Glycaemic Control with Modified Intensive Insulin Injections (MII) Using Insulin Pens and Premixed Insulin in Children with Type-1 Diabetes: A Randomized Controlled Trial

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Summary

The objective of this study was to compare glycemic control and insulin dosage in children with type 1 diabetes treated by a modified intensified insulin therapy (MII) using insulin pens (and premixed and regular insulin) with those on conventional insulin therapy. This was a longitudinal, randomized controlled trial for 6 months or more. From a cohort of 125 children with previously diagnosed type-1 diabetes (more than a year after diagnosis) two groups were randomly selected Group AI ($n = 20$) and Group B ($n = 20$). Group AI children and 10 children with recently diagnosed type 1 diabetes (Group AII) were allocated to MII using regular insulin and premixed insulin (30/70 and 40/60 and 50/50). Group B patients continued their conventional insulin therapy for the whole period of the trial. The main outcome measures were glycemic control measured by mean blood glucose concentration and percentage of glycated haemoglobin and total daily insulin dose. Mean blood glucose concentrations before the three main meals, and at midnight, (148, 147, 179 and 127 mg/dl, respectively) were lower in children receiving intensified MII compared with those receiving conventional insulin therapy (192, 174, 194 and 179 mg/dl, respectively) (standardized mean difference 34 [15 mg/dl, equivalent to a difference of 1.9 [0.8 mmol/l. This improved control during MII was achieved with no change in the average daily insulin dose in group-AI. In group-AII insulin dose decreased significantly during their first 6 months of treatment (honeymooning). Glycemic control is better during MII using insulin pens and premixed and regular insulin compared with conventional insulin therapy, without any significant change in insulin dose needed to achieve this level of control. The difference in glycemic control between the two methods is significant and could reduce the risk of micro-vascular complications.

Introduction

The Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) proved that intensive treatment with tight glycemic control markedly reduced the risks of retinopathy, nephropathy and neuropathy compared with conventional treatment. Both studies recommended intensive flexible insulin therapy to achieve near normal blood glucose values [1–7].

Intensive flexible insulin therapy involves the utilization of multiple daily injections of insulin (both long and immediate or short acting formulation) or an insulin pump to obtain the best diabetes control possible. This has also been called flexible insulin therapy or basal-bolus insulin therapy.

The objective behind it is to utilize a regimen that mimics more closely the way a healthy body produces insulin in response to food consumed and activity performed. The basal or background insulin is used to control glucose excursions between meals due to production of glucose by the liver. The immediate acting or short acting insulin is given with meals to compensate for change in glucose levels that result from the food ingested. Frequent self-monitoring blood glucose (SMBG) is necessary to follow the response to a change in insulin doses, timing and other factors. An understanding of diet composition, specifically carbohydrates counting of the meal is very important to decide on meal dose of short-acting insulin [7–19].

There are several difficulties in applying Intensified insulin therapy (IIT) for diabetic children in developing countries. Most patients cannot intensify their regimen because of:

1. Lack of a cohesive and organized diabetes team essential for frequent interaction and discussion, in many of the developing countries.
2. Lack of financial support leads to difficulties to perform frequent SMBG and record results.

3. Poor availability of different types of insulin and equipment needed for IIT, as they are often expensive for patients with low socioeconomic status. Furthermore, it is still difficult to control life style of children and to make them accept multiple daily sticks either for insulin injections or for blood glucose monitoring [20–24].

The use of insulin injection pens is an accurate and easy method especially attractive for children and adolescents. The availability of different combination of premixed insulin preparations consisting of fixed combination of soluble and NPH insulin in different proportions (10/90, 20/80, 30/70, 40/60, 50/50) can further facilitate the procedure of injection and increase the compliance of patients [25–28]. Practically, both insulin pump and multiple-injection therapy based on prandial and basal insulin injection are comparably efficient means to achieve good glycemic control [29–32].

