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ARTICLE

Feasibility and Safety of Insulin Pump Therapy in Children Aged 2 to 7 Years With Type 1 Diabetes: A Retrospective Study

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ABSTRACT

BACKGROUND AND OBJECTIVES. Although insulin pump therapy has been successful in adults, adolescents and school children, its use has been limited in young children. The purpose of this study was to evaluate the glycemic control, safety and efficacy of continuous subcutaneous insulin infusion via pump in young children (2–7 years old) with type 1 diabetes who were transitioned from twice-a-day insulin injection (neutral protamine Hagedorn/Lente + Humalog/Novalog) to insulin pump therapy. Hemoglobin A1c, BMI, average fasting blood glucose, episodes of severe hypoglycemia, episodes of diabetic ketoacidosis, episodes of lipohypertrophy, blood glucose variability, and number of sick day calls were compared before and after insulin pump therapy.

METHODS. Data were collected retrospectively by chart review over a 2-year period during quarterly diabetes clinic visits from 33 patients who were managed on neutral protamine Hagedorn/Lente + Humalog/Novolog twice-a-day injections for at least 1 year prior to transitioning to insulin pump therapy.

RESULTS. There was a significant improvement in the average hemoglobin A1c after continuous subcutaneous insulin infusion therapy. The average fasting blood sugar was lower in the continuous subcutaneous insulin infusion group. Severe episodes of hypoglycemia and episodes of lipohypertrophy were significantly higher before insulin pump therapy initiation. There were significantly fewer sick day calls after continuous subcutaneous insulin infusion. Blood sugar variability improved significantly after insulin pump therapy. There was no significant difference in BMI or amount of carbohydrate consumed. None of the patients experienced diabetic ketoacidosis requiring emergency treatment before or after insulin pump therapy.

CONCLUSIONS. Continous subcutaneous insulin infusion therapy in young children with type 1 diabetes is a safe, effective and superior alternative to a twice-a-day insulin regimen.

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Key Words
children, type 1 diabetes, insulin pump, hypoglycemia, hemoglobin A1c

Abbreviations
HbA1c— hemoglobin A1c
DCCT—Diabetes Control and Complications Trail
CSII— continuous subcutaneous insulin infusion
MDI—multiple daily injection
NPH—neutral protamine Hagedorn
TDD—total daily dose
DKA— diabetic ketoacidosis

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THE INCIDENCE OF type 1 diabetes in children is increasing significantly.[1–3] The rate of increase in type 1 diabetes has shifted by as much as two- to threefold toward the younger age group, specifically those in the range of 0 to 5 years.[4,5] The management of diabetes in preschool-aged children presents a unique set of problems to parents and health care providers.[6] Difficulty in achieving glycemic targets is the result of fluctuations in physical activity, marked sensitivity to insulin, very small insulin requirement, unpredictable eating habits, small but frequent meals, limited ability of children to communicate, frequent intercurrent infections, and increased family stress.[7,8]

Recurrent hypoglycemia is a barrier to achieving lower hemoglobin A1c (HbA1c) levels in this age group.[9] There is some evidence that hypoglycemia may predispose children younger than 6 years to neurocognitive developmental defects.[10,11] The fear of hypoglycemia has led health care providers to set higher target ranges in this age group.[12] On the other hand, chronic hyperglycemia may result in impaired intellectual function.[13] The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy reduces complications of diabetes in adults.[14] Vascular complications may start a few years after diagnosis, especially early nephropathy, retinopathy, and even impairment in neurocognitive development.[15] Thus, intensive insulin therapy in young children may reduce the development of chronic complications of diabetes in later life.

The goal of intensified insulin therapy could be achieved by either multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII). The disadvantage of MDIs is that at least 3 injections per day are needed, and intermediate- and long-acting insulins must be used as basal insulin.[19] These intermediate- and long-acting insulins (neutral protamine Hagedorn [NPH], Lente, Ultralente [Lilly, Indianapolis, IN]) have variable absorption (up to 50%) in the same patient, leading to variable blood-sugar excursions.[16] On the other hand, the short-acting insulins used in CSII have better pharmacokinetics, greater timing of foods and snacks, less activity-induced hypoglycemia, and less variability of absorption (<3%).[17]

