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# Comparison of Continuous Subcutaneous Insulin Infusion and Multiple Daily Injection Regimens in Children With Type 1 Diabetes: A Randomized Open Crossover Trial

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**ABSTRACT.** *Objective.* To compare the efficacy and feasibility of continuous subcutaneous insulin infusion (CSII) with multiple daily insulin injections (MDI) in children with type 1 diabetes.

*Methods.* The study sample included 23 children (10 males) aged 9.4 to 13.9 years with type 1 diabetes. An open randomized crossover design was used to compare 3.5 months of CSII to 3.5 months of MDI therapy for the following variables: diabetic control, incidence of adverse events, daily insulin requirement, body mass index standard deviation scores, treatment satisfaction, and quality of life.

*Results.* The changes in HbA<sub>1c</sub> and fructoseamine values were similar in the 2 arms over time. At the end of the study, mean HbA<sub>1c</sub> level measured  $8.05 \pm 0.78\%$ . There were no differences between the treatment modes in frequency of symptomatic hypoglycemic or hyperglycemic events. There was 1 event of severe hypoglycemia during pump therapy and 3 during MDI, yielding a rate of 0.26 events per patient-year. There were no episodes of diabetic ketoacidosis. Body mass index standard deviation scores decreased during CSII and increased during MDI, as did mean insulin dose. Patients expressed a higher treatment satisfaction from CSII than MDI, although there was no difference in quality of life between the 2 modes.

*Conclusions.* Intensive insulin therapy by either insulin pump or MDI is safe in children and young adolescents with type 1 diabetes, with similar diabetes control and a very low rate of adverse events. We suggest that both modes be available to the diabetic team to better tailor therapy. *Pediatrics* 2003;112:559–564; *pump, continuous subcutaneous insulin infusion, multiple daily insulin injections, type 1 diabetes, intensive therapy, children.*

ABBREVIATIONS. DCCT, Diabetes Control and Complication Trial; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injection; SBGM, self-blood glucose monitoring; NPH, neutral protamine hagedorn; DKA, diabetic ketoacidosis; BMI, body mass index; SDS, standard deviation score; DTSQ,

Diabetes Treatment Satisfaction Questionnaire; DQOLY, Diabetes Quality of Life Questionnaire for Youth.

The Diabetes Control and Complication Trial (DCCT)<sup>1</sup> demonstrated that in patients with type 1 diabetes, tight metabolic control achieved with intensive insulin therapy is superior to conventional treatment in reducing the risk of long-term microvascular complications. Evidence is accumulating that the prepubertal and pubertal years have an impact on microvascular complications in diabetes.<sup>2,3</sup> Therefore, tight metabolic control may be an important determinant during these years. However, young patients, especially adolescents, may find it difficult to comply with regular insulin injections, frequent blood glucose monitoring, and regular meals.<sup>4</sup> Indeed, the adolescent group in the DCCT had higher HbA<sub>1c</sub> levels than the adults, and a higher rate of severe hypoglycemic events.<sup>5</sup> Episodes of severe hypoglycemia carry a low risk of mortality, neurologic morbidity, and permanent cognitive dysfunction; they also exaggerate the fear of hypoglycemia with a consequent deterioration in metabolic control.<sup>6</sup> At the same time, strict metabolic control is itself associated with an increased risk of severe hypoglycemic episodes<sup>1,5</sup> and significant weight gain<sup>1,5,7</sup>—both limitations with particular significance in children and adolescents who tend to have erratic eating behaviors<sup>5,8</sup> and worry about their body image.<sup>9</sup> Therefore, there is a clear need for an intensive insulin regimen that will appeal to these age groups and enable strict metabolic control without the increased risk of severe hypoglycemic events.

Several studies have suggested that intensive therapy with continuous subcutaneous insulin infusion (CSII) could provide better glycemetic control,<sup>7,10–12</sup> with a lower risk of severe hypoglycemia and a lesser weight gain<sup>7</sup> than multiple daily insulin injections (MDIs). However, only a few of these studies were randomized,<sup>11,12</sup> and most were done in adults. The present study was prompted by the scarcity of randomized crossover studies comparing the 2 modes of therapy in children with type 1 diabetes. We evaluated CSII and MDI for glycemetic control, incidence of hypoglycemia and hyperglycemia, dose requirements, weight gain, quality of life, and satisfaction.