The aim of the study was to evaluate various parameters of glycemic control and growth in children (3–13 years) with type 1 DM before and after 3 and 6 months or more of applying a modified intensified insulin regimen using insulin injection pens and premixed insulin [regular (R) and NPH(N)] in various proportions (30/70, 40/60, 50/50) according to the need (activity and quality and quantity of meals) of children with type 1 DM and compare them with those patients on conventional two-dose therapy.

**Subjects and Methods**

Forty children with type 1 DM attending were randomly selected from a cohort of 120 diabetic children attending the outpatient clinic of Alexandria University Children's Hospital. They were randomly assigned at the beginning of the study to make two groups, group A (n = 20, 9 males and 11 females, mean duration of DM = 3.2 ± 1.5 years) and group B (n = 20, 10 males and 10 females, mean duration of DM = 3.5 ± 1.3 years). Their ages ranged from 3 to 15 years. Another 10 children with recently diagnosed type 1 diabetes (group AII) were included as a control group.

Patients with any micro-albuminuria or neuropathy or other endocrine or systemic diseases were excluded from the study. Those who did not comply with the terms of the study were excluded from the analysis.

Informed consent was obtained from all the parents of the children included in the study and the ethics committee of Alexandria University approved the protocol of the study.

**Group A (MII-Intensive therapy group)**

This group included:

- Group A1 patients (n = 20) with type 1 DM for more than one year duration who were receiving two daily injections of insulin therapy either Mixtard (30/70) (Novo Nordisk) or NPH and regular insulin and changed to the MII therapy.
- Group AII (n = 10) with recent onset type 1 DM for less than 1 month.

Both subgroups (A1 and AII) were followed up for 6–12 months after applying a modified flexible intensive insulin regimen adjusted to the timing and meal pattern of the Egyptian children which entailed:

- A (pre-lunch, between 12 and 1 pm) dose of regular insulin (to cover the prandial insulin requirements of the lunch meal, which is the main meal for Egyptian children (average of 50% of the total caloric intake, taken between 1 and 3 pm).
- Two daily doses (before breakfast (between 6 and 8 am) and dinner (between 8 and 10 pm) of premixed insulin of mixtard (30/70, 40/60 or 50/50). The percentage of regular insulin in the premixed insulin is selected according to the carbohydrate count of the usual breakfast and dinner evaluated by the dietitian.
- Educating and training the patients and parents about using self-monitoring of blood glucose (SMBG) and supplying glucometers to check blood glucose levels and record them before meals, midnight and 3 and 4 am.
- Education about carbohydrate counting of the lunch meal, hypoglycemia, and the use of diet and exercise to achieve good glycemic control.

**Group B (control group)**

Comprised n = 20 with type 1 DM for more than 1 year and receiving two daily injection of Mixtard (30/70) or mixture of NPH and regular insulin. This group continued their conventional insulin regimen with two daily doses of mixed insulin (regular and intermediate mixture) before breakfast and dinner, in addition to receiving the same education and SMBG as for group A.

All patients were followed in the clinic weekly for 4 weeks then monthly for the rest of the study. During the clinic all the children were submitted to:

- Complete clinical examination including measuring the weight, height, calculating the body mass index (BMI) and height SDS (HtSDS), recording the blood pressure (recumbent and standing) with fundus and nervous system examination.
- Review of the results of SMBG and adjusting the dose/s of insulin accordingly.
- Measurement of glycated hemoglobin (HbA1C) every 8 weeks.
Values of 6.2–7.1% represent good metabolic control, values of 7.1–8.2% fair control and values greater than 8.2% poor control [33].

Results are expressed as the mean ± SD and analyzed by ANOVA to compare analyte concentrations among groups. Paired Student’s t-test was used to compare changes after vs. before treatment for 6 months or more in each group. Correlations between variables of interest were examined by linear regression analyses.

