OBJECTIVE — This study assesses the effects of insulin pump therapy on diabetes control and family life in children 1–6 years old with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Twenty-six children with type 1 diabetes for ≥6 months were randomly assigned to current therapy (two or three shots per day using NPH insulin and rapid-acting analog) or continuous subcutaneous insulin infusion (CSII) for 6 months. After 6 months, current therapy subjects were offered CSII. Changes in HbA1c, mean blood glucose (MBG), hypoglycemia frequency, diabetes-related quality of life (QOL), and parental adjustment were recorded.

RESULTS — Eleven subjects from each group completed the trial (age 46.3 ± 3.2 months [means ± SE]). At baseline, there were no differences between groups in HbA1c, MBG, age, sex, diabetes duration, or parental QOL. Mean HbA1c, MBG, and parental QOL were similar between groups at 6 months. Mean HbA1c and MBG did not change from baseline to 6 months in either group. The frequency of severe hypoglycemia, ketoacidosis, or hospitalization was similar between groups at any time period. Subjects on CSII had more fasting and predinner mild/moderate hypoglycemia at 1 and 6 months. Diabetes-related QOL improved in CSII fathers from baseline to 6 months. Psychological distress increased in current therapy mothers from baseline to 6 months. All subjects continued CSII after study completion.

CONCLUSIONS — CSII is safe and well tolerated in young children with diabetes and may have positive effects on QOL. CSII did not improve diabetes control when compared with injections, despite more mild/moderate hypoglycemia. The benefits and realistic expectations of CSII should be thoroughly examined before starting this therapy in very young children.

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The Diabetes Control and Complications Trial clearly demonstrated the benefits of good blood glucose control (1,2). However, achieving the necessary good control is not easy and is especially challenging in infants and toddlers with type 1 diabetes. Several factors contribute to the difficulty in managing diabetes in these young children, including unpredictable insulin absorption (3,4), variable eating patterns and activity, increased sensitivity to small amounts of insulin, parental fear of hypoglycemia (5,6), and difficulty in treating hypoglycemia because of their refusal to eat or drink. These problems can lead to widely fluctuating blood glucose levels or frequent hypoglycemia, which could have adverse developmental effects (7,8). Thus, a better way to provide insulin therapy to toddlers and young children with diabetes is desirable.

Insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) is an attractive way of treating patients with diabetes (9), but there are limited data comparing insulin injection therapy with CSII in toddlers and preschool-aged children with type 1 diabetes (10–12). Furthermore, although there is an extensive body of literature concerning the complex psychological factors and family management of diabetes (13,14), there are few data assessing these quality of life (QOL) issues in this young population. We therefore designed this study to determine whether the use of CSII in young children improves diabetes control, decreases the frequency of hypoglycemia, and improves the family’s QOL.

RESEARCH DESIGN AND METHODS — After institutional review board approval, children between the ages of 12 and 72 months with type 1 diabetes for at least 6 months were recruited for the study between January 2001 and September 2003. Parental informed consent was obtained, and enrolled subjects were randomly assigned to either continue their current insulin regimen (current therapy group) (consisting of two or three injections per day of NPH insulin and a rapid-acting analog) or receive CSII (using the Medtronic MiniMed 508; Medtronic, Northridge, CA). Insulin pumps and supplies were provided at no charge to all study participants for the duration of the trial. Families randomly assigned to CSII underwent proper pump education over the next 2–4 weeks before starting CSII.

Blood glucose levels were monitored at home at least four times per day in both treatment groups. Blood glucose records were analyzed to assess frequency of mild,
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Table 1—Baseline characteristics of the two treatment groups

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>Current therapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (enrolled/completed)</td>
<td>11/11</td>
<td>12/11</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>7/4</td>
<td>6/5</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>47.5 ± 4.8</td>
<td>45.3 ± 4.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>15.3 ± 3.4</td>
<td>19.7 ± 4.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Injections/day</td>
<td>2.5 ± 0.3</td>
<td>2.3 ± 0.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Total daily dose (units · kg⁻¹ · day⁻¹)</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.65</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>7.4 ± 0.5</td>
<td>7.6 ± 0.3</td>
<td>0.62</td>
</tr>
<tr>
<td>MBG (mg/dl)</td>
<td>175 ± 20</td>
<td>182 ± 8</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Data are means ± SE. Baseline data analyses do not include subjects who dropped out immediately after randomization (two CSII and one current therapy).

