Intensive Insulin Therapy With Insulin Lispro

A randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection

OBJECTIVE — To evaluate glycemic control, hypoglycemic events, and quality of life in patients treated with continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injection (MDI), with insulin lispro as the principal insulin.

RESEARCH DESIGN AND METHODS — This clinical trial enrolled 27 patients with type 1 diabetes. They were randomly assigned to CSII (n = 13) or MDI (n = 14) treatment regimens. Glycemic control (HbA1c level) was the primary outcome and was measured monthly for 9 months. Secondary outcomes were patient reports of hypoglycemic events (recorded monthly for 9 months) and quality of life assessed at 9 months using the Diabetes Quality of Life (DQOL) questionnaire.

RESULTS — A significant decrease in HbA1c from baseline was shown for both groups. However, the overall treatment effect (CSII − MDI) for HbA1c was +0.08% (95% CI −0.23 to +0.39, P > 0.10). This was significantly less than the a priori limit of ±0.5% (P = 0.004). The relative treatment effect ([CSII − MDI]/MDI) for the overall number of hypoglycemic events was +9% (95% CI = 37 to +87, P > 0.10). There were no statistically significant differences between treatment groups for any of the DQOL subscales.

CONCLUSIONS — No statistically significant differences in glycemic control, reported hypoglycemic events, or quality of life were found in this study. Furthermore, a clinically significant difference of more than ±0.5% HbA1c between the two regimens can be confidently ruled out. We conclude that the choice of intensive insulin therapy should be a matter of patient preference, consistent with lifestyle.

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The importance of intensive management of diabetes in improving long-term outcomes for patients with type 1 diabetes on insulin therapy was demonstrated by the Diabetes Control and Complications Trial (DCCT) (1).

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Abbreviations: CSII, continuous subcutaneous infusion; DCCT, Diabetes Control and Complications Trial; DQOL, Diabetes Quality of Life; MANOVA, multivariate analysis of variance; MDI, multiple daily insulin injection.

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

Other studies have further suggested that when human regular insulin was used, CSII could reduce the rate of severe hypoglycemia compared with MDI (4,5).

Despite the success of the DCCT, fewer than 5% of the patients in the intensively treated group within the trial maintained normal HbA1c levels for the duration of the study (1). Part of the reason that intensive treatment regimens failed to achieve sustained euglycemia was the less-than-satisfactory pharmacokinetics of subcutaneously injected regular insulin. To overcome this problem, rapid-acting insulin analogs were developed to more closely mimic the normal physiologic profile of insulin release in response to a meal (6).

The rapid-acting human insulin analog, insulin lispro, has been shown to have significantly faster onset and shorter duration of action than human regular insulin (7,8). In MDI regimens, insulin lispro improves postprandial blood glucose levels and decreases the rate of hypoglycemia (9–12). Using CSII regimens, we previously demonstrated that the use of insulin lispro results in a significant decrease in HbA1c, an improved postprandial blood glucose, and a lower rate of hypoglycemia compared with CSII with human regular insulin (13). This was later confirmed by other investigators (14,15).

However, to date there has been only one short-term controlled clinical trial directly comparing the outcome of treatment using a short-acting insulin analog in a CSII regimen versus an MDI regimen (16). Therefore, we undertook a randomized long-term trial to evaluate glycemic control and reported hypoglycemic events and quality of life in subjects with type 1 diabetes using CSII with insulin lispro, compared with MDI with insulin lispro as the premeal insulin.

RESEARCH DESIGN AND METHODS — The study, undertaken at the Leadership Sinai Center for Diabetes at Mount Sinai Hospital, Toronto,
Canada, was approved by the Human Subjects Review Committee of the University of Toronto. Adult patients between 18 and 60 years of age with endocrine diagnosis of type 1 diabetes were considered for inclusion in the trial if they had been diabetic for more than 2 years, had onset of diabetes on or before the age of 40 years, and were able to comply with the treatment regimen. Patients were excluded if they had a history of more than two severe hypoglycemic episodes (coma, seizure, loss of consciousness) in the last year; hemoglobinopathy; insulin resistance; extreme obesity (BMI > 35 kg/m²); severe late complications of diabetes; evidence of significant cardiovascular, hepatic disease, cancer, or cerebrovascular or severe peripheral vascular disease; alcohol or drug abuse; and/or participation in another clinical trial in the past 4 weeks. Female patients who were pregnant or likely to become pregnant were also excluded from the study. Patients were eligible for participation in the study if they currently received two or more injections per day and were interested and motivated to use CSII. The patients were given a free pump and supplies and, if randomized to MDI, were given the opportunity to initiate CSII at the end of the study.