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## METHODS

The study protocol was approved by the Ethics Committee of Rabin Medical Center, and all the patients and their parents gave written informed consent.

### Patients

All patients were followed at the National Institute for Childhood Diabetes of Schneider Children's Medical Center of Israel, which serves 1200 children and youth with type 1 diabetes. Inclusion criteria were as follows: type 1 diabetes treated by insulin for at least 2 years; aged 8 to 14 years; deficient C-peptide secretion (fasting level <200 pmol/L); and ability to cope, together with the parents, with the treatment procedures, as judged by the diabetic team. Participation in the study was offered on a consecutive basis; of the 258 patients aged 9 to 14 years in our institute who were eligible for the study, the first 24 who expressed a desire to be included were enrolled. One girl was excluded because of endogenous insulin secretions (fasting C-peptide 370 pmol/L). The mean duration of diabetes in the study group was 2.8 to 11.9 years (median 5.5), and mean prestudy HbA<sub>1c</sub>, 8.9 ± 1.0%. At enrollment, all the children were being treated with multiple (≥3) daily injections of either Insulatard and Actrapid (NovoNordisk, Bagsvaerd, Denmark) or Humulin N and Humulin R (Eli Lilly, Indianapolis, IN). They performed self-blood glucose monitoring (SBGM) 1 to 4 times per day using home glucose meters, and visited the clinic every 2 to 3 months. None of the patients had used CSII before the study. None had clinical evidence of microvascular complications, hypoglycemia unawareness, concomitant disorders, mental retardation, or a psychiatric disorder, and none had participated in another study in the past 3 months.

### Study Design and Protocol

A randomized crossover design was used. The MDI protocol consisted of combined neutral protamine hagedorn (NPH) and regular insulin before breakfast, regular insulin before lunch and supper, and NPH at bedtime; CSII was delivered with a programmable external pump (MiniMed 508; MiniMed, Sylmar, CA) using lispro (Humalog; Eli Lilly). The regular insulin was given 20 to 30 minutes before meals, and the lispro, immediately before meals. The 23 children were randomly assigned to start with either CSII (group A) or MDI with their prestudy insulin (group B) for 3.5 months, after which they were switched to the other mode of therapy for another 3.5 months, with a 2-week washout period (Fig 1).

Three months before onset of the study, an educational session was conducted with the children and their families to motivate them to practice strict SBGM and insulin dose adjustment to prevent diabetic ketoacidosis (DKA) during pump therapy. The patients were taught carbohydrate counting and insulin bolus dosing based on the insulin-to-carbohydrate ratio, using 1 U insulin per 10 to 20 g carbohydrate. According to the post-meal SBGM and food diary, additional insulin was added to the regimen, to cover for proteins and lipids, as necessary. The children were asked to perform SBGM 7 times per day (before meals, after meals, and weekly at 3 AM). The target range for glycemia was 4.4 to 8.3 mmol/L before meals and at midnight, and 6.6 to 10 mmol/L at 2 hours after meals.<sup>13</sup>

The insulin dosage was determined by decreasing the average total insulin dosage per day over the preceding 2 weeks by 20%; 50% was given as a basal rate, and 50% as premeal boluses. In both regimens, blood glucose levels above 8.3 mmol/L were corrected with additional insulin given before meals and snacks, using 1 U for every 2.8 to 5.5 mmol/L above 8.3 mmol/L. During pump therapy, the participants were asked to change the infusion site

every 3 days and also under the following conditions: when blood glucose was >16.6 mmol/L with positive urinary ketones or when blood glucose was >16.6 mmol/L and failed to respond to corrective insulin dose, and at any sign of insertion site infection.

