Intensive insulin treatment versus conventional regimen for adolescents with type 1 diabetes, benefits and risks

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ABSTRACT

Objective: The aim of the study is to compare the frequencies of complications among adolescents with type 1 diabetes (age 12-18 years) treated with either intensive insulin regimen (4 injections per day) or conventional regimen (2 injections per day).

Methods: The study was carried out at the Childrens Hospital, Quebec, Canada during the period 1997 to 1999. This retrospective survey involves a chart study of type 1 diabetic children aged 12-18 years. The frequency of retinopathy, nephropathy (albuminuria), diabetic ketoacidosis (DKA) and hypoglycemia were determined among the children on 4 insulin injections per day and those on 2 injections per day. The 2 groups were matched for age, sex, body mass index, insulin dosages and glycosylated hemoglobin levels.

Results: The frequencies of DKA (25% versus 30%) and hypoglycemia (25% versus 30%) were comparatively less among the intensive therapy group compared with the conventional therapy group. The incidence of retinopathy was approximately the same (8% versus 7%) in the 2 groups and nephropathy did not feature in any patient in the series.

Conclusion: Intensive insulin therapy appears safe and advantageous over conventional regimen in the age bracket 12-18 years as has already been proven for individuals above the age of 18 years and adults. It can be recommended for this age group to forestall the morbidity of childhood diabetes.

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There are various reports claiming the superiority of intensive insulin dosing (3 or more injections per day) over the conventional therapy (1 or 2 injections per day) for the treatment of type 1 diabetes. The best evidence came from the diabetes control and complications trial (DCCT) where intensive insulin therapy with the goal of achieving glycemic levels as close to non-diabetic levels as possible, effectively delays the onset and slows down the progression of diabetic complications retinopathy, neuropathy and nephropathy.[1,2] Following their findings, intensive therapy was proposed to be the treatment of choice in suitable subjects with type I diabetes.[1-4] The recommendation of the DCCT came from the analysis of the patients who were mostly more than 18-years of age. Such a recommendation may not universally apply to children 12-18 years of age. Differences may occur because the biologic and psychosocial changes that happen during adolescence might independently affect the response to both treatment modalities.[4-6] The present study is aimed at comparing the response of 2 groups of adolescents within the age bracket of 12-18 years in which one group was on intensive therapy while the other group was on the conventional therapy. The focus of this study is to compare the frequency of major complications of type 1 diabetes among the adolescents

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who receive intensive insulin therapy with those on conventional regimen. The response to metabolic control was guided by frequent monitoring of the glycosylated hemoglobin (HbA1c). The period of study was 3 years.

Methods. A retrospective survey of adolescent children undergoing management for type 1 diabetes at the Children Hospital, Quebec, Canada, between 1997 to 1999 was undertaken. Their charts were reviewed to abstract the following data: age, sex, duration of diabetes, BMI, insulin dose per day, HbA1c levels, number of hospitalization and the presence of complications. The complications in focus were retinopathy, albuminuria, and the frequency of diabetic ketoacidosis (DKA) and hypoglycemia. All the patients had been enrolled in the adolescent education program (ADEP) whereby a team consisting of a pediatric endocrinologist, diabetes nurse educator; social worker and a psychologist were involved as facilitators/trainers. The team closely monitored compliance. The program started in 1994 and children had the option to enter the program or stay in the ordinary follow up clinic. Patients in the study population entered the program at different ages; at the time of this review some had been in the program for periods varying from 2-4 years. Metabolic control was assessed on each patient by serially estimating the HbA1c level every 3 months starting from a one year prior to enrolling in the program till 2 years thereafter. The method used was immunoturbidimetry (Unimate HbA1c, Roche Diagnostics, Mississauga, Canada; normal non-diabetic range: 4.5-6.1%). Assessment for the presence of diabetic retinopathy was conducted once a year by an ophthalmologist using indirect ophthalmoscope after dilatation of the pupils with atropine in patients who were diabetic for at least 5 years. The retinal lesions were graded as normal, non-proliferative, and proliferative. Diabetic nephropathy was monitored using a 24-hour urine collection for microalbumin assay. Albuminuria was determined yearly by radioimmunoassay method on the 24-hour urine sample. An output of less than 30 mg/24 hour was regarded as normal; microalbuminuria is defined as 30-300 mg/24 hour. Only episodes of hypoglycemia requiring assistance or leading to coma or convulsion were considered significant. Only subjects in the age range 12-18-years were considered in the final analysis. Subjects on 4 daily insulin injections were matched for age, sex, BMI, insulin dose and compliance with those on 2 insulin injections per day.

