Original Article

Efficacy of Thrice-daily versus Twice-daily Insulin Regimens on Glycohemoglobin (Hb A1c) in Type 1 Diabetes Mellitus: A Randomized Controlled Trial

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Abstract

Objectives: To improve glycemic control and prevent late complications, the patient and diabetes team need to adjust insulin therapy. The aim of this study is to evaluate the efficacy of thrice-daily versus twice-daily insulin regimens on HbA1c for type 1 diabetes mellitus by a randomized controlled trial in Hamedan, west of Iran.

Methods: The study included 125 patients under 19 years of age with type 1 diabetes mellitus over a 3- month period. All patients with glycohemoglobin (HbA1c) ≥8% were followed prospectively and randomized into two trial and control groups. The control group received conventional two insulin injections per day: a mixture of short-acting (regular) + intermediated acting (NPH) insulins pre-breakfast (twice daily), and the trial group was treated by an extra dose of regular insulin before lunch (three times daily). Main outcome measure was HbA1c at baseline and at the end of 3 months. The mean blood glucose level and number of hypoglycemia were recorded. All patients underwent monthly intervals follow up for assessing their home blood glucose records and insulin adjustment.

Results: Overall, 100 patients completed the study protocol. 52% were females, mean ± SD of age of 12.91 ± 3.9 years. There were no significant differences in baseline characteristics including age, gender, pubertal stage, adherence to diet, duration of disease and total daily insulin dose ($p>0.05$). There was a significant decrease individually in both groups in HbA1c level ($p<0.05$), but there was no significant difference in HbA1c reduction in patients on twice-daily insulin injections and those on thrice-daily insulin injection groups (1.12 ± 2.12 and 0.98 ± 2.1% respectively, $p>0.05$).

Conclusion: Compared with twice daily insulin, a therapeutic regimen involving the addition of one dose regular insulin before lunch caused no significant change in the overall glycemic control of patients with type 1 diabetes mellitus. Our results emphasize that further efforts for near normoglycemia should be focused upon education of patients in terms of frequent outpatient visits, more blood glucose monitoring and attention to insulin adjustments

Key words: HbA1C, insulin, Type 1 diabetes mellitus.

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Introduction

The optimal glycemic control is a key component in the treatment of diabetes mellitus. Long term studies indicate that good metabolic control delays the onset and slows down the progression of microvascular complications.[1] Diabetes Control and Complications Trial (DCCT) confirmed that near normal glycohemoglobin (HbA1c) prevents the development of complications or delays their progressions.[2]

Recommendations therefore issue that youths with diabetes should be treated with intensive therapy to normalize glycemic control as early as possible.[3] Achieving optimal glycemic control is especially challenging in patients with type 1 diabetes mellitus (T1DM). Intensive therapy involves multiple daily injections of insulin or insulin pump therapy, as well as other essential components of diabetes care, such as self- monitoring of blood glucose.[4,5] In multiple daily insulin injection regimens, the use of rapid acting analogs, rather than regular insulin therapy is associated with improvements in both postprandial glycemia and HbA1c concentration.[6,7] On the other hand, treatment costs with rapid acting analogs are expensive and sometimes they are also not available. For these reasons, diabetic children sometimes may need an extra dosage of regular insulin before lunch for intensifying treatment. To recommend this, clarity is needed with respect to the effects of adding a dose of insulin before lunch treatment. To that aim, we systematically reviewed the accessible impact on the effects of extra dosage of insulin before lunch on blood glucose control. By our knowledge, limited researchers have investigated the effect of three times daily insulin dose versus twice regimens on HbA1c on type 1 diabetic recently.[8] Therefore, in this prospective randomized controlled trial, we investigate whether the addition of insulin regular pre-lunch is superior to that of a conventional two-injection therapy on glycemic control of type 1 diabetic patients.

Methods

This prospective randomized clinical trail was conducted in Ekbatan Hospital, Hamedan University of Medical Sciences of Iran in 2004. The primary efficacy endpoint was to compare the change in HbA1c from baseline to endpoint (3months). The

major inclusion criteria were; type 1 diabetic patients ≤19 yrs with duration of diabetes for at least 1 year and baseline HbA1c ³ 8% who were being followed at the diabetes outpatient clinic. To be included in the study, subjects were also required to have blood glucose meter for self monitoring of their blood glucose.

