7 vs. 1.1±1.0), and hypoglycemic episodes, nocturnal (6.4±4.5 vs. 2.9±1.9), asymptomatic (21.3±13.4 vs. 8.8±6.7), or symptomatic (3.7±2.2 vs. 1.6±1.3), all showed the efficacy of pump therapy compared to the one-year period prior to the commencement of this protocol (Fig. 1 and 2).

Three episodes of DKA occurred in two patients during the CSII period with all of them due to catheter occlusion (0.24 events/one patient-year). This rate was similar to that in the pre-pump period, where a total of three events occurred in three patients (0.30 events/one patient-year, p>0.05).

Other problems related to pump therapy were an allergic reaction to the needle's sticking plaster (one case) that resolved after another type was used, and technical problems due to pump failure (4 cases), in which the pumps were renewed.

DISCUSSION

There are a considerable number of studies reporting experiences with CSII, but most of them are concerned with adult patients, and its use in children with T1DM remains to be evaluated, especially in those countries in which this therapy is considered a new approach for the management of diabetes. In Turkey, there are few centers using pump therapy as an alternative treatment method in T1DM with individual experiences involving about 5-15 patients, and to the best of our knowledge there is no study reporting outcome measures of pump use in Turkish children with T1DM.

Considering hyperglycemia related episodes, we found that CSII therapy offers fewer overall hyperglycemic episodes including Dawn and Somogyi phenomena. There are very few studies in children that focused basically on hyperglycemic episodes, some of them giving results comparable with

ours,^{5,10,11} but there are also others that report that CSII therapy in children offers no difference in terms of this particular topic.^{2,12,13} Furthermore, two of the three studies that report favorable results depend on the data of a continuous glucose monitoring system (CGMS), which in fact deals with a limited period of time (i.e. up to 72 hours) comparing this type of therapy with others.^{5,10} Therefore, although a limited number of patients were included, our results dealing with 12.5 patient-years of pump experience with blood glucose values closely monitored both in pre- and post-pump periods deserve considerable interest.

There are also few reports in children considering overnight blood glucose control and the phenomena which represent the extensions of this: Dawn and Somogyi phenomena. We were not able to detect overnight blood glucose control, because our study design does not include monitoring of this particular period of time. The episodes of Somogyi phenomenon presented here involve only those patients who awakened during the night because of hypoglycemic symptoms and measured their blood glucose levels, and for those who performed monitoring at 03.00 a.m. as a part of their routine during pump therapy. Therefore, although noteworthy, the data showing the efficacy of pump therapy in terms of the Somogyi phenomenon should not be considered objective. Some patients who had hypoglycemia but did not recognize it may be considered in the “Dawn phenomenon” group. The objective data about overnight glucose control in our study are fasting morning blood glucose values, which are significantly lower than those detected during the pre-pump period. Most of the previous studies also report similar results.^{8,11,12}

We demonstrated that patients experienced fewer hypoglycemic episodes during pump therapy compared to the pre-pump period. This has a special significance, because hypoglycemia presents a particular problem in the therapy of type 1 DM in children, since at a younger age hypoglycemic episodes may lead to negative outcomes in cognitive development.¹⁴ Hypoglycemia has been regarded as an unavoidable consequence of tight glycemic control, as underlined by the DCCT study.¹ Our results, together with most other studies, suggest that CSII treatment does not potentiate such a risk compared to other forms of insulin treatment.^{9,11,15-19}

The mean HbA1c values seem to be improved in our patients by 0.4%-0.7% at each follow-up interval of pump therapy compared to the mean values of the pre-pump period, but this difference did not reach statistical significance. According to DCCT results, this degree of sustained lowering of HbA1c levels can result in a considerable amount of reduction (up to 40%) in the risk of development and progression of long-term diabetic complications.¹⁷ The statistical insignificance may originate from the small number of patients in our study cohort. Most of the previous studies comparing an average of one year of pump therapy with other forms of treatment in which alterations reached statistical significance report improvements of 0.2%-0.7% in HbA1c values, similar to what was observed in our study.^{7,9,12,15,17,19,20} There are very few of them in which a better improvement in HbA1c was observed.^{21,22}

Yet, examination of HbA1c levels alone may be misleading, because HbA1c represents the average blood glucose levels including hypo- and hyperglycemic events, both of which are found to be lowered in our cohort. Thus, even if HbA1c values are similar compared to the pre-pump period, this result should be interpreted as showing that our patients had spent more time with blood glucose values within the desired target ranges. Moreover, the observation period is relatively short in most of our patients and includes the adaptation period to a new form of therapy. Problems in orientation to the technical aspects of pump therapy may have had a negative effect in reaching desired HbA1c levels.

Other advantages of pump therapy observed in our study were the lowered insulin dose and, although not documented by means of objective data, better quality of life. None of our patients wanted to change their form of therapy during the course of the study, and they generally report that they achieved a better quality of life with fewer injections and with more flexibility.

Increased risk of DKA, increased BMI, site infection, and technical problems are among the adverse events related to pump therapy.^{7,9,15,18,20} Studies reporting an increased risk of DKA in pump therapy are usually older ones, reported before 1993.³ The results of DCCT forced the clinicians to be more alert about preventive measures. Furthermore, much has changed in diabetes management during this time, including the use of insulin analogs as well as improved pump technology. The current literature reports fewer or similar DKA rates during pump treatment compared to other forms.^{3,18,23,24} Our study population had a similar frequency of DKA during pump treatment compared with the pre-pump period.

Although the DCCT study revealed that intensive insulin treatment was accompanied by excessive weight gain and a twofold increase in the prevalence of obesity,¹ BMI has been shown to increase in very few studies,^{9,18} but there are many others in which it remained similar^{5-8,15,17,21} or even decreased^{13,20} during pump therapy. Our study has demonstrated that the Z score for BMI remained steady up to two years after initiation of this form of treatment. Therefore, the expected BMI gain as a result of more flexible meal intake that pump therapy offered did not take place in our cohort, as was the case in most other studies.

Other adverse events in our study population related to pump therapy were sticking plaster allergy in one case and technical problems in the pump's software, which were not of clinical significance.

Our study may be considered to be limited by its non-randomised, uncontrolled design and its relatively small number of patients. Selection was not performed randomly, but this bias can be ignored because no differences involving diabetes management like the frequency of blood glucose monitoring or follow-up intervals (except for the first appointment) were involved. Although patients were carefully selected, the outcomes of pump therapy were compared with the pre-pump period using the data of the same cohort. One important is-

sue in pump therapy is the additional education sessions, but our cohort consisted of patients who were already aware of intensive diabetes management and the education sessions at the start of pump therapy involved only an overview of these concepts and specifically dealt with the technology of CSII.

In conclusion, although there were some inherent design weaknesses, the consistency of the improvement in outcome measures and their maintenance over time in our study suggest that pump therapy is a safe and effective mode of treatment in Turkish children with T1DM. Further prospective studies performed in larger cohorts are needed to confirm these preliminary data and to better define the ideal basal insulin supplementation for our children.

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