Since its introduction in the late 1970s, use of CSII has dramatically increased due in part to the push for improved metabolic control in the post-DCCT era.[8,19] Although its use has increased dramatically in adults, adolescents, and school-aged children, it has not been fully extended to preschool-aged children, who may be the group who would benefit from it the most. The safety and efficacy of CSII in preschool-aged children has not been well studied. There are published reports that demonstrate that CSII is a safe and effective mode of insulin therapy in this age group.[18–21]

The purpose of this retrospective study was to assess the feasibility, efficacy, and safety of CSII in children <7 years old. We compared their HbA1c levels, body mass index (BMI), and frequency of severe hypoglycemia before and after CSII initiation. Although this is a retrospective observational study, we believe it will shed some light on the growing body of knowledge regarding the safety and efficacy of using CSII in toddlers and preschool-aged children.

METHODS

Thirty-three children (aged 2–6 years) were included in the study. All the children were cared for in DeVos Children's Hospital Diabetes Center (affiliated with Spectrum Health). Before the initiation of CSII,[22] patients were on the traditional (conventional) insulin regimen, with 2 daily injections of short-acting Novolog (Novonordisk, Bagsvaerd, Denmark)/Humalog (Lilly, Indianapolis, IN) insulin and intermediate-acting NPH/Lente insulin. The remaining 5 patients were treated similar to the rest of the patients, but their evening insulin injection was split into dinner Humalog/Novolog and bedtime NPH/Lente (3 injections per day). All patients were on the traditional treatment for at least 1 year before initiation of CSII. Patients were started on CSII at the discretion of their attending pediatric endocrinologist. There were no specific inclusion or exclusion criteria to start insulin pump therapy. For the purpose of this study, however, children >6 years old at the initiation of the insulin pump, patients who were still in their honeymoon phase (a partial remission phase when the insulin dose required to maintain excellent metabolic control is <0.5 U/kg body weight per day) either before or after initiation of insulin pump therapy, and those who were on MDIs were excluded from the study. Our diabetes educators provided extensive education on the principle of CSII to parents/guardians before initiation of insulin pump therapy. This included insulin adjustment and dietary strategies to calculate insulin bolus dosing and supplemental insulin for high blood glucose. All patients and caregivers used carbohydrate counting before initiation of CSII. Parents/guardians received additional nutrition and meal-planning recommendations and education on the application of carbohydrate counting to insulin pump therapy by a dietician based on established guidelines.[23] Height, weight, and BMI were assessed at each visit. Patients were evaluated every 3 months in our diabetes clinic. All patients contacted the diabetes team every week initially for 3 to 4 weeks and thereafter whenever they had difficulties. Parents or guardians were advised to fax blood-sugar levels every 3 to 5 days initially until reasonable blood-sugar levels were achieved. This study was approved by the institutional review board of Spectrum Health for the retrospective review of patients' clinic charts; therefore, no informed consent was required. Any details that might disclose the identity of the subjects were omitted.

Data were collected retrospectively 1 year before and

1 year after CSII initiation. At each clinic visit, blood-glucose records were reviewed, and HbA1c level, BMI, and lipohypertrophy were determined. Lipohypertrophy was assessed by the same physician-observer for each individual patient throughout the study period. Therefore, we did not try to assess interobserver variability. Blood-sugar variability was evaluated by determining the weekly blood-sugar range from weekly blood-sugar logs faxed to our diabetes clinic. A mean blood-sugar range was established for each patient for the duration of 1 year before the pump and 1 year after the initiation of insulin pump therapy. Hypoglycemic data were recorded at each visit for the preceding 3 months. Severe hypoglycemic episodes were defined as blood glucose below 50 mg/dL associated with uncontrolled shaking, inconsolable crying, disorientation, or unconsciousness with or without seizure. The frequency of severe hypoglycemia was estimated from parental reports recorded through telephone calls and at clinic visits. Moderate hypoglycemia was defined as a blood glucose level <60 mg/dL with or without behavioral involvement.[24] The frequency of moderate hypoglycemia was estimated retrospectively by review of the patients' charts and telephone logs. The HbA1c level was determined by using the Bayer DCA 2000+ (Bayer Diagnostics Inc, Tarrytown, NY) with a nondiabetic range of 4.5% to 6.5%.

