Safety and Effectiveness of Insulin Pump Therapy in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE — To evaluate the safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — All 95 patients who began insulin pump therapy at Johns Hopkins Hospital between January 1990 and December 2000 were included in the study. The mean age was 12.0 years (range 4–18), and 29% of the patients were <10 years old. Data were obtained by chart review beginning 6–12 months before pump start. The median duration of follow-up was 28 months.

RESULTS — There was a small but significant decrease in HbA_{1c} at 3–6 months after pump start (7.7 vs. 7.5%; $P = 0.03$). HbA_{1c} levels then gradually increased and remained elevated after 1 year of follow-up; however, this association was confounded by age and diabetes duration, both of which were associated with higher HbA_{1c} levels. After adjusting for duration and age, mean HbA_{1c} after pump start was significantly lower than before pump start (7.7 vs. 8.1%; $P < 0.001$). The number of medical complications (diabetic ketoacidosis, emergency department visits) was similar before and after pump start. There were fewer hypoglycemic events after pump start (12 vs. 17, rate ratio 0.46, 95% CI 0.21–1.01).

CONCLUSIONS — This study suggests that pump therapy is safe and effective in selected children and adolescents with type 1 diabetes.

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Continuous subcutaneous insulin infusion, or insulin pump therapy, has been used to treat diabetes since the late 1970s (1–3). Since the completion of the Diabetes Control and Complications Trial in 1993 (4) and the introduction of lispro insulin in 1996 (5), children and adolescents with diabetes, and their parents, have increasingly requested insulin pump therapy as an alternative to insulin injections. The Johns Hopkins Pediatric Diabetes Program has been using insulin pumps with children since the early 1980s (6).

The theoretical advantage of insulin pump therapy is its ability to mimic physiological insulin release and meet physiological insulin needs in people with insulin deficiency. The basal and bolus functions of the pump allow separate determination and adjustment of both these insulin requirements and also allow flexibility in timing and amounts of nutritional intake and physical activity, allowing for wide variations in lifestyle. In addition, use of short-acting insulin makes coverage of the early-morning glucose rise ("dawn phenomenon") possible, eases sick-day management, and matches nutrient absorption more physiologically, thereby reducing the risk of hypoglycemia.

Prior studies of pump users show a high degree of satisfaction (7–9,12–14), and most show a decreased risk of severe hypoglycemia (7–9,14). However, previous studies are mixed regarding safety and effectiveness. Some show a decrease in HbA_{1c} (7,8,12), whereas others show no durable improvement (9,10). Some report that HbA_{1c} improved in the first few months but returned to prepump status after 1 year (9,11). Some show an increased risk of diabetic ketoacidosis (DKA) and BMI (9–11). The inconsistency in the literature may be due in part to small sample sizes, short follow-up periods, and a failure to account for confounding factors.

Therefore, we reviewed data in our insulin pump population to evaluate safety and efficacy in children and adolescents and to identify predictors of metabolic control. We hypothesized that pump therapy would improve glycemic control without an increased risk of hypoglycemia or DKA.

RESEARCH DESIGN AND METHODS

Subjects

All patients who were followed in the Pediatric Diabetes program of the Johns Hopkins Hospital and started insulin pump therapy between 1 January 1990 and 31 December 2000 were included in this study. Medical records were reviewed for 95 patients, ages 4–18 years at pump start. The mean (± SD) age was 12.0 ± 3.1 years, and children under the age of 10 years comprised 29% of the group. There were 52 girls and 43 boys; 91 were Caucasian and 4 were African-American. Duration of diabetes at pump start was 5.6 ± 3.3 years. Frequency of blood glucose monitoring was 4.6 ± 1.7 times per day.

Patients and families chose insulin pump therapy for several reasons, in-

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Abbreviations: DKA, diabetic ketoacidosis; ED, emergency department; RR, rate ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

cluding better control, less blood glucose variability, fewer injections, and improvement in lifestyle flexibility. Before insulin pump therapy was started, all patients and families needed to demonstrate a desire and ability for intensive management with multiple daily injections, frequent blood glucose monitoring, satisfactory record-keeping details, ability to make appropriate insulin dose adjustments, and accurate carbohydrate counting.