At onset of the study, visits were scheduled at 2 weeks, 2 days (CSII arm only), 1 and 3 weeks, and then twice every 5 to 6 weeks (Fig 1). The patients and their parents were asked to record all adverse events in a daily diary. Hypoglycemia was defined as symptoms relieved by the ingestion of glucose or food and/or a capillary blood glucose level of <3.8 mmol/L. Severe hypoglycemia was defined as any hypoglycemic event requiring assistance from another person or resulting in seizure or coma. Hyperglycemia was defined as symptoms of polyuria, polydipsia, or nocturia and/or a capillary blood glucose level of >22.2 mmol/L with or without urinary ketones. DKA was defined as a ketotic event requiring hospital admission with venous blood pH of <7.30.

At each office visit, weight and height were measured by a wall-mounted stadiometer, injection or cannula insertion sites were checked, the diary was reviewed, and insulin dose adjustments were made. Weight and height measurements were used to calculate body mass index (BMI) in kilograms per squared meter; the BMI standard deviation score (SDS) was calculated as previously described.<sup>14</sup>

Patients and families were instructed and followed by the same physician, diabetic educational nurse, and dietitian. As part of the routine clinic procedure, the team was available 24 hours a day for patient calls and faxes.

Capillary HbA<sub>1c</sub> levels were determined 3 months before the study (at the educational session), at onset of the study, and in the middle and at the end of each study arm. We used a DCA 2000 analyzer (Bayer Diagnostics, Tarrytown, NY) with a nondiabetic range of 4.3% to 6.3%. The DCA 2000 analyzer standards were run 6 times annually and were always in the accepted ranges. The correlation between the capillary method and our laboratory (turbidimetric inhibition immunoassay using the Hitachi 911 [normal range: 4.3%–5.8%]) was 0.93 (*P* < .001). Fructoseamine levels were measured with the colorimetric assay using the Hitachi 917 (Roche Diagnostics, Mannheim, Germany [normal range: 205–285 μmol/L]).

All patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ)<sup>15</sup> and the Diabetes Quality of Life Questionnaire for Youth (DQOLY),<sup>16</sup> at the beginning of the study and at the end of each treatment arm.

### Statistical Analysis

The data were analyzed with the BMDP program.<sup>17</sup> Data are presented as mean ± standard deviation or median (range), as appropriate. Analysis of variance was used to compare baseline variables between the 2 randomized groups, and analysis of variance with repeated measures was applied to compare the changes in the variables over time between the 2 study arms. Discrete variables were compared with McNemar's test for matched pairs. All reported results are 2-tailed; significance level was set at *P* = .05.

## RESULTS

All 23 children who started the study completed the 2 study arms. The clinical data on entry to the study are shown in Table 1; there were no significant differences between the 2 groups. Seven children were prepubertal, 13 were in Tanner stages 2 to 4 and 3 were fully pubertal. Comparison of the parameters between the 2 modes is shown in Table 2.

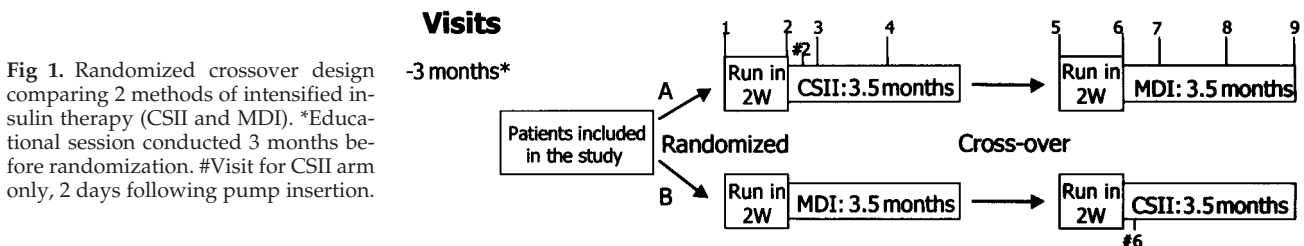


Fig 1. Randomized crossover design comparing 2 methods of intensified insulin therapy (CSII and MDI). \*Educational session conducted 3 months before randomization. #Visit for CSII arm only, 2 days following pump insertion.