RESULTS — Thirteen children were randomly assigned to each group (Table 1). Two patients dropped out of the CSII group before starting pump therapy because the children refused to wear the pump. One subject dropped out of the current therapy group immediately after randomization because the family did not want to wait for pump therapy. One current therapy subject was lost to follow-up before the 6-month visit. Therefore, 11 subjects completed 6 months in each treatment group. Eight of the 11 subjects who completed current therapy also completed 6 months of pump therapy.

At baseline (Table 1), there were no differences between CSII and current therapy groups in HbA₁c, MBG, age, race, duration of diabetes, number of injections per day, total daily insulin dose, or socioeconomic status.

Mean HbA₁c values were similar between CSII and current therapy groups at baseline (7.43 ± 0.48 vs. 7.57 ± 0.27, CSII vs. current therapy), 3 months (7.20 ± 0.29 vs. 7.46 ± 0.22), and 6 months (7.24 ± 0.31 vs. 7.46 ± 0.18). Paired-sample t tests were used to compare maternal and paternal scores on all measures at baseline and at 6 months and to compare psychological functioning from baseline to 6 months in CSII and current therapy. P < 0.05 was considered significant.

Statistical analysis

Statistical evaluation was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL). Data are expressed as means ± SE. A 2 × 4 factorial ANOVA with repeated measures on one factor (two groups of subjects and four time periods of baseline, 1, 3, and 6 months) was used to test for differences in HbA₁c and MBG. Paired Student’s t tests were used to test for differences between baseline and 3- and 6-month HbA₁c. χ² analyses were used to compare the frequency of hypoglycemia between groups. Unpaired t tests were used for between-group analyses of other baseline characteristics. The psychological measures were analyzed using separate independent sample t tests to compare current therapy with CSII. ANOVA with baseline as a covariate was used to analyze the differences between the two groups at 6 months to control for differences in baseline values between the two groups.

Figure 1—HbA₁c (means ± SE) results for the 6-month study period in current therapy (CT) (– – –) and CSII (——) groups. Number of subjects are indicated for each group. Repeated-measures ANOVA revealed no significant differences for baseline, 3 months, and 6 months between groups (P = 0.537). There was no group effect (P = 0.592) nor time period effect (P = 0.935).
There was no group effect \((P = 0.59)\) or interaction effect for group and time period \((P = 0.94)\). There was no significant change in HbA1c in either group from baseline to 3 months \((P = 0.475\) for CSII; \(P = 0.509\) for current therapy) or 6 months \((P = 0.58\) for CSII; \(P = 0.60\) for current therapy). HbA1c did not change in the current therapy subjects after starting CSII \((P = 0.848\) comparing current therapy at 12 and 6 months).

MBG analysis (repeated-measures ANOVA) revealed no significant differences between time periods (baseline, 1 month, 3 months, and 6 months; \(P = 0.964\)) or between groups \((P = 0.308\)), nor was there a time period by group interaction \((P = 0.533)\). Comparison of MBG from the current therapy subjects after starting pump therapy with the CSII group revealed no significant differences for mean glucose by time \((P = 0.578)\), between groups \((P = 0.406)\), or for a time by group interaction \((P = 0.230)\). Comparison of MBG values in the current therapy group while receiving pump therapy with the current therapy group while receiving injections revealed no significant differences in MBG by time \((P = 0.135)\), by type of therapy \((P = 0.576)\), or for a time by therapy type interaction \((P = 0.682)\).

The frequency of mild/moderate hypoglycemia (defined as blood glucose <80 for this age-group) was similar at baseline between the two treatment groups before meals and at bedtime (Fig. 1). However, CSII subjects experienced more hypoglycemia before breakfast at 1 month but not afterward and more hypoglycemia before dinner at 3 months and 6 months (Fig. 2). These differences were present at 1 month even if mild/moderate hypoglycemia was defined as blood glucose level <70, <60, or <50. As shown in Fig. 2, CSII subjects also experienced more frequent mild/moderate hypoglycemia at breakfast at 6 months if low blood glucose was defined as <70 or <60. Furthermore, after adjusting for multiple comparisons with a significance level set at \(P < 0.004\), the amount of hypoglycemia was still significantly more in the CSII group at these time periods \((P < 0.001)\).