Implementation of pump therapy

Before initiation of pump therapy, all patients and families were instructed in carbohydrate counting, including written assignments to document learning. They also were taught the mechanics of pump use and wore a demonstrator pump with saline for 2–5 days. Some parents also chose to wear a demonstrator pump, although this was not a requirement. Both Disetronic (St. Paul, MN) and MiniMed (Northridge, CA) insulin pumps were used. The patient and family chose the pump brand.

At the time of pump placement, all patients were admitted to the Johns Hopkins Hospital for 24–48 h. During the admission, in addition to frequent blood glucose monitoring (usually every 2 h, including preprandial, postprandial, and overnight levels), insulin doses were determined for basal rates, insulin-to-carbohydrate ratios at each meal, and correction boluses. These doses were adjusted and refined based on blood glucose responses. Nutrition evaluation and assessment were also done. Patients recorded all blood glucose levels, basal and bolus doses, and carbohydrate grams on pump recording sheets. Initially, all insulin used was buffered regular. The majority of patients used lispro insulin when it became available.

Risks of pump use and risk prevention were discussed in depth with all patients. This included site infections and the potential of increased risk of hyperglycemia, ketosis, and DKA. Hypoglycemia awareness, prevention, and treatment were also reviewed. Problem-solving strategies were discussed, such as potential mechanical problems (e.g., air bubbles, kinked infusion sets, and dislodged tubing) that could cause lack of expected insulin delivery. After the pump start, all patients had daily phone contact with the diabetes nurse educator for 3–7 days and then fax or phone contact (once or twice per week) for at least the next 1–2 months. The first follow-up appointment was within 2 months of the pump start and always included a nutrition evaluation. After the first follow-up appointment, visits took place at the usual clinic schedule every 3–4 months. These visits included medical, nurse educator, and nutrition evaluation and assessment. Glycemic goals were discussed at each clinic visit, and if not met, more intensive diabetes team involvement was recommended.

Data collection

All data were obtained by chart review by the advanced practice registered nurse (certified diabetes educator). Data were collected for a period of 6–12 months before initiation of the insulin pump and for as long as we followed each patient in our clinic and he or she remained on pump therapy, or until the end of the study observation period (31 December 2000). After graduation from high school, patients transitioned care to adult endocrinology. The study was approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Information was obtained at each visit (generally every 3 months) both before and after pump therapy was started. This information included height, weight, pubertal stage, HbA_{1c}, frequency of blood glucose monitoring, insulin doses, number of insulin injections per day (prepump), DKA, emergency department (ED) visits, hospitalizations, infusion site infections, and episodes of severe hypoglycemia (defined according to the Diabetes Control and Complications Trial protocol to include coma, seizures, or any other inability to self-treat) (4). In addition, we made a subjective assessment of parental availability to help with diabetes management. We assessed 41.5% of parents to be highly involved and 58.5% to be moderately involved.

Outcomes

HbA_{1c} was measured at each visit by cation-exchange high-performance liquid chromatography (Variant; Bio-Rad Laboratories, Hercules, CA), with a nondiabetic range of 4.5–6.1%. Frequency of blood glucose monitoring was obtained by review of blood glucose records (either written or by downloading their meters) or by patient report. Number of insulin injections per day before pump placement was determined from the number of prescribed injections and patient records and report. Insulin doses were determined by prescribed doses, patient records and report, and pump memory of bolus doses and 24-h totals. Height was measured using a Harpendon stadiometer and weight by hospital balance-beam scales. Height and weight percentiles were determined by National Center for Health Statistics growth curves (www.cdc.gov/growthcharts). Parental availability to help with diabetes management was classified as moderate or high based on the subjective assessment of the advanced practice registered nurse's experience with the family.

At each clinic visit, the number of severe hypoglycemia episodes, DKA episodes, ED visits, and hospitalizations that occurred since the prior clinic visit were recorded. DKA was defined as requiring intravenous fluids and insulin in the ED or during inpatient hospitalization. All ED visits and hospitalizations were counted, regardless of the reason. All self-reported site infections were included.

