A Randomized Clinical Trial of Insulin Glargine and Aspart, Compared to NPH and Regular Insulin in Children with Type 1 Diabetes Mellitus

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Abstract

Objective: Appropriate treatment of patients with Type 1 diabetes mellitus (T1DM) is necessary to avoid further complications. This study was performed to compare the efficacy of insulin Glargine and Aspart with NPH insulin and regular insulin regimen in a group of children with T1DM.

Methods: Forty patients with T1DM were enrolled in this study. During run-in, all subjects were treated with conventional therapy consisting of twice-daily NPH and thrice-daily regular. Following randomization, 20 subjects received Glargine and Aspart and 20 subjects received NPH and Regular insulin.

Findings: Mean HbA1c was 8.8% and 8.6% at first and 8.4% and 8.2% at the end of study for subjects randomized initially to Glargine and Aspart and for those randomized to NPH and Regular, respectively (*P*>0.05). Mean fasting blood glucose (FBS) of the subjects randomized initially to Glargine and Aspart was 217±101 mg/dL, with no significant difference to 196±75 mg/dL for those randomized to NPH and Regular (*P*=0.48). This was also true at the end of the study. The difference in total cholesterol and triglyceride between the two groups in the beginning of study and at the end did not show any significance.

Conclusion: The current study showed no significant difference in glycemic control [Glycated hemoglobin (HbA1c) and FBS] and lipid profile (total cholesterol and triglyceride) between two regimes.

Introduction

Type 1 diabetes mellitus (T1DM), also known as insulin dependent or juvenile diabetes, is a form of diabetes mellitus resulting from autoimmune destruction of insulin-producing pancreatic islet β cells[1]. The incidence of T1DM has increased rapidly over recent decades, particularly in young children[2]. It has been persuasively demonstrated that better metabolic control retards or prevents the onset and/or progression of long-term diabetic complications[3,4]. However, tight glycemic control is typically accompanied by increased risk of hypoglycemia; a compromise is needed for optimal glycemic control. At present, this goal is practical with physiological models of insulin replacement therapy.

Several issues such as adjustment in timing of insulin administered as well as dosage of insulin requirement variability[5], diversity in insulin

pharmacokinetic and variable absorption due to difference in site of injection[6] make it difficult for type 1 diabetic patients to maintain long-term near-normoglycemia. Parenthetically, good metabolic control can be achieved by daily self-monitoring of blood glucose (SMBG), regular Glycated hemoglobin (HbA1c) measurements and multiple daily insulin injections.

Since T1DM commonly affects subjects within the first 15 years of life[7], cooperation of the diabetic children in their metabolic management is of great importance; thus education and psychological therapy should be delivered by specialists[8].

Recently, recombinant DNA technology has led to synthesis of short-acting human insulin analogs such as Lispro and Aspart and long-acting insulin such as Glargine[9]. Insulin Glargine is a long-acting insulin analog that mimics normal basal insulin secretion without pronounced peaks[10]. Insulin Aspart, a 30% soluble, 70% intermediate-acting protamine-bound rapid-acting insulin, is often used with Glargine[11].

Numerous studies previously compared Glargine and Aspart with multiple daily injections of NPH and Regular insulin in T1DM patients. Several studies have revealed better patients' satisfaction[10], less frequency in hypoglycemic events[12,13] and superior glycemic control[14] with Glargine versus NPH insulin in T1DM. Furthermore, recent studies have shown more effective glycemic control with insulin Glargine mixed with a rapid-acting insulin analog such as Aspart as compared to the standard (NPH and Regular) therapy in T1DM[10,15].

The aim of the current study was to compare the efficacy of insulin Glargine and Aspart with insulin NPH and Regular regime in T1DM children who were well educated regarding insulin therapy. In addition, this study assesses the quality of life and satisfaction of patients treated with rDNA recombinant insulin.