Medical history was obtained from all eligible patients who consented to participate, to ensure the entry criteria were met, and hematologic and physical examinations were performed. After a 2-week screening period, patients were randomized using sealed envelopes that had been independently prepared using a computer-generated randomization schedule. Patients were allocated to receive intensive therapy with either CSII or MDI.

In patients in the CSII group, insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) CSII was administered via a MiniMed (Sylmar, CA) 507 insulin infusion pump. In patients in the MDI group, insulin lispro (Humalog) MDI was administered with NPH insulin at bedtime (no later than 11:30 P.M.). All patients completed two educational sessions with the study dietitian and nurse, including dietary advice relevant to the therapy program.

Patients were asked to perform self-monitoring of blood glucose levels before each meal and at bedtime, using the Advantage meter (Roche Diagnostics, Bale, Switzerland), and to record any adverse events such as episodes of diabetic ketoacidosis. An algorithm-based insulin dose adjustment was used with supplemental insulin as needed to achieve target blood glucose level, with a premeal target of 4–6 mmol/l and a 2-h postmeal target of <9 mmol/l. The CSII group used the Insulin Pump Therapy Book (17) guidelines and were asked to change the insulin infusion setting every 2 days to minimize subcutaneous reactions. In addition, the patients in the CSII group were instructed regarding insulin replacement in the event of pump failure. The patients in the MDI group used DCCT guidelines for insulin dose adjustment, with prebreakfast NPH insulin added if the premeal lunch and dinner blood glucose level was not controlled sufficiently with insulin lispro (18).

Patients were invited for follow-up each month after randomization for 9 months. At each follow-up visit, patients were asked to bring their glucose and adverse event diaries and to give a blood sample for measurement of HbA₁c. All tests of HbA₁c level were performed in the Mount Sinai Hospital central laboratory using monoclonal antibodies attached to latex particles (Integra 700; Roche Diagnostics). Hypoglycemia was defined as

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**Figure 1**—Flow chart of patients through the trial. *One patient was not considered suitable because he was too hirsute for the pump adhesive to stick; 6 one patient dropped out from the CSII group after 3 months; 6 one patient from the MDI group missed a single visit.
symptoms relieved by the ingestion of glucose and/or capillary blood glucose <3 mmol/l. Severe hypoglycemic events were defined as those requiring assistance or resulting in coma. At the final visit, patients were asked to complete the Diabetes Quality of Life (DQOL) questionnaire (19).

Statistical methods
SAS Version 8.0 software (SAS Institute, Cary, NC) was used for all statistical analyses. HbA1c measurements, the primary study outcome, were analyzed with a random-effects regression model (20). The numbers of monthly hypoglycemic events were analyzed with Poisson regression using a generalized estimating equations approach to handling correlated responses within subjects; baseline HbA1c was used as a covariate in the model. In both analyses, an autoregressive (1) covariance structure was used to model the repeated measurements. Linear contrasts were used to estimate differences between treatment groups for each monthly follow-up as well as the overall treatment effect. The linear contrasts for the HbA1c model were adjusted for baseline values of HbA1c.

The DQOL questionnaire was analyzed in five different subscales as described by the DCCT Research Group: satisfaction, global health, impact, social/vocational worry, and diabetes worry (19). The average of nonmissing items within each subscale was subtracted from 5 and multiplied by 25 to give a score on the scale of 0–100, with higher scores indicating higher quality of life. Multivariate linear modeling was used to model each subscale separately and globally with multivariate analysis of variance (MANOVA). For both univariate and MANOVA models, each treatment group was tested on its own and with age, sex, disease duration, baseline HbA1c, total number of hypoglycemic events, and the number of severe hypoglycemic events included separately and combined as covariates. Distributions were examined to ensure that residuals were approximately normally distributed.