Patients were excluded if they were taking any other medication, had other diseases, refused treatment or failed for follow-up. In terms of ethical considerations; patients and their parents gave their informed consent and the protocol was approved by the local ethics committee and research of Hamedan University of Medical Sciences, in 2004. All diabetic patients were already on conventional insulin regimen and receiving two insulin injections per day. In this plan, two thirds of the daily total dose was given before breakfast and one third was given before evening meal. Each injection consisted of intermediate and short acting insulins (NPH and Regular respectively) in proportions of 2:1. At the onset of diabetes, the total daily insulin varies from 0.5-1.0 Unit/kg. Adjustments in the dose of insulin are made in relation to the pattern of blood glucose values monitored before each meal.

A total of 125 patients withT1DM were enrolled in the study. At entry into the study; mean age, gender, diabetes duration and total daily insulin dose in both groups were comparable. The yearly frequency visits of the studied patients was 3.8 ± 2.0 times. Diet, physical activity, correct injection in different sites were similar before and after the study.

The patients were trained properly for frequent contact and more home blood glucose monitoring. The primary endpoint of our study was HbA1C. Subjects were randomly divided into two groups; trial and control groups. The control group received conventional insulin regimen: a mixture of short-acting (regular) + intermediate (NPH) insulins pre-breakfast and before evening meal (twice daily), and the trial group was treated by three daily injections regimen: mixture of regular + NPH insulins pre-breakfast, an extra dose of 0.2 Unit/kg regular insulin before lunch and mixture of regular + NPH insulin before supper (three times daily).

All patients were seen at monthly intervals during the study for evaluation of their blood glucose records. HbAlc was measured at baseline and at the end of the study. HbA1c was measured using the DCA

2000 Analyzer (Bayer, Tarrytown, NY). Meanwhile, the mean of self-monitoring and monthly serum glucose, hypoglycemic attack and occurrence of diabetic ketoacidosis were recorded. The data was manually extracted and displayed in a descriptive manner.

Statistical analysis: Chi square test and t- test or paired t test were used for non-parametric and parametric variables respectively using SPSS 11 software. A p-value less than 0.05 was defined as statistically significant.

Results

A total 100/125 subjects completed the study protocol. Nine patients from the control group and 16 of the study group refused the allocated regimen and dropped out of the study. 50 patients were randomly assigned to trial (Thrice-daily insulin injection) and 50 were enrolled into the control group (twice-daily insulin injections). The clinical characteristics of each group are summarized in Table 1. HbA1c values were similar in both study groups at baseline. Meanwhile the total daily insulin intake increased similarly in both the trial and the control groups.

In both groups, the mean HAb1c decreased significantly after three months ($p<0.05$) but the reduction of HbA1c at the end of 3 months was not different between the two insulin regimens (1.12 ± 2.12 and 0.98 ± 2.1% respectively), ($p>0.05$). (Table 2)

The mean blood glucose levels after the study were 241.5 ± 78.8 mg/dL and 211.3 ± 49.4 mg/dL in control and trial groups respectively, ($p=0.14$), the difference was not significant ($p>0.05$). Hypoglycemic (defined as blood glucose <45mg/dL) occurred in 10% of the patients in both groups, but the difference was not significant, ($p>0.05$). (Table 1).

Table 1: Patients' Characteristics of Control and Trail groups

Parameter	Daily insulin Regimen		
	Twice-daily	Thrice-daily	p value
Sex			
female	24 (48%)	28 (56%)	*p=0.42
male	26 (52%)	22 (44%)	
Age (year)	11.9 ± 4.3	14.3 ± 3	**p=0.056
Duration of diabetes mellitus(year)	2.97 ± 2.9	4.7 ± 3.3	**p=0.72
Blood glucose after treatment (mg/dL)	241.5 ± 78.8	211.3 ± 49.4	**p=0.14
Hypoglycemia	4 (8%)	6 (12%)	p=0.34

*Chi-square,**t-test*

Control group (n=46) and Trail group (n=46)

Data presented as No.(%) or mean ±SD where appropriate.