There were no differences between current therapy and CSII groups at any time period throughout the study when hypoglycemia was defined as blood glucose level <40.

We also compared the frequency of hypoglycemia in current therapy subjects after starting pump therapy (6–12 months) with when they were receiving injections (0–6 months). Subjects had more frequent mild/moderate hypoglycemia while receiving pump therapy than with injections at breakfast, whether the definition of hypoglycemia was defined as blood glucose level <80 (number of recorded episodes = 50 CSII vs. 16 current therapy; \(P < 0.01\)), <70 (36 vs. 11; \(P < 0.01\)), <60 (24 vs. 3; \(P = 0.001\)), or <50 (7 vs. 0; \(P < 0.03\)). There were no differences between current therapy subjects receiving injections versus pump therapy at any time period throughout the study when hypoglycemia was defined as blood glucose level <40.

One current therapy patient had a severely low blood glucose level within 1 month after randomization. There were no severe hypoglycemic events for patients enrolled in the CSII group, although one patient initially enrolled in the current therapy group had two severe low blood glucose readings after starting pump therapy. One subject in the CSII group was admitted for diabetic ketoacidosis ~2 months after starting pump therapy. One current therapy subject had three hospitalizations for diabetic ketoacidosis within 2 months after starting pump therapy because of a failure to follow sick-day management protocol while using the pump.

Mothers in the current therapy group reported a greater impact of diabetes on the family than did mothers in the CSII group at baseline \((P = 0.04)\), but there were no differences between the mothers in the two groups at 6 months when controlling for the baseline differences. Fathers in the CT group reported more psychological distress than did fathers in the CSII group at baseline \((P = 0.05)\), but there were no significant differences between the two groups at 6 months when correcting for these baseline differences.
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There were no differences between groups for mothers or fathers on the Pediatric Diabetes QOL scale at any time period. However, fathers in the CSII group reported significantly more positive QOL changes for themselves from baseline to 6 months ($P = 0.03$). Mothers in the CT group reported more parenting stress than did mothers in the CSII group at baseline ($P = 0.05$). The differences in maternal parenting stress did not remain significant at 6 months. No differences were found between mothers and fathers for any of the psychological measures at baseline or 6 months.

There were no significant problems with the placement and care of infusion sites in these young children, and no subjects experienced site infections. All subjects who completed 6 months of current therapy ($n = 11$) began CSII after the 6-month study period, including two who started CSII outside of the study. All subjects treated with CSII have continued this therapy after study completion.

**CONCLUSIONS** — Our data indicate that CSII is safe and well tolerated in this population, consistent with three recent reports in this age-group (10–12). In our study, however, CSII did not result in improved diabetes control when compared with insulin injections, similar to the study by DiMeglio et al. (11) and the more recent paper by Wilson et al. (12) but in contrast to two other studies (10,18). In the study by Litton et al. (10) comparing CSII with multiple daily injections in toddlers between 20 and 58 months of age, HbA$_1c$ levels decreased after using CSII for an average of 13 months. There are several reasons for the difference in results; one is difference in study design. Their study was not a randomized trial; each patient served as his or her own control, and it included only nine subjects. A second potential reason is difference in patient selection. It is possible that insulin pump therapy did not lower the average HbA$_1c$ in our subjects because it was already low at baseline ($7.5 \pm 0.3$% for all subjects); the subjects reported by Litton et al. (10) had a higher HbA$_1c$ at baseline ($9.5 \pm 0.4$%). Safely lowering an already low HbA$_1c$ may not be better achieved with insulin pump therapy and may certainly be accompanied by increased hypoglycemia. The low HbA$_1c$ in our subjects indicates that some of them may have been in the remission phase, also suggested by the low total insulin daily dose ($0.6 \pm 0.1$ units $\cdot$ kg$^{-1}$ $\cdot$ day$^{-1}$ in both groups) at the start of the study. Lastly, although we studied more subjects than those reported by Litton et al. (10), using the effect size of our population, 40–60 subjects per group would have been needed to demonstrate a significance difference in HbA$_1c$ or MBG. This population size would be best evaluated in a large, multicenter trial.

