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Efficacy and Safety of Insulin Glargine in Type 2 Diabetic Patients with Renal Failure

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Abstract

Aim and Background: In patients with type 2 diabetes mellitus complicated with renal failure achieving good glucose control and reduction of risk of hypoglycemia should be balanced. The aim of this study was to determine the safety and efficacy of insulin glargine in type 2 diabetic patients with diabetic nephropathy.

Methods: A total of 89 subjects with type 2 diabetes (mean age 62.9 ± 10.7 and diabetes duration 13.9 ± 7.6 years) who had diabetic nephropathy (mean Glomerular Filtration Rate [GFR] 34.1 ± 11.5 ml/min) were included in the study. Patients who were not optimally controlled or experienced frequent hypoglycemia on Oral Antidiabetic Drugs (OAD) or NPH insulin received insulin glargine at bedtime. The starting dose was 0.1 unit/Kg and adjusted to obtain target fasting blood glucose (5-7.2 mmol/l). The medical records were obtained before and 2 and 4 months after beginning insulin glargine.

Results: At the end of four month treatment period, significant reduction in glycated hemoglobin (HbA1c) was observed (from 8.4% ± 1.6 to 7.7% ± 1.2) (p<0.001).

The treatments were associated with significant reduction in fasting glucose levels (from 159.7 ± 67 to 119.4 ± 28.4mg/dl) (p<0.001). Patients’ Body Mass Index (BMI) did not increase at the end of study (26.2 ± 3.9 and 26.2 ± 3.8 kg/m²) (p=0.96). Mild symptomatic hypoglycemia was seen in 12.5% of subjects. No other side effects were noted throughout the study.

Conclusion: Insulin glargine improved HbA1c at short-term and proved to be safe and well tolerated in type 2 diabetic patients with diabetic nephropathy.

Keywords: Insulin glargine; Diabetic nephropathy; Hypoglycemia

Introduction

The increasing prevalence, variable pathogenesis, progressive natural history, and complications of Type 2 Diabetes Mellitus (T2DM) emphasize the urgent need for new treatment strategies [1,2]. T2DM is a metabolic disease that is diagnosed on the basis of sustained hyperglycemia. Patients with T2DM are at increased risk of serious health problems, including cardiovascular disease, blindness, renal failure, orthopedic, and mental disorders [3-5]. Diabetic nephropathy occurs in almost 40% of patients with diabetes and is single leading cause of end-stage renal diseases. Large studies have shown that one third of the patients on hemodialysis or renal transplant recipients are diabetics [6]. Moreover patients with diabetic nephropathy, especially with type 2 diabetes, have a high cardiovascular risk. Once diabetic nephropathy is established and renal failure has started, specialists should consider what the blood glucose objectives are for the patient and which drugs should be chosen to achieve them [7] to reduce microvascular and macrovascular complications [8].

Ideal insulin therapies in diabetic patients with advanced renal failure are difficult to establish given the lack of pharmacokinetic studies for the various types of insulin in patients with different degrees of renal insufficiency [9,10]. Avoidance of long-acting insulin preparations has been recommended in patients with advanced renal failure by some authors [11], while others support the use of such preparations [12].

The long-acting insulin analogs have relatively flat pharmacokinetic profiles and a longer duration of action [13]. Insulin glargine has been reported as safe and effective in improving glycemic control in severe T2DM patients [14]. It provides an effective basal insulin supply when administered once daily in patients with type 2 diabetes [15,16] and reduces the risk of nocturnal hypoglycemia compared with NPH insulin, with at least equivalent glycemic control in type 2 diabetes [14,17]. Although insulin analogues are commonly prescribed for the management of diabetes mellitus, there is uncertainty regarding their optimal use especially in complicated patients [5]. This study aimed to determine the safety and efficacy of insulin glargine in type 2 diabetic patients with diabetic nephropathy.

Materials and Methods

This pilot multi-center clinical trial was conducted in the diabetes clinic of 4 medical centers including Tehran, Tabriz, Ghazvin and Kerman Universities on “patients with type 2 diabetes mellitus complicated with renal failure” since May-2010 to April-2011.

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A total of 89 patients with type 2 diabetes mellitus, aged 40 to 80 years, and creatinine clearance less than 50 ml/min (based on Cockroft-Gault formula) were included in the study [18]. Subjects were excluded for any of the following criteria: patients with hepatic failure, those undergoing hemodialysis or peritoneal dialysis, patients with type 1 diabetes mellitus, and pregnancy.

The study was confirmed by ethic committee of Tabriz University of Medical Sciences and all enrolled patients gave written informed consent before participation. Entry criteria included those who were either not optimally controlled on OAD or had frequent hypoglycemic episodes on NPH insulin received bedtime glargine 0.1 u/Kg. Patients were instructed on proper self-monitoring technique and in the first step using the dose titration schedule target Fasting Blood Sugar (FBS) level was set to be 90-130 mg/dl. The insulin glargine dose was titrated every three days according to self-monitored fasting plasma glucose levels by increasing 2 units every 3 days to meet target values.