The 95% CIs and P values were calculated for all estimates. A P value of 0.05 was used to assess statistical significance. None of the P values were adjusted for multiple comparisons. A difference in HbA1c of 0.50% was considered clinically significant.

All patients were analyzed according to the treatment group to which they were randomized. Follow-up data were not available for subjects withdrawing from the study subsequent to randomization and hence could not be included in the analysis. The statistical models for both HbA1c and the number of hypoglycemic events implicitly accounted for incomplete responses from subjects; therefore, least-square means and treatment effects are based on predictions for the complete set of enrolled subjects, while still providing correct estimates of precision based on the information actually available.

The study permitted an additional opportunity for follow-up of the 12 patients from the MDI group who started CSII at the end of the 9-month experimental period. The patients were followed for an additional 6-month period with review at monthly intervals. This crossover group allowed us to estimate the treatment effect with greater precision than the estimate obtained by comparing the two treatment groups in the 9-month trial due to the large intersubject variability. However, a single crossover group requires the absence of a period effect; therefore, the first 3 months of follow-up were excluded to ensure stationarity. While yielding a more precise estimate,
this component of the study is limited by its post hoc nature and the potential for bias due to a period effect.

**RESULTS** — A total of 27 patients were included in the study: 13 in the CSII group and 14 in the MDI group (Fig. 1). The groups were similar at baseline (Table 1). Mean HbA1c at baseline was 7.73% for the CSII group and 8.16% for the MDI group; however, the difference of −0.42% (95% CI −0.94 to +0.09) was not statistically significant (P > 0.10).

**HbA1c**

HbA1c showed a significant decrease from baseline in both groups (Fig. 2); the 95% CI was <0 at each of the time points. Adjusted for differences in baseline values, the overall treatment effect (CSII − MDI) for HbA1c was +0.08% (95% CI −0.23 to +0.39, P > 0.10). None of the treatment differences observed at follow-up were statistically significant (P > 0.10), and there was no apparent pattern to indicate any departure from the constant treatment effect model used.

**Hypoglycemia**

During the 9-month study period, all patients in both groups reported hypoglycemic events. Of these events, six in the CSII group and four in the MDI group were severe (P > 0.10).

The relative treatment effect ([CSII − MDI]/MDI) for the overall number of hypoglycemic events was +9% (95% CI −37 to +87%, P > 0.10). None of the treatment differences were statistically significant (P = 0.06 at 2 months, P > 0.10 otherwise) (Table 3), and there was no apparent pattern to indicate any departure from the constant treatment effect model used.

**Insulin dose at the end of 9 months**

At the end of the experimental period, the mean total daily dose of insulin did not differ between groups: CSII mean 0.6 units/kg (SD 0.2), MDI 0.7 (SD 0.2); the difference (CSII − MDI) was −0.10 units/kg (95% CI −0.26 to 0.07), P > 0.10. The final number of basal doses for the CSII group ranged from 1 to 4 per day (mean 2.23), and the final number of NPH injections for the MDI group was 1 or 2 per day (mean 1.43).

**Quality of life**

The DQOL questionnaires were completed well; only 3 of 1,128 items were missing (all dealing with sexual matters).

There were no statistically significant differences between treatment groups for any of the DQOL subscales, using either the univariate model with only treatment group included (Table 4) or any of the multivariate models that included age, sex, disease duration, baseline HbA1c, total number of hypoglycemic events, and the number of severe hypoglycemic events as covariates (either together or individually). None of these covariates showed a statistically significant association with any of the DQOL subscales. Similarly, the MANOVA showed no global treatment differences for the five subscales, with or without any of the covariates, and the MANOVA models did not show a significant association for any of the covariates.