Statistical analyses

Incidence rates of complications were determined per 1,000 person-months of follow-up. All events were counted, including repeated events if they occurred. To account for effects of within-person correlation with repeated measures, we used clustered analysis for comparison of incidence rates before and after pump start and generalized estimating equations for all other comparisons, including linear trends between HbA_{1c} and diabetes duration and HbA_{1c} and age. To assess the independent impact of insulin pump use, all predetermined covariates were entered simultaneously into a multivariate model. All reported *P* values were two-sided. Analyses were conducted using STATA 7.0 (College Station, TX).

RESULTS — The population was composed primarily of Caucasians, with a mean age of 12 years. Slightly over half the population was female, and the mean duration of diabetes was 5.6 years. Table 1 shows the rate of complications by pump status. Pre- and postpump data and rate ratios (RRs) are shown for each complication and the overall complication rate. The number of hypoglycemic events was lower after pump start than before pump start (RR 0.46, 95% CI 0.21–1.01). There were 14.3 hypoglycemic events per

Table 1—*Number and rate of selected complications in 95 children and adolescents with type 1 diabetes by pump status*

	Total	Before pump start	After pump start	RR (95% CI)*
Person-months of follow-up	3,072	1,257	1,815	
Complication				
Hypoglycemia				
Number of events	30	18	12	
Rate per 1,000 (95% CI)	9.77 (6.62–15.02)	14.32 (9.37–23.06)	6.61 (3.01–17.41)	0.46 (0.21–1.01)
DKA				
Number of events	2	1	1	
Rate per 1,000 (95% CI)	0.65 (0.16–2.60)	0.80 (0.11–5.65)	0.55 (0.08–3.91)	0.69 (0.01–54.4)
Infection				
Number of events	8	0	8	
Rate per 1,000 (95% CI)	1.34 (0.51–3.59)		4.41 (1.53–18.74)	
ED visit†				
Number of events	41	17	24	
Rate per 1,000 (95% CI)	13.35 (9.51–19.25)	13.53 (9.00–21.34)	13.22 (8.28–22.45)	0.98 (0.50–1.94)
Any complication‡				
Number of events	65	29	36	
Rate per 1,000 (95% CI)	21.16 (16.43–27.70)	23.08 (16.90–32.40)	19.83 (13.56–30.24)	0.86 (0.51–1.45)

Rates shown as events per 1,000 person-months. Multiply by 12 for annual rates. *RRs postpump/prepump. Ratios <1.0 indicate lower risk compared with postpump. †ED visits comprised DKA ($n = 1$), site infections ($n = 4$), hypoglycemic events ($n = 11$), and other events ($n = 26$). ‡At 14 visits, a patient(s) reported two events during the preceding interval. At one visit, a patient reported three events during the preceding interval.

1,000 patient-months before pump start and 6.6 per 1,000 patient-months after pump start. There were few episodes ($n = 2$) of DKA (one before and one after pump start). There was no difference in ED visits before and after pump start (0.98, 0.50–1.94). There were eight superficial site infections during the entire period. All were treated with warm compresses and/or antibiotics. When all adverse events were combined, there was no difference in complications before versus after pump start (0.86, 0.51–1.45).

Figure 1 shows mean (SD) HbA_{1c} for each time interval from 12 months before pump start, through initiation of insulin pump, to >48 months after pump start. HbA_{1c} at pump start was significantly lower than HbA_{1c} 6–12 months earlier ($P < 0.05$). HbA_{1c} was significantly improved 3–6 months after pump start ($P = 0.03$). However, 6 months after pump start, there was a significant upward trend in HbA_{1c} ($P < 0.001$) .

To determine whether this upward trend in HbA_{1c} after pump start was a result of pump placement or a reflection of other underlying factors, we analyzed other associations with HbA_{1c}. HbA_{1c} was highly correlated with both duration of diabetes (Spearman's $r = 0.25$, $P < 0.0001$) and chronological age (Spearman's $r = 0.11$, $P = 0.001$). After adjusting for duration and age, HbA_{1c} was lower after pump start (7.7%) than before pump start (8.1%) (Fig. 2).