In the next step Pre-Prandial (PP) Blood Sugar (BS) was checked twice a day (pre-lunch and pre-dinner, 3 times per week) and if necessary (BS>140), regular insulin was administered with dose of 0.05 unit/kg as pre-meal and was increased until the pre-prandial BS reached to 100-140 mg/dl. Patients were instructed to measure fasting blood glucose or pre- prandial glucose 6 times per week.

Baseline characteristics of all participants including demographic data were recorded (age, sex, BMI and history of diabetes). Blood samples were checked for FBS, HbA1c, Blood Urea Nitrogen (BUN), Creatinine, sodium (Na), potassium (K), Cholesterol, triglyceride, High Density Lipoprotein (HDL), and Low Density Lipoprotein (LDL). Glucose was measured using "Arkray Glucocard 01 Meter Kit" made in Japan. The method is based on interactions with Glucose Oxidase (GOx) which is standard enzyme for biosensors, it has a relatively higher selectivity for glucose [19]. The Diazyme Direct Enzymatic reagent was used for measurement of glycated hemoglobin, and the measured variable was expressed as %HbA1c.

Minor hypoglycemia was defined as plasma glucose less than 3.1 mmol/L and major hypoglycemia was determined by hypoglycemia requiring third-party assistance [20].

The medical records were obtained three times during the study: first at baseline and then two and four months after administration of insulin glargine. All patients were visited weekly during which any episode of hypoglycaemia (minor or major, if present) was recorded. All baseline laboratory tests were repeated at the end of fourth month.

Statistical analysis

The obtained data were analysed by SPSS-16 statistical Software (SPSS Science, Chicago, IL). The paired t-test and the Repeated Measurement of ANOVA test were used to compare the patient’s variables during the study before and after treatment. The P-values less than 0.05 were considered significant.

Results

A total of 89 subjects (54 male and 35 female) who had diabetic nephropathy (mean GFR 34.1 ± 11.5 ml/min) were included in the study.

The mean age of the patients and the mean duration of disease were 62.9 ± 10.7 and 13.9 ± 7.6 years, respectively.

Nearly half of the participants were taking sulfonylurea, 20% used metformin and other OADs were used in 10% of patients. Forty five percent of them had been treated by human insulin and 6.6% were on insulin plus OAD. Long term complications including retinopathy (58.7%), neuropathy (59.3%), Coronary Artery Disease (CAD) (30.4%), Cerebral Vascular Disease CVD (4.3%) and Peripheral Vascular Disease (PVD) (2.2%), were detected at baseline. The prevalence of chronic complications did not change during the study period (p>0.05). Table 1 shows the patients’ characteristics at the baseline and end of the study period.

At the end of four-month treatment period, significant reduction in HbA1c (p<0.05) and fasting glucose levels (p<0.05) were observed. Also our study showed that the significant increase in patients’ GFR (p=0.04). No increment in body mass index was seen at the end of four-month of therapy (p=0.96). Mild symptomatic hypoglycaemia was seen in 12.5% of subjects. No other side effects were noted throughout the study.

During the first 2 months of the study 6 episodes of minor hypoglycemia and 2 episodes of major hypoglycemia were recorded in the patients receiving combined regular insulin and glargine. At the end of study 4 episodes of minor hypoglycemia and 3 episodes of night time major hypoglycemia were detected in the patients receiving combined regular insulin and glargine.

Totally, regardless of the type of insulin used by patients (glargine with or without regular insulin) hypoglycemic episodes occurred in 12.5% of cases.

At the end of the fourth month, 41% of the patients needed combination of regular insulin and insulin glargine and 59% were using glargine alone.

The mean daily dose of insulin glargine was 19.4 ± 8.2 units/day and the mean of total (regular and glargine) insulin in the subjects of the study was 24.4 ± 12 units/day.

Twelve patients needed short acting insulin with mean dose of 6.4 ± 3.5 units once a day (5 patients in pre-breakfast, 4 patients in pre-lunch and 3 patients in pre-dinner time).

Regular insulin with mean dose of 15 ± 8.6 units was administered in 24 patients twice daily (13 patients in pre-breakfast and pre-dinner, 6 patients in pre-lunch and pre-dinner and 5 patients in pre-breakfast and pre-lunch time).

### Table 1: Comparison of patients variables during the study.

| Variable | Baseline | 4 month later | P- value |
|----------|----------|---------------|----------|
| BMI(kg/m²) | 26.2±3.9 | 26.2±3.8 | 0.96 |
| Systolic BP (mmHg) | 137.8±19.8 | 137.8±20.4 | 0.49 |
| Diastolic BP (mmHg) | 82.4±10.9 | 82.7±11.2 | 0.78 |
| BUN(mg/dl) | 57.5±27.2 | 56.5±26.2 | 0.77 |
| Creatinine(mg/dl) | 2.3±0.9 | 2.4±1.4 | 0.3 |
| K+(mg/dl) | 4.8±0.6 | 4.7±0.5 | 0.15 |
| Na+(mg/dl) | 139.8±9.4 | 139.7±3.1 | 0.28 |
| GFR(m/min) | 34.1±11.5 | 36.2±14.8 | 0.04 |
| TG(mg/dl) | 181.8±86.7 | 163.4±80.0 | 0.03 |
| Cholesterol(mg/dl) | 177.4±7.6 | 175.4±9.1 | 0.54 |
| LDL(mg/dl) | 98.2±36.4 | 92.4±33.7 | 0.13 |
| HDL(mg/dl) | 41.1±20 | 42.1±10.3 | 0.01 |
| FBS(mg/dl) | 159.7±67 | 119.4±28.4 | 0.0001 |
| HbA1c(%) | 8.4±1.6 | 7.7±1.2 | 0.001 |