Subjects and Methods

Setting

The study was a clinical trial held in 2012 on pediatric patients who were referred to outpatient clinic of endocrinology and metabolism department of the Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of Tehran University of Medical Sciences. Written informed consent was obtained from all subjects. Recruitment took place between January 2011 and January 2012. This study was registered in the Iranian Registry of Clinical Trials (IRCT201203079224N1).

Subjects with type 1 diabetes were recruited from a single specialist outpatient clinic. The inclusion criteria were age between 6 and 10 years, type 1 diabetes on insulin for at least 6 months, body mass index less than 90% percentile, baseline HbA1c 6–11%, and ability and willingness to perform self-blood-glucose monitoring.

Diagnosis of diabetes was made, based on fasting blood glucose (FBS) ≥126 mg/dl or random BS ≥200 in the presence of polyuria and polydipsia.

Patient Enrollment

Subjects completed a 4-week run-in period during which they received equal regime of NPH Insulin and Regular Insulin. Subsequently, they were allocated to two groups. Allocation was based on opening consecutively numbered sealed envelopes in which the name of the basal insulin had previously been randomly inserted (balanced block method).

Group one received Glargine Insulin once daily or twice at bedtime accompanied by thrice-daily pre-prandial insulin Aspart. Since insulin dosage adjustment was based on patient's bodyweight, a number of patients in group 1 who received less than 20 insulin units received Glargine twice daily. Group two received twice-daily NPH insulin accompanied by thrice-daily Regular Insulin approximately 30 minutes before meals.

The Lantus Pen injection was used to administer insulin Glargine and the Novo Rapid Pen was used to administer insulin Aspart and NPH. The initial dosage of insulin was prescribed based on weight and age of patients. NPH dose reduction of 20–30% was made, when transitioning from two-daily NPH insulin to insulin Glargine.

Visits took place at screening (visit 1), 1 week after screening (visit 2), baseline (visit 3) and then every 4 weeks until the end of study (visits 4-9). Telephone contact was made to advise changes in insulin dosage every two weeks until the end of the study. All the patients were educated regarding nutrition, physical exercise and self-monitoring blood glucose. It was proposed that blood glucose be measured prior to injecting and 2 hours after the start of a meal. The subject was advised about symptoms of hypoglycemia and educated to record the following information in a diary: date and time of episode, time of last injection and last meal prior to episode, type of insulin and blood glucose value at the time of episode.

Hypoglycemia was defined as a blood glucose concentration of <70 mg/dL[16] and hyperglycemia as blood glucose >150 mg/dL. Blood samples for HbA1c, FBS and lipid profile were taken at visit 1 (screening), and at visits 6 and 9. Lipid profile was measured only at visits 3 and 9. Weight was also recorded at these visits.

The data were collected and analyzed after 24 weeks.

Statistical analysis

Quantitative data were described by mean difference±S.D and Qualitative data were described by relative frequency. For comparing the quantitative data within groups paired t-test and between groups independent t-test was used.

The data on HbA1c were analyzed using mixed models analysis of variance with the subject effect as random. The data on the total number of hypoglycemic events were analyzed using generalized linear models fitting a Poisson distribution. Data were presented as mean± standard error of mean. *P* values of less than 0.05 were considered statistically significant. Secondary endpoints were FBS, weight, fasting lipids during the last 12 weeks of each treatment period.

Findings

Characteristics of study population

A total of 40 subjects with type 1 diabetes were recruited. Baseline characteristics are shown in Table 1. During run-in, all subjects were treated with conventional therapy consisting of twice-daily NPH and thrice-daily Regular. Following randomization, 20 subjects received Glargine and Aspart and 20 subjects received NPH and Regular insulin.

HbA1c

At the beginning of the first period, mean HbA1c was 8.8% for subjects randomized initially to Glargine and Aspart and 8.6% for those randomized to NPH and Regular. At the end of the study, mean HbA1c was 8.4% with Glargine and Aspart as compared to 8.2% with NPH and Regular. The difference between two groups was not significant (*P*=0.7).