Results. There were 24 adolescents on intensive insulin regimen and 57 on conventional regimen (controls) who satisfied the criteria to be included for final analysis. The mean duration of diabetes was 6.31 ± 4.00 years for each group. The demographic data of the 2 groups were fairly similar regarding mean age, height, and weight (**Table 1**). The male/female ratio was 1:1 among the subjects and 1.2:1 among the controls. **Table 2** demonstrates the very close similarity of the mean insulin dose (0.95 ± 0.15u/kg/day versus 0.95 ± 0.26 u/kg/day for the subjects and controls; and the HbA1c levels at entry and at the ends of one and 2 years in the 2 study groups. Body mass index among the 2 groups at the entry into the program was closely similar and did not change significantly over the period of the study

Complications. The complications of the disease recorded among patients in the 2 groups included DKA, severe hypoglycemia and diabetic retinopathy (**Table 3**). Among 24 subjects on intensive regimen, there were 6 admissions (25%) for DKA, 4 admissions (16.6%) for

Table 1 - Demographic status of adolescents in the intensive and conventional therapy groups.

Variables	Intensive therapy group	Control therapy group
Patient n	24	57
Males	12	31
Females	12	26
Mean age (yr)	17.9	16.6
Mean height (cm)	168 ± 7.7	164 ± 9.1
Mean weight (kg)	65.9 ± 8.9	61.7 ± 12.5

Table 2 - Insulin dose and glycosylated hemoglobulin (HbA1c) levels in the subjects and control group.

Variables	Intensive group	Control group
Mean insulin dose/kg/ day	0.95 ± 0.15u	0.96 ± 0.16
Mean HbA1c at entry	9.34 ± 1.55	9.37 ± 1.8
Mean HbA1c at first year	9.2 ± 1.7	9.46 ± 1.61
Mean HbA1c at second year	9.49 ± 1.55	9.59 ± 1.59

Table 3 - Frequencies of complications of diabetes in the subjects (n=24) and control group (n=57).

Variables	Intensive group (%)	Control group (%)
Diabetic ketoacidosis	6 admissions (25)	17 admissions (30)
Severe hypoglycemia	4 admissions (16.6)	16 admissions (28)
Diabetic retinopathy	2 cases (8.3)	4 cases (7)

severe hypoglycemia and 2 cases (8.3%) of retinopathy. Correspondingly, in the control group there was 17 (30%) of DKA, 16 (28%) of severe hypoglycemia and 4 cases (7%) of retinopathy. None of the patients in the 2 study groups had a significant albuminuria. The adolescents reported improved life style while on multiple injections as compared to conventional therapy group.