Note: BMI: Body Mass Index; BP: Blood Pressure; BUN: Blood Urea Nitrogen; GFR: Glomerular Filtration Rate; K: Potassium; Na: Sodium; TG: Triglyceride; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; FBS: Fasting Blood Sugar; HbA1c: Glycated Hemoglobin
Discussion

In this study, HbA\textsubscript{c} values were found to be significantly reduced in study subject's and regardless of avoiding tight glycemic control, significant increase was seen in GFR. HemoglobinA\textsubscript{c} level is correlated with cardiovascular events in the patients with type 2 diabetes. ACCORD study showed that, as compared with standard therapy, the use of intensive therapy to target normal hemoglobinA\textsubscript{c} levels for 3.5 years increased mortality and did not reduce major cardiovascular events significantly [4]. These findings confirm the harm of intensive glucose lowering in high-risk patients with type 2 diabetes.

We did not use tight control and the patients BMI did not changed during the study period although the duration of our study was very short. Indeed in our study good glycemic control favorably affects lipid profile. These findings were in agreement with the previous studies which showed similar results [21,22].

Rashid et al. in a dose finding cross-sectional study enrolled 88 type 2 patients with diabetes and end stage diabetic nephropathy (stage 5) [23]. They used regular insulin, NPH insulin or pre-mixed NPH and regular insulin in the ratio of 70% and 30%. In their series, mean insulin requirement was 14.8 ± 14.6 units/day and men required more insulin than women (21.0 ± 17.2 vs.13.6 ± 13.0 units). In our patients the mean insulin requirement (regular and glargine) was 24.4 ± 12 units/day and women required more insulin than men (27.76 ± 13.18 vs. 22.11 ± 10.93 units) (p=0.02). Also, the daily dose requirement of insulin glargine was higher in women (22.06 ± 8.7 vs.17.92 ± 7.73). In Rashid et al. study there was a significant correlation between serum creatinine and the total units of insulin required and with increasing serum creatinine levels patients required less insulin. However, in our series, no significant relation could be found between creatinine, GFR and the total units of insulin required (p>0.05). Our result seems to be consistent with results of another conducted study by Rave et al. [24]. In this study he did not find any statistically significant differences in diabetic patients with impaired renal functions as compared to diabetic controls with normal renal functions. They have shown that in contrast to the higher plasma insulin levels, the overall metabolic response to regular insulin was lower in patients with diabetic nephropathy as in diabetic control patients.

Also in our study, using linear regression model, no significant relation could be found between the patients' BMI and the total units of insulin required (r=0.18).

Glargine was equivalent to NPH in terms of glycemic control but had modest advantages in terms of hypoglycemia, especially nocturnal. Glargine appear to have only slight clinical advantages over NPH, but has much higher costs and does not appear to be cost-effective as first-line insulins for type 2 diabetes [25,26]. In clinical trials, a single daily injection of insulin glargine provides glycemic control equivalent to that afforded by NPH insulin [27], but with a lower risk of hypoglycemia [28-30]. Peterson suggested that glargine, provides better glycemic control than NPH insulin without increasing the risk of hypoglycemia [31]. In our study there is no significant increases in patient's weight despite improvement in glycemic control reflects the less frequent hypoglycemia seen with insulin glargine. Indeed poor appetite and nutritional status due to uremia may explain lack of weight gain in the present study. Clinical efficacy and safety profile of insulin analogues are not clearly defined in patients with moderate renal failure and most of the reported studies are case reports [32] or consist small series of diabetic patients on dialysis [33,34].

Pcherer et al. reported the results of their study performed on 20 diabetic (4 type 1 and 16 type 2) patients with end stage renal disease on hemodialysis treated with insulin glargine [35]. In this nine-month study, HbA\textsubscript{c} was reduced 0.9% (p < 0.01), severe hypoglycemic events were not reported and dry weight increased approximately 1.5 kg. In the present study, at the end of four month treatment periods with insulin glargine the significant reduction in HbA\textsubscript{c} (0.7%) and a few hypoglycemic episodes were achieved.

Our short term experience confirmed the safety and efficacy of insulin glargine in type 2 diabetic patients with diabetic nephropathy.

Study Limitations

In this study we followed the patients only for four months. It seems that studies with longer duration and precise monitoring of side effects are required.

In addition we did not compare other long acting insulin analogs with insulin glargine.

Conclusions

Insulin glargine improved HbA\textsubscript{c} at this short-term study and proved to be safe and well tolerated in patients with type 2 diabetes and diabetic nephropathy.

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