In another recent study (18), children with type 1 diabetes using insulin pumps were compared with children receiving multiple daily injections (using insulin glargine and insulin aspart), a more intensive regimen than that used in our subjects receiving injections. In that randomized trial, patients receiving CSII had significantly lower HbA$_1c$ levels at 16 weeks compared with multiple daily injections. However, subjects were older (>8 years) than in our study, and the duration of CSII therapy was shorter, making direct comparisons difficult.

Fear of hypoglycemia is often a deterrent to good diabetes control (5,6). Our data do not indicate that the frequency of severe hypoglycemia is affected when using CSII, similar to the results reported by Maniatis et al. (19) and more recently by Wilson et al. (12). However, CSII subjects in our study experienced more mild/moderate hypoglycemia at certain time periods (most often fasting or before dinner) than subjects receiving injections; that difference persisted even when a lower definition of hypoglycemia was used. It is interesting to note that even though subjects receiving CSII in our study had more frequent fasting hypoglycemia, they did not have frequent hypoglycemia at bedtime. This suggests that CSII may predispose subjects to late-night or early-morning hypoglycemia.

The frequency of hypoglycemia seen in pump subjects is highly variable in published reports. Litton et al. (10) had results similar to ours (i.e., an increase in mild/moderate hypoglycemia with the use of pumps), whereas two other studies (19,20) showed that the frequency of hypoglycemia decreased with the use of CSII in children and adolescents. Our results may reflect the tighter diabetes control as reflected in the lower HbA$_1c$ levels in our subjects, indicating that they are more likely to have hypoglycemia. Although the number of children in our study was relatively small, other investigators have studied a comparable number of children, or even less as in the report by Litton et al. (10). Additionally, only one other study (18) analyzed the data with respect to time of day. Nonetheless, although care should still be taken when interpreting these data, our results are important as they demonstrate that CSII is at least as good as insulin injection therapy in toddlers and preschoolers, and our experimental design using a randomized control arm makes our observations strong. A large-scale randomized trial would best be suited to further assess whether mild/moderate hypoglycemia is more likely with pump therapy in toddlers.

As with injection therapy, the family must adjust to a variety of new tasks with CSII, which can have a psychosocial impact. Wilson et al. (12) reported that diabetes QOL slightly improved in those receiving either treatment (injections or pumps), although only the improvement in the CSII group was significant. They found no difference between the two treatment groups. Our findings are congruent with this report and suggest that CSII does not adversely affect diabetes-related QOL and parental stress/distress when compared with current therapy. On the contrary, fathers in the CSII group reported improved diabetes-related QOL from baseline to 6 months, even though comparisons of those changes over time in the current therapy and CSII groups were not significant. Mothers and fathers reported similar levels of distress and impact on QOL, suggesting that for these families CSII and current therapy did not have differential effects within the family. Caution should be taken when interpreting these analyses given the large number of statistical tests that were performed relative to the small sample size. Lastly, the fact that all subjects continued CSII after study completion is itself an excellent indicator of parent satisfaction. Other studies had also suggested high levels of parental satisfaction with CSII (10,11), although QOL issues were not formally tested in young children in those studies.

This randomized controlled trial showed that CSII is safe and well tolerated in toddlers and young children with diabetes and is as good as current therapy with two or three daily insulin injections in maintaining good diabetes control.
However, CSII did not result in improved diabetes control when compared with injection therapy in that age-group, despite a trend toward increased frequency of mild/moderate hypoglycemia with CSII use. CSII may have some positive effects on QOL. The possible benefits and realistic expectations for diabetes control of CSII need to be thoroughly examined and reviewed with the family before starting this form of therapy in young children. Even though pump therapy may increase the costs associated with diabetes management, other potential benefits must be taken into account when considering this regimen in young children. A description of CSII to parents of children with type 1 diabetes in this age-group must emphasize that this pump therapy may not necessarily improve diabetes control, although it may provide a more precise tool for insulin therapy, avoiding frequent injections in very young children.

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References