In additional analyses, we studied the association between HbA_{1c} and several potential determinants (Table 2). In a univariate analysis, age, duration of diabetes, parental involvement, and monitoring frequency (more than four times per day) were associated with HbA_{1c} levels. Pump use was not associated with HbA_{1c} in univariate analyses over the entire study period. However, when we included all variables in the model, pump use was associated with lower HbA_{1c} ($P < 0.001$). Other factors associated with lower HbA_{1c} in multivariate analysis included greater parental involvement, duration of

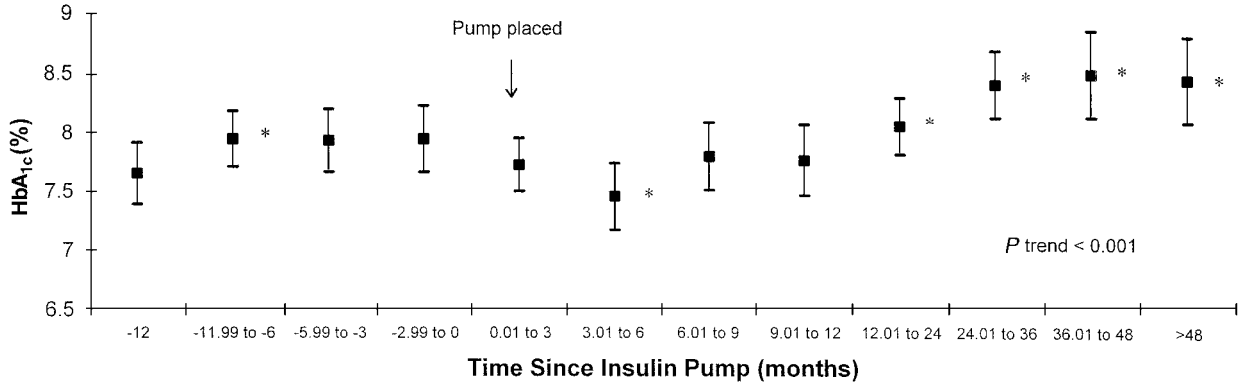

Figure 1—*Unadjusted mean (95% CI) HbA_{1c} in 95 children and adolescents with type 1 diabetes by time since insulin pump placement.* *P < 0.05 for t test compared with time of pump placement. Upward trend after pump placement was statistically significant (P < 0.01 for trend).*

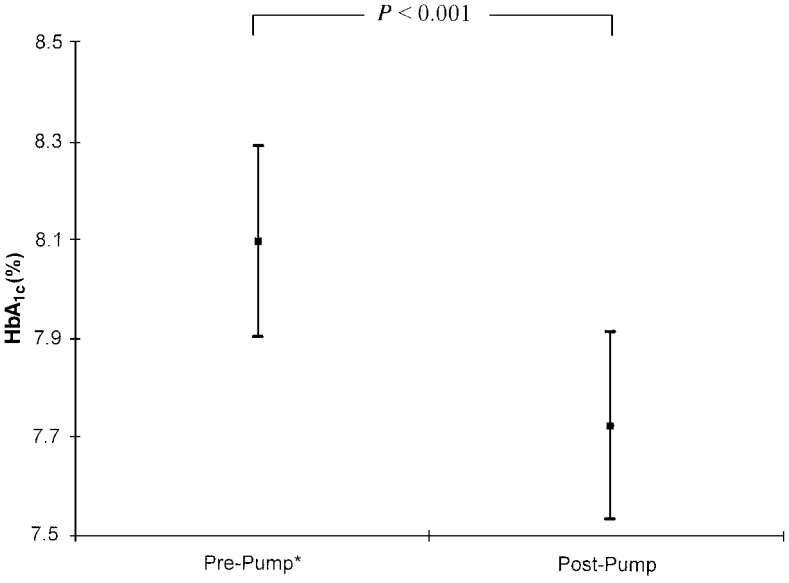

Figure 2—*Mean HbA_{1c} (95% CI) before and after insulin pump placement after adjusting for age and duration of diabetes.*

diabetes, and monitoring frequency. BMI was identical before and after pump start (mean ± SE = 20.3 ± 0.3 vs. 20.2 ± 0.3, $P = 0.23$, after adjusting for age and sex).