FBS

At the beginning of the first period, mean FBS was 217±101 mg/dL for subjects randomized initially to Glargine and Aspart and 196±75 mg/dL for those randomized to NPH and Regular (*P*=0.5). At the end of the study, mean FBS was 169±55 mg/dL with Glargine and Aspart as compared to 173±2 mg/dL with NPH and regular (*P*=0.4).

Table 1: Baseline characteristics of study population

Characteristics	Group 1 (Glargine, Asp) (n=20)	Group 2 (NPH, Reg) (n=20)	*P.* value
Mean age (year)	8.1 (1.1)	8.6 (1.5)	0.2
Duration of diabetes	9.3 (16)	18 (31)	0.4
BMI (kg/m²)	15.9 (2.3)	17.8 (1.8)	0.1
HbA1c (%)	8.8 (1.4)	8.6 (1.4)	0.7
FBS (mg/dL)	217 (101)	196 (75)	0.5
BS (After 1m Run-in)	229 (50)	197 (35)	0.5
Cholesterol (mg/dL)	140.7 (33.5)	146.5 (30.2)	0.6
Triglyceride (mg/dL)	77.2 (28.8)	79.7 (23.4)	0.8

Hypoglycemia

The severe hypoglycemic attacks, which could lead to seizures or other symptoms, did not happen during 24 weeks of treatment with NPH, Regular and Glargine, Aspart regiments. The number of nocturnal hypoglycemic during treatment with Glargine and Aspart clearly reduced, but the difference was not significant (P=0.39). The overall frequency of hypoglycemia during treatment in both groups was decreased significantly (Before treatment with Glargine and Aspart: 4 episodes of moderate hypoglycemia in 3 patients and 2 episodes in 2 patients in Group 1, while 3 episodes in 5 patients in Group 2; after treatment with Glargine and Aspart: 1 episode in 2 patients in postprandial state in Group 1 and 2 episodes in 2 patients and 1 episode in 3 patients in Group 2).

Lipid profile

The difference in total cholesterol and triglyceride between two the groups in the beginning of study and at the end did not show any significance.

At the beginning of the first period, mean cholesterol was 140.7±33.5 mg/dL in group 1 and 146.5±30.2 mg/dL in group 2. At the end of the study, cholesterol changed to 141.9±38.5 mg/dL in group and 141.9±28.6 mg/dL in group 2 (P=1). Mean triglyceride was 77.2±28.8 mg/dL in group 1 and 79.7±23.4 mg/dL in group 2. At the end of the study, triglyceride altered to 76.3±21.9 mg/dL in group 1 and 85.2±35 mg/dL in group 2 (P=0.36). In the current study, weight gain in both groups did not differ significantly (P=0.4).

Discussion

In this study, two regimens of Glargine Insulin once daily accompanied by thrice-daily Aspart and twice-daily NPH insulin accompanied by thrice-daily Regular were compared with each other in T1DM children. The current study showed no significant difference in glycemic control (HbA1c and FBS) and lipid profile (total cholesterol and triglyceride) between the two regimes.

HbA1c reduced 0.4% in both groups with the both mentioned regimes. FBS decreased 48 mg/dL in group 1 and 23 mg/dL in group 2. Even though, the reduction of FBS in group 1 was greater than group2, but this difference was not significant. The result of this study is consistent with the study reported by Home et al[17] who has compared insulin Glargine with NPH human insulin in 585 adults with T1DM. In the mentioned study, there was no significant change in HbA1c in both regimes after treatment period of 28 weeks. In this regard another study has investigated the difference between NPH and Glargine insulin by dividing the T1DM patients to three groups: 1. NPH insulin once daily at bedtime with more intensive self monitoring; 2. NPH insulin twice daily; 3. Insulin Glargine once daily[10].