**TABLE 1.** Baseline Characteristics of the Children by Randomization Group

Variable	Group A (Started With CSII)	Group B (Started With MDI)	Total
N (female)	11 (7)	12 (6)	23 (13)
Age (y)	11.9 ± 1.4	11.6 ± 1.5	11.8 ± 1.4
Duration (y)	5.3 ± 1.9	6.3 ± 2.6	5.8 ± 2.3
BMI SDS*	0.3 ± 1.0	0.3 ± 0.4	0.3 ± 0.8
HbA <sub>1c</sub>			
3 mo	8.6 ± 0.8	9.2 ± 1.0	8.9 ± 1.0
At randomization	7.9 ± 1.3	8.6 ± 0.8	8.3 ± 1.1‡
Daily insulin dose (μ/kg)	0.93 ± 0.22	0.97 ± 0.22	0.95 ± 0.22

Data are presented as mean ± standard deviation unless otherwise indicated.

No significant difference was noted for any of the variables between the 2 groups.

\* BMI SDS calculated according to the 2000 growth charts of the Center for Disease Control, National Center for Health Statistics, USA.<sup>14</sup>

‡ *P* = .003 for HbA<sub>1c</sub> at randomization versus 3 months before.

**TABLE 2.** Glycemic Control, Insulin Dose, BMI SDS, and Adverse Events by Study Regimen

Variable	CSII	MDI	<i>P</i>
HbA <sub>1c</sub> (%)			
Start	8.0 ± 1.1	8.3 ± 0.7	
Middle	7.9 ± 0.7	8.2 ± 0.8	
End	8.0 ± 0.7	8.1 ± 0.8	.03*
Increment	0.03 ± 1.0	-0.23 ± 1.0	NS
Fructoseamine (nmol/L)			
Start	360 ± 64	368 ± 56	
Middle	354 ± 45	358 ± 57	
End	362 ± 43	354 ± 56	NS
Daily insulin dose (μ/kg)			
Start	0.93 ± 0.22	0.97 ± 0.22	
End	0.84 ± 0.16	1.09 ± 0.21	.003
BMI SDS			
Start	0.40 ± 0.79	0.29 ± 0.81	
End	0.35 ± 0.83	0.37 ± 0.85	.012
Hypoglycemic events‡			
Mild	19.8 ± 12.1	22.0 ± 13.2	NS
Severe§	1	3	NS
Rate per patient-year (95% CI)	0.13 (0.0–0.4)	0.39 (0.0–0.84)	NS
Hyperglycemic events‡			
Ketouria‡	7.9 ± 7	6.7 ± 7.3	NS
DKA	1.6 ± 1.5	0.4 ± 0.8	.003
DKA	0	0	

NS indicates not significant.

Data are presented as mean ± standard deviation, unless otherwise indicated.

\* On repeated measures.

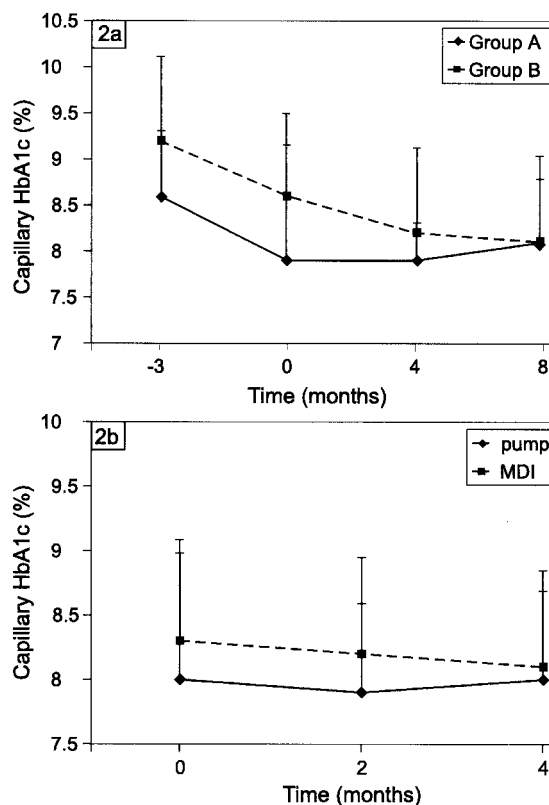
‡ Mean events/patient/arm.