CONCLUSIONS — This study suggests that insulin pump therapy in children and adolescents is safe and effective. There were fewer episodes of severe hypoglycemia and no increase in DKA or ED visits with pump use. There was a small number of easily manageable site infections, none of which required surgical intervention. Although HbA_{1c} increased with time on the pump, this appeared to be attributable to increasing age and duration of diabetes. In other words, regardless of pump status, glycemic control tended to loosen as diabetes duration increased and as children moved into and through adolescence. After adjusting for age and duration of diabetes, HbA_{1c} levels were lower on the pump. We also found that monitoring more than four times per day and greater parental involvement were associated with lower HbA_{1c} levels.

Strengths of this study include data over a wide age range, with children as young as 4 years of age and 29% under 10 years of age at pump start. In addition, we had follow-up data for 3,072 person-months and as long as 6 years after pump start. Also, because of frequent follow-up with the same diabetes team, we had good data capture. Only two patients discontinued pump therapy.

Several limitations of our study deserve consideration. The patients who received the pump were highly selected. The majority of patients were very motivated and demonstrated knowledge of and willingness to do the work of diabetes care. However, our data compare well to other populations of patients using insulin pump therapy (7,14,15). It is likely that any patient receiving an insulin pump would undergo similar selection. Thus, although our population may not represent the general pediatric population with diabetes, it is likely similar to other patient populations who are using the insulin pump. Another limitation of this study was that our assessment of parental involvement was subjective. However, parental involvement has been shown to be an important factor in achieving lower HbA_{1c} levels (16).

Recent comprehensive reviews of insulin pump therapy (17,18) in both pediatric and adult populations show that blood glucose and HbA_{1c} levels are similar or slightly improved when pump therapy is compared with multiple injection regimens. Rates of DKA were similar and hypoglycemia was less frequent with pumps, as seen in our study. Our study adds the dimensions of age and duration as variables affecting HbA_{1c}.

This study has several implications. First, in our population, insulin pump use was safe and effective. The increase in HbA_{1c} with age and duration of diabetes may reflect the progression of diabetes and the reality of daily life with diabetes. After adjusting for these factors, HbA_{1c} was in fact lower after pump placement. Second, our results highlight the importance of modifiable behaviors in achieving optimal glycemic control. Consistent with prior findings, both monitoring frequency and parental involvement were significantly associated with lower HbA_{1c} levels (16). Thus, personal behaviors, not just the mode of insulin delivery, appear to be important and need to be consid-

Table 2—*Association of selected patient characteristics with HbA_{1c} level*

Characteristics	Unadjusted	Fully adjusted*
Male (vs. female)	0.13 (−0.23 to 0.50)	0.20 (−0.122 to 0.53)
Current age (per 1 year)	0.10 (0.06 to 0.13)†	0.03 (−0.12 to 0.53)
Parental involvement (high vs. moderate)	−0.61 (−0.95 to −0.27)†	−0.37 (−0.71 to −0.03)†
Duration of diabetes (per year)	0.11 (0.08 to 0.15)†	0.11 (0.06 to 0.16)†
Insulin pump (present vs. absent)	−0.07 (−0.19 to 0.05)	−0.31 (−0.47 to −0.15)†
Monitoring frequency ≥4 times per day (vs. <4 times per day)	−0.40 (−0.56 to −0.25)†	−0.27 (−0.44 to −0.11)†

Data are β coefficients (95% CI). *Adjusted for all variables in table. †$P < 0.05$.

ered when addressing management issues with families.

In summary, our findings suggest that insulin pump therapy is safe and effective in children and adolescents with type 1 diabetes. Moreover, these data suggest that greater parental involvement may augment the impact of the pump on HbA_{1c} levels. Clinical trials of insulin pump therapy in children with type 1 diabetes could help to clearly define the impact of insulin pump therapy on metabolic control, morbidity, and mortality.

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