Before initiation of CSII, patients were treated with short-acting insulin Humalog/Novolog and intermediate-acting insulin NPH/Lente (conventional therapy). After transitioning to CSII, patients were treated with either Humalog or Novolog. The total daily dose (TDD) of the insulin analog Humalog/Novolog/ + NPH/Lente regimen was used to calculate bolus and basal doses delivered by the insulin pump. The initial Humalog/Novolog insulin dosage for meals was calculated by dividing 500 by the TDD of insulin based on the rule of 500, which determines the amount of grams of carbohydrate per unit of insulin. Supplemental Humalog/Novolog insulin for high blood-sugar levels (correction or sensitivity factor) was calculated initially by dividing 1700 by the TDD of insulin based on the rule of 1700, which estimates the blood-sugar drop in mg/dL for every unit of Homolog or Novolog insulin taken to bring the blood sugar to a target range.[25] The initial insulin-dosage algorithm was individualized for most patients during the course of the therapy to accommodate variable insulin sensitivity. Patients were instructed to eat or drink 10 to 15 g of carbohydrates if the blood sugar was below the lower limit of the target range before administering insulin. The insulin-to-carbohydrate ratio was adjusted frequently on the basis of 2-hour postprandial blood-sugar patterns, whereas different basal rates were made on the basis of fasting blood-sugar levels.

Half of the TDD of insulin was given as a basal insulin. All insulin-dose changes were made initially through consultation with our diabetes clinic every 3 to 4 days for the first 2 weeks and every 2 weeks thereafter for the first 2 months by fax or telephone contact.

Before initiation of insulin pump therapy, all patients and families were instructed in the mechanics of pump use, and each patient wore a demonstrator pump with saline for 1 week. Because we are not aware of any significant difference between the pumps commonly used by our diabetic patients (mini Med [Medtronic, Northridge, CA], Animas [Animas Corp, West Chester, PA], and Cozmo [Smiths Medical MD Inc, St. Paul, MN]), the patients and the family chose the pump brand they preferred. Before insulin pump therapy with Humalog/Novolog was initiated, a 3-day saline trail was performed in all patients. Patients and families were instructed on the risks of pump use, including catheter-site infection, ketoacidosis, hyperglycemia, hypoglycemia, and potential mechanical problems that could interfere with insulin delivery.

The new TDD for the pump therapy was calculated at 80% of the TDD before insulin pump initiation. Fifty percent of the TDD was used for bolus dosing, and the remainder was used for basal rate. During the first 2 weeks of pump therapy, patients were instructed to perform frequent blood-sugar monitoring before each meal, 2 hours postprandial/bedtime, and 2 AM. Most patients were started on 1 to 2 basal rates, and correction doses were calculated for each patient on the basis of the 1700 rule.[25] All patients had daily telephone contact with a diabetes nurse educator for the first week, followed by fax or telephone contact for at least 2 months.

Differences among sample means were assessed by using analysis of variance. Baseline characteristics were compared with paired t test and χ^2 analyses. The rate of moderate and severe hypoglycemia and lipohypertrophy were analyzed by using a generalized-estimating-equation approach with Poisson regression. $P < .05$ was considered significant.

RESULTS

Table 1 summarizes the patients' general characteristics, age of onset, and duration of diabetes. The average age of onset of diabetes was 3.2 ± 1.4 years, with an average age of pump initiation of 4.6 ± 1.5 years. The average duration of diabetes after 1 year of insulin pump therapy was ~3.4 ± 1.2 years.

Table 2 summarizes the number of clinic visits, TDD of insulin, reported caloric intake, bolus insulin/basal insulin ratio, HbA1c level, frequency of hypoglycemia, blood-

TABLE 1 **Patient Demographics Before Initiation of CSII**

Characteristics	
No. of patients	33 (17 females,16 males)
Age of onset of diabetes, mean ± SD, y	3.2 ± 1.4
Age of pump start, mean ± SD, y	4.6 ± 1.5
Duration of diabetes, mean ± SD, y	3.4 ± 1.2

TABLE 2 **Clinical Characteristics of Patients Before and After 1 Year of CSII (Insulin Pump Therapy)**