§ Total number of events of severe hypoglycemia.

|| Of severe hypoglycemic events.

### Glycemic Control

The capillary HbA<sub>1c</sub> levels at the start of the study were significantly lower than the levels measured 3 months before the study, at the first educational session (8.9 ± 1.0% vs 8.3 ± 1.1%, *P* = .003). This reduction was maintained throughout the study in both groups, and the difference in levels between 3 months before the study and at the end of the study was statistically significant (8.9 ± 1.0% vs 8.0 ± 0.8%, *P* < .001). The values for each group separately are shown in Fig 2A. HbA<sub>1c</sub> values were lower during CSII than MDI on repeated measures (*P* = .03; Table 2), secondary to the differences at the start of the



**Fig 2.** A, Glycemic control over time for the whole study sample, by group. Group A started with CSII and group B with MDI. \*Educational session conducted 3 months before randomization. For the whole study group, *P* = .003 for HbA<sub>1c</sub> at randomization versus 3 months before and *P* < .001 for HbA<sub>1c</sub> at the end of the study versus 3 months before. Analysis of variance with repeated measures by group showed no significant difference between groups A and B (*P* = .13), a highly significant change in mean HbA<sub>1c</sub> levels overtime (*P* < .001) and no significant interaction between group and the change in HbA<sub>1c</sub> overtime. B, Glycemic control with CSII versus MDI (mean ± standard deviation).

treatment arm. However, there was no significant interaction of the study arms and the change in HbA<sub>1c</sub> levels over time (Fig 2B). Fructoseamine levels were similar throughout the study.

### Insulin Dose and BMI

The total daily insulin dose (units/kg/d) was similar for the 2 regimens at initiation of the study. There was a significant interaction between the therapy regimen and the change in insulin dose over time, decreasing during pump therapy and increasing during MDI (*P* = .003). Baseline BMI SDS was also similar at study onset, but it decreased during CSII and increased during MDI (*P* = .012). At baseline, and to the end of the study, 1 boy and 1 girl (8.7% of the study population) were overweight, defined as BMI >2 standard deviations for age.<sup>14</sup> Both had familial obesity.

### Adverse Events

The frequency of mild diurnal and nocturnal hypoglycemic and hyperglycemic episodes reported by the patients was similar in the 2 study arms, although the number of ketotic events per patient was higher during CSII than MDI (*P* = .003). There were

no cases of DKA; all ketotic episodes that were secondary to infusion set problems were treated at home. There was 1 event of severe nocturnal hypoglycemia without coma during CSII and 3 (2 nocturnal) during MDI, yielding an overall rate of 0.26 events per patient-year (95% CI: 0.01–0.51). During pump therapy, there were 12 minor infusion-set site infections (treated by local antibiotic cream), 16 blockages, and 42 dislodgements. There were 3 hospital admissions for intercurrent infection, 2 during pump therapy and 1 during MDI therapy.

#### Treatment Satisfaction and Quality of Life

There was a significant difference between treatment groups in treatment satisfaction, expressed by the DTSQ total score. The total score, which can range from 6 to 36, was  $21.4 \pm 3.3$  at the beginning of the study,  $21.9 \pm 3.8$  at the end of the MDI arm, and  $30.6 \pm 3.7$  at the end of the CSII arm ( $P < .001$ ). There was no statistically significant difference between treatment groups for any of the DQOLY subscales, using either a univariate model with treatment group included or a multivariate model that included sex as a covariate. (satisfaction scale:  $71.9 \pm 14.5$  at the beginning of the study,  $73.5 \pm 14.0$  at the end of the MDI arm, and  $74.8 \pm 13.5$  at the end of the CSII arm; impact scale:  $68.8 \pm 10.6$ ,  $73.5 \pm 9.7$ ,  $73.2 \pm 9.6$ ; worry scale:  $77.0 \pm 13.5$ ,  $79.8 \pm 12.8$ ,  $81.6 \pm 12.4$ ).