**Results**

Auxologic data including age, Height Z-score (HtSDS) and body mass index (BMI) did not differ significantly among the three study groups. Insulin dose (unit/kg/day) and HbA1C concentrations did not differ between group AI and group B before initiation of intensified insulin therapy for group AI.

The HtSDS and BMI for diabetic children in the three groups did not change significantly after 6 months or more of initiating intensified insulin therapy in groups AI and AII (Table 1). Total daily insulin dose (U/kg) did not change after vs. before therapy in groups AI and B. However, insulin dose decreased significantly in group-AII, due to the occurrence of honeymooning in 5 out the 10 children in this group (newly-diagnosed). Two patients did not comply with the intensive insulin regimen and were excluded from the analysis.

Table 2 summarizes the mean blood glucose concentrations before meals and at midnight in the three groups of diabetics before and after 6 months of follow-up. After 3 and 6 months of applying MII, groups AI and AII showed significant reduction in glucose concentration before the three main meals and at mid-night after 6 months of initiating intensified insulin therapy. Although reduction of the mean

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Auxologic data and insulin requirements before and after intensified insulin therapy</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Group AI</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>SD</td>
</tr>
<tr>
<td>Group AII</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>SD</td>
</tr>
<tr>
<td>Group B</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>SD</td>
</tr>
</tbody>
</table>

Group AI = previously-diagnosed diabetics put on intensified insulin therapy.
Group AII = newly-diagnosed diabetics put on intensified insulin therapy.
Group B = previously-diagnosed diabetics on conventional insulin therapy.
b = before
a = after intensive insulin therapy.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean blood glucose before meals and at mid-night before and 6 months of the study</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Before breakfast</td>
<td>207.3 ± 81.38</td>
</tr>
<tr>
<td>p value</td>
<td>0.009</td>
</tr>
<tr>
<td>Before lunch</td>
<td>205.5 ± 116.5</td>
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<tr>
<td>p value</td>
<td>0.04</td>
</tr>
<tr>
<td>Before dinner</td>
<td>267.8 ± 93.6</td>
</tr>
<tr>
<td>p value</td>
<td>0.004</td>
</tr>
<tr>
<td>Midnight</td>
<td>172.45 ± 64.79</td>
</tr>
<tr>
<td>p value</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*p < 0.05.
Group AI = previously-diagnosed diabetics put on intensified insulin therapy.
Group AII = newly-diagnosed diabetics put on intensified insulin therapy.
Group B = previously-diagnosed diabetics on conventional insulin therapy.
blood glucose before meals was also noted in group B (on conventional therapy) however, the changes were not statistically significant.

The glycated Hb (HbAlC) data (Tables 3 and 4) revealed significant reduction of HbAlC level by 18.5% in group AI and 35% in group AII after 6 months of therapy. The percentage change of HbAlC concentration was insignificant in group B.

In group AI ten out of the 15 patients who had bad glycemic control (HbAlC >8.2%) attained better glycemic control. Five of them achieved good control (HbAlC <7.1%) and the other five attained fair control (HbAlC <8.2%). In group B, three patients (out of 17) attained better glycemic control. One of them attained good glycemic control.

Two patients in group AI and two in group AII had 1 or more symptomatic hypoglycemic episodes after initiation of intensified therapy but none of them necessitated hospital admission. Adjustment of the insulin doses abolished these attacks in the four patients. None of the diabetic children in our study showed evidence of autonomic neuropathy, microalbuminuria or retinopathy before or after the study.

Correlation studies did not show any significant relation between BMI, insulin dose or HbAlC in the three studied groups.