Parameters	Before Pump Therapy	1 y After Pump Therapy	Statistical Significance, *P*
Clinic visits, mean ± SD, *n*/y	4.2 ± 0.4	3.9 ± .0.3	NS
TDD, mean ± SD, U/kg	0.74 ± 0.3	0.68 ± 0.25	NS
Bolus basal ratio, mean ± SD		1.34 ± 0.5	
Basal insulin, mean ± SD, U/kg		.3 ± 0.1	
HbA1c, mean ± SD, %	8.7 ± 0.6	8.0 ± 0.5	<.001
BMI, kg/m^2	18.2 ± 1.6	18.4 ± 1.7	NS
Frequency of moderate hypoglycemia, events/100 patient-years	28.6	15.2	<.04
Severe hypoglycemia, events/100 patients-year	17.8	0	<.001
Blood-sugar variability, mean ± SD, mg/dL (average blood-sugar ranges)	318 ± 50	220 ± 30	<.03
Average fasting blood sugar, mean ± SD, mg/dL	195 ± 41	155 ± 30	<.005
Average sick-day calls per year, events /100 patient-year	22.9	12.6	<.01
Episodes of DKA, events/100 patients-year	0	0	NS
Episodes of lipohypertrophy, events/100 patient-year	27.2	4.2	<.003
Average daily carbohydrate intake, mean ± SD, g	178 ± 15	197 ± 18	NS

NS indicates not significant.

sugar variability, average sick-day calls, degree of lipohypertrophy, average fasting blood-sugar levels, diabetic ketoacidosis (DKA), and change in BMI before and after insulin pump therapy. There was no significant difference between the number of clinic visits before and during pump therapy. The TDD of insulin was lower after the pump initiation but did not reach statistical significance. In addition, there was no significant difference in reported caloric intake before and after 1 year of pump therapy.

There was no significant difference in BMI before and after initiation of insulin pump therapy (18.2 ± 1.6 vs 18.4 ± 1.7 kg/m^2). There was a significant reduction in HbA1c level after 1 year of pump therapy compared with the baseline (before pump initiation) (8.0 ± 0.5% vs 8.7 ± 0.6%; $P < .001$). The greatest improvement in HbA1c level was seen 6 weeks after initiation of insulin pump therapy (7.6 ± 0.4%). Before initiation of pump therapy, 65% of the children had HbA1c levels >8.5%. After initiation of pump therapy, 76% of the patients had HbA1c levels <8.5%. After insulin pump therapy, ~40% of the patients demonstrated reduction of >0.8% in HbA1c levels.

The rate of severe hypoglycemia was significantly reduced in the insulin pump group (0 vs 17.8 events/100 patient-year; $P < .001$). There was no reported history of hypoglycemic seizures during the CSII therapy. There was also a decrease in the reported history of moderate hypoglycemia in the CSII group (15.2 vs 28.6 events/100 patient-years; $P < .04$). None of the patients in either group reported a hospital admission or physician visit for DKA either 1 year before starting pump therapy or during the CSII therapy. Once they were started on the CSII regimen, all of the patients wanted to remain on insulin pump therapy.

The average fasting blood glucose level was significantly lower in the CSII group (155 ± 30 vs 195 ± 41 mg/dL; $P < .005$), and there was less blood-sugar variability (swing) in the CSII group (220 ± 30 vs 318 ± 50 mg/dL; $P < .03$). There were fewer reported sick-day calls during insulin pump therapy than before pump initiation (22.9 vs 14.6 events/100 patient-year; $P < .004$). There were fewer episodes of lipohypertrophy during the CSII therapy (4.2 vs 27.2 events/100 patient-year; $P < .003$).

DISCUSSION

CSII pump therapy has gained momentum since the 1990s after an enormous technologic advancement in blood-sugar–testing devices and insulin pump systems.[26] There is a drive by clinicians to improve blood-glucose control to achieve better metabolic control. The DCCT demonstrated the value of improved blood-glucose control in reducing microvascular and macrovascular complications.[14] It is well established that adults, adolescents, and school-aged children have benefited from this great push toward intensive therapy.[26–29] However, the use of insulin pump therapy has been limited in preschool-aged children, presumably because of the fear of hypoglycemia and concerns that young children are too immature and may meddle with the insulin pump.[8,20]

Our study evaluated the safety and efficacy of insulin pump therapy in children aged 2 to 7 years with type 1 diabetes. There was a significant improvement in glycemic control, moderate and severe hypoglycemia, fasting blood-sugar levels, blood-sugar variability, and degree of lipohypertrophy. The main concern with the use of CSII therapy in patients with type 1 diabetes was the risk of severe hypoglycemia, especially in young children, which may result in impaired neurocognitive development.[11–13,30–32] Our results showed a reduction in the occurrence of moderate and severe hypoglycemia in CSII-treated patients compared with conventionally treated patients. There was no increase in the incidence of DKA in our CSII group, which is consistent with other studies.[18,20,33,34] The concern that young children are too

immature and would interfere with the pump system was not found in our CSII study group.