At termination of the study, the patients were asked which regimen they preferred for continuation of therapy. Sixteen (6 males) of the 23 children chose CSII because it provided them greater flexibility with meal times, avoided the pain of injections, and conferred a sense of smoother blood glucose profiles and/or better glycemic control. Among the 7 children (4 males) who preferred to continue with MDI therapy, 5 had started with CSII and then switched to MDI. Their reasons for unwillingness to resume CSII therapy were as follows: deteriorating glycemic control and fear of overeating and weight gain in 2 boys; scars at infusion-set site in 1 girl; fear of infusion-set insertion in 1 girl; desire to keep the diabetes a secret and shame at wearing the pump in 1 boy; pain in catheter-insertion site in 1 girl; and bothersome, frequent self-measurements of blood glucose in 1 boy.

#### DISCUSSION

To the best of our knowledge, this is the first randomized crossover trial comparing the outcome of CSII and MDI in children with type 1 diabetes. Our study shows that patients treated intensively with CSII and MDI achieve a similar metabolic control and have the same rate of adverse events. The use of CSII led to a lower insulin requirement and higher satisfaction rate, with no change in BMI. Both modes of therapy were associated with fair glycemic control, comparable to that achieved by the intensive-therapy adolescent group in the DCCT.<sup>5</sup> The lower HbA<sub>1c</sub> values during CSII on repeated measures ( $P = .03$ ) were accounted for solely by the lower HbA<sub>1c</sub> value at the start of the treatment arm but there was no significant difference between modes of therapy in the change over time.

Studies comparing glycemic control and the fre-

quency of adverse events in patients using CSII and MDI have shown conflicting results. Those reporting slightly better glycemic control with CSII than MDI, such as the DCCT<sup>10</sup> and others,<sup>7,18</sup> were not randomized with regard to mode of therapy, so the results may have been at least partly subject to patient or physician bias. Our findings are in line with 2 previous randomized trials in young patients<sup>19,26</sup> and adults<sup>20</sup> with type 1 diabetes, but disagree with 2 other studies using a similar design,<sup>11,12</sup> which reported a slight but statistically significant improvement in glycemic control during CSII. In the latter studies, either the sample was older (adults) with previous experience with pump use<sup>11</sup> or the pump was used only at night and the sample was younger,<sup>12</sup> when care is supervised by the parents.<sup>21</sup> Most of our patients were early pubertal and pubertal, when compliance with therapy is more difficult to achieve<sup>4,5</sup> and inconsistent meals and boluses might counterbalance the advantage of the better basal insulin replacement offered by CSII. In addition, CSII was a new modality for the patients and parents. Whether a longer period of CSII therapy would improve glycemic control with a decreased rate of hypoglycemia has yet to be determined.

We used regular insulin in the MDI arm of therapy. The choice was based on the observation that for optimal pre-meal and bedtime glycemic control during MDI therapy, a small amount of NPH needs to be added to each pre-meal lispro injection.<sup>22</sup> As the children preferred to use insulin pens for pre-meal shots, we decided to continue with the regular insulin during MDI. In view of the recent study comparing insulin analog to regular insulin in children treated with MDI,<sup>23</sup> wherein glycemic control and rate of hypoglycemia were found to be similar in the 2 groups, we assume the difference in insulin types did not have a major effect on the results.

The frequency of severe hypoglycemia during CSII was slightly, and not significantly, lower than during MDI. This small difference might be secondary not only to the different modes of therapy but also to the different short-acting insulins used in the 2 treatment modalities. A meta-analysis of randomized studies comparing rates of severe hypoglycemia between lispro and regular insulin during MDI showed that although findings in the individual studies were not significant, there was a significant overall difference favoring lispro.<sup>24</sup>

Another concern of patients who achieve improved glycemic control with intensive therapy is weight gain.<sup>1,5,7</sup> In our group, there was a significant interaction between mode of therapy and change in BMI SDS, with no change during CSII and a significant, albeit slight, increase during MDI, despite a similar level of glycemic control. This finding might be attributable to the significantly lower insulin requirements in our series, and in others,<sup>11</sup> and the decreased need for snacks during CSII therapy. Should this difference be sustained for a longer period of time, it would confer a distinct advantage on pump therapy.