### Table 3

<table>
<thead>
<tr>
<th>Degree of glycaemic control</th>
<th>Group AI</th>
<th>Group AII</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good control (6.2–7.1)</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Fair control (7.1–8.2)</td>
<td>4</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Poor control (&gt;8.2)</td>
<td>15</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td>X2</td>
<td>2.96</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>p</td>
<td>0.13</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good control (6.2–7.1)</td>
<td>6</td>
<td>35.3</td>
<td>9</td>
</tr>
<tr>
<td>Fair control (7.1–8.2)</td>
<td>6</td>
<td>35.3</td>
<td>0</td>
</tr>
<tr>
<td>Poor control (&gt;8.2)</td>
<td>5</td>
<td>29.4</td>
<td>1</td>
</tr>
<tr>
<td>X2</td>
<td>4.98</td>
<td></td>
<td>0.04*</td>
</tr>
<tr>
<td>p</td>
<td>0.04*</td>
<td>0.001*</td>
<td>0.13</td>
</tr>
</tbody>
</table>

X2 comparisons between the three studied groups before intervention and after intervention.

### Table 4

<table>
<thead>
<tr>
<th>Glycated hemoglobin change in the three diabetic groups</th>
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</thead>
<tbody>
<tr>
<td>HbAlC (before)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Group AII ‘new cases’</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>S.D.</td>
</tr>
<tr>
<td>Group AI ‘old cases’</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>S.D.</td>
</tr>
<tr>
<td>Group B ‘old cases’</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>S.D.</td>
</tr>
</tbody>
</table>

( ) = p<0.05.

Group AI = previously-diagnosed diabetics put on intensified insulin therapy.

Group AII = newly-diagnosed diabetics put on intensified insulin therapy.

Group B = previously-diagnosed diabetics on conventional insulin therapy.

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Discussion

In this study, a modified intensive insulin therapy (MII) was applied and consisted of a mid-day extra-dose of short acting insulin, to cover the main meal of the day, added to the two daily injections of premixed insulin (using pens), self-monitoring of blood glucose (SMBG), and education of diabetic children and their parents.

The results showed that the diabetic children (group AI and AII) had significantly lower mean SMBG levels and HbAIC concentrations three and six months after vs. before applying intensified insulin regimen. The mean reduction in HbAIC at and six months of intensified therapy was 18% and 35% respectively. After 3 and 6 months of intensified insulin therapy they had significantly lower glycated hemoglobin level compared to the control group (group B). The change to intensified insulin therapy was not associated with any significant change in BMI or insulin dose (unit/kg/day) in group-AI. Hypoglycemia occurred in four patients during the initiation of insulin therapy but disappeared after adjustment of insulin doses.

In the newly-diagnosed diabetics (group AII) insulin requirement decreased significantly after 6 months of intensified insulin therapy denoting increased endogenous insulin secretion (honeymoon period) in a considerable number of them.

A meta-analysis of 12 randomized controlled trials showed that use of insulin pumps results in better glycaemic control than optimized insulin injection therapy but that the difference is relatively small – about 1 mmol/l for blood glucose concentration and 0.5% for percentage of glycated haemoglobin [34–42]. In this study, MII therapy resulted in an average reduction of the mean blood glucose concentration by 3 mmol/l and 1.9% reduction of the glycated Hb by 1.9% vs. before MII therapy in group AI.

The risk of development and progression of microvascular complications extends over the entire range of glycated haemoglobin values and there is no threshold (short of normoglycaemia) below which there is no risk. In this study intensification of insulin therapy using different types of premixed insulin in a pen injector appeared safe and advantageous over conventional regimen between 3 and 13 years of age and can be recommended for this age group to improve glycemic control and decrease the morbidity of childhood diabetes. In group-AI the significant reduction of glycated Hb by 1.9 mmol/l (18.5%) after compared to before MII and compared to group B denoted a significant effect of this insulin regimen. The mean glycated Hb values (7.7 ± 1 mmol/l) were comparable to those for patients either on insulin-pump therapy or on multiple daily injection therapy reported in other studies [42–44].

In summary, if the physician’s experience, financial and support team for continuous subcutaneous insulin therapy (CSII) management is limited, intensive conventional therapy probably is acceptable. Using premixed insulin of different concentrations in pen injectors is a useful and acceptable mode of therapy by many children that can improve markedly glycemic control.

References