Table 2: Comparisons of the HbA1c of the control and trial groups

HbA1c (%)	Daily insulin regimen		
	Twice-daily	Thrice-daily	* p value
Baseline	11.21 ± 2.46	10.64 ± 1.66	p=0.032
After study	10.23 ± 2.47	9.51 ± 1.94	p=0.043
Decrease in HbA1c	0.98 ± 2.1	1.12 ± 2.12	p=0.82

**t-test*

Data is presented as mean ±SD

Discussion

HbA1C has been recognized as the gold standard for monitoring blood glucose control.[9] The most widely recommended strategy for treating of T1 DM patients is conventional insulin regimen twice daily; a mixture of short-acting (regular) + intermediate

(NPH) insulins pre-breakfast and pre supper in the region of Iran.

The main purpose of this study was to investigate the efficacy of three-times daily insulin regimen on mean HbA1c of type 1 diabetic children and adolescents. This was done by comparing twice daily versus three times daily insulin regimen on patients who participated in the study.

The primary analysis showed that in this group of patients, improved metabolic control was not achieved with three times daily insulin regimen. This can probably be explained by the fact that the starting HbA1c was lower in thrice-daily injections than twice-daily injection group. In some previous studies, other authors have also reported similar results. Hinde and Johnston demonstrated that three injections of insulin caused no significant reductions in HbAlc level in adolescence.[8] Also, Dorchy et al. reported that in comparison with the two daily insulin in children, four injections did not significantly reduce the mean HbA1c of adolescents.[10] Mortensen et al. during a 2-year period were faced with deterioration in metabolic control of diabetic patients despite the use of multiple injection regimens. They claimed that the possible reasons for deterioration of HbA1c could be attributed to the increased body mass index in all the study groups.[11] In a cross-sectional study involving 22 pediatric departments, Mortensen et al. concluded that in spite of tendency towards intensive attention, the goal of near normoglycemia was achieved in only a few.[12] Some studies have failed to support our findings. Bougnères et al. showed improved metabolic control in adolescents with T1DM who had previously failed to respond to two insulin injections a day.[13]

An important finding of the current study is that the similar reductions in HbA1c occurred in both the trial and the control group at the study endpoint. Since, the studied patients were asked to perform in average, four times blood glucose measurements per week and were asked to keep in contact for insulin dosage adjustment between monthly interval visits, and all did so therefore, the reduction of HbA1c could be attributed to the intensive medical attention including frequent contact, more outpatient visits and increased frequency of home blood glucose monitoring. This highlights the need for intensive education of the patients and their families. Some reports have shown that increased frequency of home blood glucose monitoring, results in significant improvements in glycemic control.[10,14,15] This finding is in contrast to the results by Worth et al. who reported that home blood glucose monitoring did not lead to a significant improvement in glycemic control of 46 diabetic patients.[16]

Hypoglycemia is a frequent and sometimes dangerous acute complication of T1DM. There were no differences encountered in rates of hypoglycemia between the control and trial groups. Similar findings were reported by other workers.[17]

The study limitations include the fact that the study was not double blinded according to the procedure. Also, the duration of the study was short coupled with a small sample size of subjects. Thus further research should be conducted with larger sample size and longer follow up periods. In addition, the result of this modest intensification in insulin treatment was not sufficiently powered to be extrapolated to the general clinical setting. Therefore, it warrants compaction with results of previously reported findings.

Conclusion

The overall glycemic control in patients using three-times daily insulin regimen was similar with conventional two-injection therapy. Twice-daily insulin administration is the most simple and cost- effective regimen. Our study suggests that frequent follow up, regular outpatient visits, more blood glucose monitoring and attention to insulin adjustment are fundamentally important for improving glycemic control. Overall, glycemic control, frequency of hypoglycemic events, and total insulin dose were not different between the two groups.

Acknowledgements

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