The results of the mentioned study consistent to the current study revealed that either twice daily NPH insulin or Glargine can result in similar glycemic control when combined with meal time insulin Aspart. In this issue, GLASS (Glargine and Aspart) study by Chatterjee et al[18] which was performed on sixty patients with T1DM has indicated a better glycemic control in patients treated with Glargine and Aspart as compared to NPH and Aspart. In GLASS study, HbA1c was with 1.9 lower with Glargine and Aspart than with NPH and Aspart (8.07% versus 8.26%); though, there were no significant differences in hypoglycemia rate, weight or lipid profile between the two regimes.

One of the most important and frequent side-effect of insulin therapy is weight gain[19]. In this regard, a previous study on 196 subjects with T1DM consisting of 98 patients transferred from NPH to insulin Glargine and 98 patients remained on NPH throughout the study has revealed a higher significant weight gain in the NPH group at the end of the study as compared to the Glargine group[20].

Regarding the satisfaction of T1DM patients with different insulin therapy, Witthaus et al assessed 517 participants satisfaction and well-being treated with insulin Glargine and NPH in 28 weeks by Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Well-being Questionnaire (W-BQ)[12]. It has been shown that patients treated with insulin Glargine were more satisfied than the NPH treated patients. However, outcome in DTSQ items were different between two treatment groups; there was no significant difference in W-BQ.

The findings of the current study consistent to Witthaus et al study indicated that the patient's satisfaction is enhanced by Glargine and Aspart in group 1 despite frequent daily injections as compared to NPH and regular group. As well, human recombinant insulin like Aspart and Glargine are more commonly to be used in a pen-like device which simplifies injection. Therefore, T1DM patients would achieve more self-confidence by injecting their own insulin in early adolescent.

This issue would become of great importance particularly in school year since there would be no need of parents presence for insulin injection with screw-thread needles. In this concern, Hansen et al have shown preference of insulin pen in diabetic patients (type 1 or 2) to conventional needles (79% *vs* 21%)[21]. Some other previous observations have shown a better quality of life and glycemic control[22], increased experience of freedom and less dependency[23] and more flexible life[24] in DM patients by insulin-pen treatment.

At the end of the present trial, all the twenty patients treated with Glargine and Aspart were willing to continue their treatment despite the high price of human recombinant insulin.

Regarding education and telephone case management, Howe et al have compared three nursing interventions as standard care (SC), an education (ED), or an education plus telephone case management (ED+TCM) on glycemic control in T1DM children[25].

The study has concluded no significant change in HbA1c among three groups but has shown a significant improvement in trend toward diabetic care in ED+TCM group. The adherence of patients in ED+TCM group to diabetic care and treatment may lead to following glycemic control improvement.

In the present study, behavioral training consisted of insulin adjustment dosage based on weight and nutrition, diet modification and self-monitoring blood glucose was applied to patients of both groups. Telephone contact was made to follow-up changes in insulin dosage, patient's blood glucose and episodes of hypoglycemia every two weeks in NPH and Regular group and every 48 hours in Glargine and Aspart group. The patients were oriented for a better glycemic control by telephone contacts and serial visits. All through the study, improvement in glycemic control was noticed in both groups.

Patients and their parents were more satisfied due to ongoing follow-up and being involved in diabetic management program. The constant follow-up reduced the patients stress and led to better spirit for continuing their treatment. One of the main limitations of this study was the small sample size of enrolled cases. Further studies with large number of patients are suggested.

Conclusion

In the current study, there was no significant difference regarding glycemic control, hypo-glycemic episodes and lipid profile between two groups; even though it has shown that new DNA recombinant insulins are more feasible to use. In addition, the study emphasized the importance of ongoing educational programs and follow-up regardless of type of insulin injected.

Authors' Contribution

P. Rostami: Data collection, Interpretation of data
A. Setoodeh: Concept/design, Interpretation of data and Study supervision
A. Rabbani: Concept/design, Study supervision and Fund raising
M. Nakhaei-Moghadam: Data collection
F. Najmi: Writing the article
N. Rezaei: Article writing supervision
All authors approved final version of the paper.

Conflict of Interest: None

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