**Table 2—Treatment effects for HbA1c**

<table>
<thead>
<tr>
<th></th>
<th>Mean HbA1c(%)</th>
<th>Treatment effect (adjusted for baseline HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSII group</td>
<td>MDI group</td>
</tr>
<tr>
<td>Baseline (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.73</td>
<td>8.16</td>
</tr>
<tr>
<td>2</td>
<td>7.06</td>
<td>7.49</td>
</tr>
<tr>
<td>3</td>
<td>6.92</td>
<td>7.55</td>
</tr>
<tr>
<td>4</td>
<td>7.07</td>
<td>7.51</td>
</tr>
<tr>
<td>5</td>
<td>7.16</td>
<td>7.40</td>
</tr>
<tr>
<td>6</td>
<td>7.19</td>
<td>7.62</td>
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<tr>
<td>7</td>
<td>7.32</td>
<td>7.56</td>
</tr>
<tr>
<td>8</td>
<td>7.26</td>
<td>7.44</td>
</tr>
<tr>
<td>9</td>
<td>7.38</td>
<td>7.56</td>
</tr>
</tbody>
</table>

Note: absolute values for HbA1c are shown in both CSII and MDI groups. The treatment effect, namely CSII − MDI corrected for baseline differences, is shown. At no time point were there any clinically significant differences.

**Table 3—Treatment effects for the number of hypoglycemic events**

<table>
<thead>
<tr>
<th>Mean number of hypoglycemic events</th>
<th>CSII group</th>
<th>MDI group</th>
<th>Relative treatment effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8.0</td>
<td>7.4</td>
<td>9 (−37, 87)</td>
</tr>
<tr>
<td>1 month</td>
<td>9.2</td>
<td>10.0</td>
<td>−7 (−51, 74)</td>
</tr>
<tr>
<td>2 months</td>
<td>9.1</td>
<td>5.5</td>
<td>67 (−3, 187)</td>
</tr>
<tr>
<td>3 months</td>
<td>8.9</td>
<td>5.0</td>
<td>79 (−11, 262)</td>
</tr>
<tr>
<td>4 months</td>
<td>8.6</td>
<td>8.3</td>
<td>−20 (−58, 52)</td>
</tr>
<tr>
<td>5 months</td>
<td>8.9</td>
<td>7.2</td>
<td>24 (−39, 153)</td>
</tr>
<tr>
<td>6 months</td>
<td>7.2</td>
<td>9.0</td>
<td>−21 (−62, 65)</td>
</tr>
<tr>
<td>7 months</td>
<td>9.6</td>
<td>5.7</td>
<td>66 (−15, 223)</td>
</tr>
<tr>
<td>8 months</td>
<td>6.6</td>
<td>8.5</td>
<td>−22 (−60, 51)</td>
</tr>
<tr>
<td>9 months</td>
<td>7.0</td>
<td>9.2</td>
<td>−24 (−66, 71)</td>
</tr>
</tbody>
</table>

*Adjusted for baseline HbA1c.
Table 4—Results of the DQOL questionnaire (mean for each subscale) for the CSII and MDI groups at 9 months

<table>
<thead>
<tr>
<th>DQOL subscale</th>
<th>CSII group</th>
<th>MDI group</th>
<th>CSII − MDI</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction</td>
<td>75.6</td>
<td>68.3</td>
<td>7.2</td>
<td>(−3.4, 17.9)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Impact</td>
<td>69.9</td>
<td>68.4</td>
<td>1.6</td>
<td>(−4.6, 7.7)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Diabetic worry</td>
<td>85.2</td>
<td>79.8</td>
<td>5.4</td>
<td>(−6.7, 17.6)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Social worry</td>
<td>89.6</td>
<td>94.0</td>
<td>−4.3</td>
<td>(−18.8, 10.1)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Global health</td>
<td>68.2</td>
<td>67.3</td>
<td>0.9</td>
<td>(−12.7, 14.4)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Overall (using MANOVA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>

Data are means unless otherwise indicated.

HbA1c in subjects switching from MDI to pump

There was no evidence of nonstationarity in this group for the 6-month periods preceding and following the switch. The difference in HbA1c between months 10–15 and months 4–9 was +0.09% (95% CI −0.11 to +0.28, P > 0.10). Pooling the estimates of the treatment effect using this approach and the previous comparison between subject groups gave an estimated difference between CSII and MDI of 0.09% (95% CI −0.09 to +0.26, P > 0.10). Based on this estimate, the probability that the true treatment effect is more extreme than ±0.50% is <0.00001.