Although the DCCT and others have reported significant severe hypoglycemia and DKA in CSII in the early 1990s,[3] numerous recent studies have not demonstrated increased hypoglycemia or DKA during intensive insulin therapy with either MDIs or CSII.[18,19,24,27,35] Other studies have shown that CSII therapy was safe and effective in young children without increasing the risk of DKA and severe hypoglycemia.[20] The main reason that there is a decrease in the risk of severe hypoglycemia may be better pharmacokinetic delivery of insulin and reduced insulin requirement. Lower risk of DKA in CSII may be due to greater emphasis placed on DKA prevention, frequent blood-sugar testing, heightened patient vigilance (such as changing the insulin infusion set after 2 high blood-sugar readings), giving insulin injection subcutaneously if ketone bodies are present or if the blood-sugar level is >250 mg/dL on 2 consecutive readings, and huge advancement in CSII technology.[26]

Significant weight gain has been associated with intensive insulin therapy.[14,36,37] There may also be a general trend toward increase in overweight in type 1 diabetes similar to the general population.[38] Our patients did not experience any statistically significant change in BMI, which is consistent with other reports.[8,20,24,27] Fewer episodes of hypoglycemia with less insulin requirement may explain why our study group showed no significant change in their BMI after 1 year on insulin pump therapy.

Preschool-aged children are known to eat small, frequent meals or may graze throughout the day instead of eating distinct meals. These patients are also very sensitive to small amounts of insulin. The peak effect of long-acting insulin may fail to synchronize with food intake and may exacerbate the decrease in blood glucose that occurs during or after vigorous exercise. Insulin administered via CSII can be matched with carbohydrate intake, and basal insulin can be adjusted in response to changes in energy expenditure. CSII can be used to administer precisely a very small amount of insulin with less variability in insulin absorption. Transient elevation in blood glucose can be managed with small supplemental bolus injections without the fear of superimposing the bolus on a peak of a long-acting insulin action.[18]

CSII accurately provides the very small amount of insulin required in this age group and reduce blood-sugar excursions by providing a better match of carbohydrate intake to insulin by adjusting basal insulin at different times of the day. CSII minimizes the risk of all forms of hypoglycemia, improves glycemic control, improves quality of life, and enhances flexibility and coping with diabetes.[8,39] Our study and other recent observations[18,20,34,40] are consistent with the safety, feasibility, and effectiveness of CSII in young preschool-aged children. Although quality-of-life assessment was not analyzed in our study group, all of the patients who were on the insulin pump therapy preferred to stay with the insulin pump regimen 1 year after pump initiation rather than going back to their previous injection regimen, indirectly suggesting that they remained comfortable with the use of their insulin pump.

Our studies demonstrated that the CSII-therapy group had significantly less episodes of lipohypertrophy and blood-sugar variability. High insulin levels at an injection site can stimulate nearby subcutaneous tissue to grow and thicken, causing lipohypertrophy. This lipohypertrophy can slow insulin absorption and lead to erratic glycemic control,[41] especially with long- or intermediate-acting insulins. Because CSII therapy uses only a small amount of short-acting insulin, there may be a lower incidence of lipohypertrophy and thus may prevent erratic glycemic control.

Preschool-aged children with type 1 diabetes are at increased risk of neurodevelopmental impairment from hypoglycemia and hyperglycemia.[16,24,27,34] Complications of uncontrolled diabetes may be incipient in early childhood.[42] These observations, coupled with the need for improvement in glycemic control, makes insulin pump therapy a good option for diabetes care in this age group. With the advancement of pump technology, insulin delivery should become safer and more accurate. The impending development of alarm systems for high and low blood-sugar levels and sensor technology that could be added to the pump system will undoubtedly have a beneficial effect in the use of pump therapy in preschool-aged children. If caregivers are motivated to provide careful supervision, preschool-aged children can also benefit from insulin pump therapy and other technologic advancements in the care of diabetes. Thus, preschool-aged children receiving care from an actively involved diabetes team with a supportive family can experience improvement in diabetes control with current insulin pump therapy.

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