Discussion. Since the first administration of insulin in 1922, there has been a dramatic transformation in the management and outcome of type 1 diabetes. As Tattersall noted years ago, insulin is given in the wrong place (SC instead of portal), at the wrong time (often after blood sugar is elevated), and in the wrong amount (not enough for the meal but too much for the fast). In spite of all this, insulin proved to be the only drug therapy for the management of patients with type 1 diabetes.[4] When does the clock start running for complication has been a subject for discussion, but the general consensus is that it starts with the onset of diabetes and it accelerates markedly with the onset of puberty.[4] Complications have been recorded before or early in puberty with severely compromised control.[4] As was demonstrated in the DCCT, improving glycemic control as measured by HbA1c, markedly reduced the development and progression of retinopathy, neuropathy and nephropathy in both adults and adolescents.[1-3] While the numbers in our study is small, it has demonstrated a lower incidence in the risk of developing DKA among patients in the intensive-therapy group compared with those in the conventional-therapy group (25% versus 30%), but the risk of retinopathy between the 2 groups was at par (8% versus 7%). One known disadvantage of improved metabolic control has been the increase in the rate of severe hypoglycemia. The rate of this increase was 3 folds in the DCCT compared with those in the conventional therapy group.[1,3] At variance with this general expectation, the present survey demonstrates a comparatively lower incidence of hypoglycemia among the intensive therapy group compared with those on 2 injections per day (17% versus 28%). Perhaps this comparatively low incidence could be attributed partly to the frequent self-monitoring of the blood glucose levels in the intensive regimen group. In contrast to the DCCT, the mean HbA1c in our study was higher (9% versus 8%) and there was small difference between the 2 groups but was not statistically significant. The reason for this difference cannot be totally explained. The difference in the HbA1c assay method, follow up, and duration of the study and patient commitment possibly contributed to this difference. The application of the DCCT recommendations requires certain levels of maturity, personal commitment, and behavioral changes. Families with limited resources, psychosocial instability will be incapable of following such regimen.[4-7]

In conclusion, the findings of this study suggest that intensive insulin therapy has greater advantages over the conventional therapy in reducing the incidence of short-term diabetes complications (hypoglycemia and DKA). These findings should relief to some degree the constant fear of severe hypoglycemia when treating type 1 diabetics with such regimen. In addition, patients had a better and easier lifestyle. Like other studies, the current findings also supports the implementation of intensive therapy for adolescents with type1 diabetes as early as 12-18-years of age when feasible.[8-10]

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References

1. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. ***J Pediatr*** 1994; 125: 177-188.
2. Santiago JV. Lessons from the Diabetes Control and Complications Trial. ***Diabetes*** 1993; 42: 1549-1554.
3. Drash AL. The child, the adolescent, and the Diabetes Control and Complications Trial. ***Diabetes Care*** 1993; 16: 1515-1516.
4. Rosenbloom AL, Schatz DA, Krischer JP, Skyler JS, Becker DJ, Laporte RE et al. Prevention and treatment of Diabetes in Children. ***J Clin Endocrinol Metab*** 1999; 2: 494-522.
5. Weissberg-Benchell J, Glasgow AM, Tynan WD, Wirtz P, Turek J, Ward J. Adolescent diabetes management and mismanagement. ***Diabetes Care*** 1999; 18: 77-82.
6. Wysocki T, Taylor A, Hough BS, Linscheid TR, Yeates KO, Naglieri JA. Deviation from developmentally appropriate self-care autonomy. ***Diabetes Care*** 1996; 19: 119-125.
7. Jacobson AM, Hauser ST, Lavori P, Wolfsdorf JI, Herskowitz RD, Milley JE et al. Adherence among children and adolescents with insulin-dependent diabetes mellitus over a four-year longitudinal follow-up: I. The influence of patient coping and adjustment. ***J Pediatr Psychol*** 1990; 15: 511-526.
8. Follansbee DS. Assuming responsibility for diabetes management: what age? what price? ***Diabetes Educ*** 1989; 15: 347-352.
9. Kovacs M, Goldston D, Obrosky DS, lyengar S. Prevalence and predictors of pervasive noncompliance with medical treatment among youths with insulin-dependent diabetes mellitus. ***J Am Acad Child Adolesc Psychiatry*** 1992; 31: 1112-1119.
10. Kovacs M, lyengar S, Goldston D, Stewart J, Obrosky DS, Marsh J. Psychological functioning of children with insulin-dependent diabetes mellitus: a longitudinal study. ***J Pediatr Psychol*** 1990; 15: 619-632.