CONCLUSIONS

This study, the first long-term, randomized, controlled trial to compare the outcome of insulin lispro administered using either CSII or MDI regimens, found no differences in outcome between the two groups in terms of HbA1c levels, hypoglycemic events, or quality of life measured using the DQOL questionnaire.

The strengths of the study lie in the randomized trial design and the duration and completeness of follow-up. Our findings have the limitation that the level of difference in HbA1c between groups we considered clinically important was perhaps relatively large (0.50% HbA1c). However, the difference in HbA1c was indeed very small (95% CI −0.23 to +0.39), making a difference of >0.40% very unlikely. In addition to the trial results, we were also able to observe the treatment effect among 12 patients who switched from MDI to CSII for 6 months after the end of the trial. By pooling the estimates of the treatment effect among these patients with that observed within the trial, we found that the estimated difference was 0.09% (95% CI −0.09 to 0.26).

Previous studies comparing CSII and MDI using human regular insulin have demonstrated that control of diabetes is improved in patients using CSII compared with those using MDI (4,5,21). Two of these studies were limited by not being randomized, with either physicians or patients choosing to use CSII (4,21). Therefore, the improvement noted in the CSII groups in these studies may be influenced by patient and physician bias. The Oslo study, a randomized trial comparing outcome using CSII, MDI, or conventional twice-daily insulin injections, found that CSII was slightly superior to MDI. The only differences were that hypoglycemic coma was observed less frequently during the 2-year follow-up period (CSII 2 vs. MDI 14), but low blood glucose concentrations (<2.5 mmol/l) were more common (CSII 11% vs. MDI 7%) (5). The ease of administration of meal insulin with insulin pens and the improved pharmacokinetics of insulin lispro in the context of postprandial control may be responsible for reducing any advantage CSII may have had in previous studies with regular insulin. However, for basal insulin replacement, one would expect CSII to be superior to injections of intermediate-acting insulin.

In a recently published randomized crossover study comparing outcome for patients using insulin lispro for two 4-month periods with CSII or MDI, a significant difference of 0.35% in HbA1c was found, in favor of CSII (16). This difference was described by the authors as slight and would not have been considered clinically important according to our a priori definition. As with our study, they did not find differences between groups in numbers of hypoglycemic events, and severe events were rare.

It is important to note that although there were no significant differences between the MDI and CSII groups in our study, a decrease in HbA1c was observed in both groups, similar to that observed in our earlier trial of insulin lispro (13). This decrease was sustained during the trial and may have been a result of introducing insulin lispro to the diabetic regimen; however, it also could have been a result of the educational intervention that all patients received and improved self-monitoring within the trial.

Despite the intensive therapies used in this trial, all of the patients experienced hypoglycemic events, possibly as a result of the pharmacokinetics of insulin used to provide basal insulin. The development of a short-acting insulin analog to better replace mealtime insulin requirements has been paralleled by the development of long-acting insulin analogs. Insulin glargine is the most advanced of these analogs and has been shown to have more neutral basal pharmacokinetics (22). The plasma free insulin profile of insulin glargine is much flatter than that of NPH insulin, which has a reproducible peak action 8 h after injection. The introduction of insulin glargine can therefore be expected to reduce the problems associated with the use of NPH insulin in MDI regimens, such as nocturnal hypoglycemia, and the need for multiple NPH insulin doses. Comparison studies with glargine MDI regimens and CSII will be of obvious interest.

The findings of this trial are useful in informing clinical practice. The DCCT trial has already demonstrated the benefit of intensive therapy over conventional therapy. More recently, insulin lispro has been demonstrated to be preferable to human regular insulin for providing mealtime insulin replacement and postprandial glucose control. The findings of our study indicate that the choice of the method of intensive insulin therapy should be a matter of patient preference. Although clinical outcomes were similar in this controlled trial, individual patients may benefit significantly from CSII because of the increased flexibility in timing of meals and the increased options for basal insulin replacement. This may also apply to patients who have high rates of severe hypoglycemia. It is important for all patients with type 1 diabetes to have the option to select the therapy that is most suitable for them.
Acknowledgments—This study was supported by a research grant from Eli Lilly. The pumps and disposable supplies used in this study were provided by MiniMed. The Humalog and NPH insulin used in the study was provided by Eli Lilly.

References