Among the possible hazards of CSII is the susceptibility of patients to the rapid development of DKA

secondary to pump or infusion-set failure.<sup>10,25</sup> To reduce this risk, we conducted an educational session 3 months before initiating the study to motivate the patients and their parents to practice strict, routine self-monitoring of blood glucose and urinary ketones and to teach them how to correct hyperglycemia and ketosis. The results showed that despite the higher rate of ketonuria during CSII, there were no episodes of DKA during the study. This finding might be different in a routine clinic follow-up setting or during longer periods of CSII therapy.<sup>25</sup> Further studies are needed to determine if regular, repeated educational sessions can prevent DKA on a long-term basis.

Interestingly, a significant reduction (~0.6%) in HbA<sub>1c</sub> levels was noted at randomization, 3 months after the prestudy educational session, during which patients and parents were asked to perform 6 to 7 SBGMs and to report the results to the diabetic team for insulin dose adjustment. That is, it was the first 3 months before baseline (educational session) that accounted for the change in HbA<sub>1c</sub>. This initial improvement in metabolic control occurred within a support setting, without a change in the diabetes treatment regimen. This finding agrees with other studies.<sup>19,26</sup> It also illustrates the benefits of education alone in this population and suggests that for improvement of diabetic control, patient, parent, and team motivation, involvement, and adherence might be more important than the type of insulin regimen. The HbA<sub>1c</sub> further decreased by 0.3% to 8% throughout the study, for an overall reduction of 0.9%. This change is clinically significant, as the DCCT reported a 21% to 49% decreased risk of microvascular complications with every 1% decrease in HbA<sub>1c</sub>.<sup>27</sup>

Our study appears to be among the few randomized crossover studies to evaluate patient satisfaction. The patients seemed to be more satisfied with pump therapy than MDI therapy, as expressed by their response on the DSQT scale and their reported preference to continue with this mode. No such difference was found in the DQOLY. This discrepancy might be explained by the nature of the satisfaction score of the DQOLY, which is composed of items relating satisfaction with the treatment mode to satisfaction with life in general, and this may have masked the independent impact of the treatment mode. Be that as it may, satisfaction with pump therapy needs to be evaluated for longer periods, when the novelty of the pump is no longer a factor. In addition, the better satisfaction during CSII might be partly attributable to the different types of insulin used, with regular insulin given 20 to 30 minutes before meals during MDI and lispro given with meals during CSII.

Our study shows that intensive insulin therapy with either CSII or MDI is feasible, safe, and well accepted by children with type 1 diabetes and their families. With both modes of therapy, fair and acceptable glycemic control for this age group was maintained. The main improvement in metabolic control in our sample was achieved in the period before the study, simply by intensifying patient education. Our results suggest, therefore, that both

modes be made available to the diabetic team and the patients to better tailor therapy, and that enrolling patients in a research study is an effective tool to improve diabetic control.

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## EFFICACY OF ALBUMIN IN CRITICALLY ILL PATIENTS

“In 1998, the *British Medical Journal* published a meta-analysis that compared the effects of fluids containing albumin and crystalloids on death rates in critically ill patients. The analysis included 24 studies involving 1419 patients. The report concluded that there was no evidence that albumin reduced mortality and a strong implication that it might increase the risk of death. . . [A recent] meta-analysis included 55 trials involving 3504 patients—more than twice the numbers included in the original Cochrane review. Overall, this analysis detected no difference in mortality between patients treated with albumin and patients treated with other fluids. . . The only issue on which everyone seems agreed on is or more large, high quality, randomized controlled trials of albumin in critically ill patients are needed. . . The Australian and New Zealand Intensive Society, the Institute for International Health of the University of Sydney, and the Australian Red Cross Blood Service, have initiated a large double blind randomized controlled trial of albumin versus saline. . . They plan to recruit 7000 adult patients!”

Finfer S. *BMJ*. 2003;326:559–560

*Editor's Note:* Randomized trials all too often seem to result in a call for more and larger randomized trials. Are we doomed to forever calling for more and larger RCTs?

Noted by JFL, MD

## Comparison of Continuous Subcutaneous Insulin Infusion and Multiple Daily Injection Regimens in Children With Type 1 Diabetes: A Randomized Open Crossover Trial

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