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RESEARCH ARTICLE

EFFICACY AND SAFETY OF INSULIN GLARGINE AS BASAL THERAPY IN TYPE 2 DIABETES MELLITUS: EASE STUDY

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is assiocated with increased insulin resistance and an inexorable decline in β-cell function usually requiring intensive treatment to achieve and maintain glycemic control. The aim of the study was to assess the efficacy and safety of insulin glargine (BASALOG®,BIOCON) as a basal regimen in individuals with type 2 diabetes mellitus (T2DM) who are poorly controlled with oral antidiabetic drugs (OADs) and/or other insulins.

Methods: This observational, study included 110 adult individuals with T2DM from PANACEA Hospital, Bengaluru. Baseline glycated hemoglobin (HbA1c) ranged between 7.5% and 9.5% and for whom a basal regimen with insulin glargine was initiated. Two follow-up visits were scheduled at 12 and 24 weeks after initating the treatment. The primary outcome target was HbA1c < 7%. Safety was assessed by the frequency of hypoglycemic episodes.

Results: The target HbA1c level of < 7% was reached by 16% of patients after 3 months of insulin glargine treatment and 36% after 6 months. Mean HbA1c decreased significantly from 9.25±1.07% at baseline to 7.46±0.92% at 6 months ($P < 0.001$). Mean fasting blood glucose also decreased significantly from 247.5 ± 55.6 mg/dL at baseline to 129.7 ± 38.1 mg/dL at 6 months ($P < 0.001$). Approximately 13.6% of patients reported at least one hypoglycemic episode. No adverse events other than hypoglycemia were seen.

Conclusions: This study shows that in a realistic setting, a basal regimen with insulin glargine significantly improves glycemic control in patients with T2DM who are inadequately controlled with OADs or other insulin regimens, Hypoglycaemia incidence and rates were as similar during the early and continued treatment periods across all treatment combinations

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INTRODUCTION

Diabetes been seriously underrated as a global health issue and the human race can no longer ignore "the rise and rise" of type 2 diabetes (Paul, 2017). Tropical countries are experiencing a substantial rise in type 2 diabetes, often undiagnosed or poorly controlled. Diabetes is a risk factor for many infectious diseases, this increase probably adds to the large burden in tropical countries (Reinout van Crevel, 2017). Over the past few decades, many studies have been done to attempt to estimate the prevalence of diabetes in India (Kutty *et al.*, 2000; Zargar *et al.*, 2000; Gupta *et al.*, 2003). Most of these papers published have been small and focused on specific towns, villages, or cities. Since the size and diversity of India's geography, and the heterogeneous nature of the Asian Indian population, estimates obtained from region-specific studies do not accurately replicate the disease burden in the country as a whole. Moreover, these previous studies have been done at different times with various other methods and sampling designs, making it virtually not possible to calculate a national estimate of diabetes prevalence (Anjana *et al.*, 2011). Indian Institute of Public Health stated India has the second largest number of individuals with diabetes at 70 million, next only to China having about 110 million. The number of diabetes patients in India is expected to touch 120 million during the next two decades, due to a variety of reasons. According to the Indian Heart Association, India is projected to be home to 109 million individuals with diabetes by 2035 (Indian Heart Association Why South Asians Facts Web, 2015). A study by the American Diabetes Association reports that India will see the greatest increase in people diagnosed with diabetes by 2030. Diabetes affects individuals of all ages and races. The disease reduces both a person's quality of life and life expectancy and imposes a large economic burden on the health care system and on families. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-

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calorie, low-activity lifestyle by India's growing middle class (Wild, Sarah *et al.,* 2014). Epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population (Mohan *et al.,* 2007). This rapid increase is mostly attributed to lifestyle transitions resulting in obesity and physical inactivity, population aging, and urbanization (Ramachandran *et al.,* 2001). Early feeding may also play a subsequent role in the development of type 2 diabetes in later life (Liu *et al.,* 2000). The main reason of T2DM pandemic is growing prevalence of obesity. The precise mechanism by which obesity leads to insulin resistance and to T2DM is not completely known but it may be related to several biochemical factors such as abnormalities in free fatty acids, adipokines, leptin and other substances (Bennett, 1999; Ginter *et al.,* 2012). Low-fiber diet with a high glycemic index is positively associated with a higher risk of type 2 diabetes mellitus. Huge increase in the number of individuals with diabetes mellitus over recent decades raises questions about early diagnosis, intensive treatment and primary prevention. Insulin and oral antidiabetic agents have improved the prognosis of individuals with diabetes, but vascular complications still remain the main cause of increased morbidity and mortality. Strategies oriented to the prevention of diabetes and its complications are the main goal in the care of diabetic patients (Skrha, 2014). Though, prospective studies have shown that many individuals in routine clinical practice do not achieve good glycemic control (Ringborg *et al.,* 2009; Farouqi *et al.,* 2010; Al-Elq, 2009). International guidelines highlight the importance of early initiation of T2DM therapies, particularly the start of insulin therapy, in individuals who are poorly controlled with other antidiabetic medications, to modify the course of hyperglycemia and to prevent or delay the development of future long-term macrovascular and microvascular complications. Early initiation followed by timely intensification can help reverse glucotoxicity, reduce insulin resistance and preserve beta-cell function for longer than is possible with OADs alone (Nathan *et al.,* 2009). Assessing the use of therapeutic alternatives to standard insulin regimens is extremely essential. In South India, few data are available on the efficacy and safety of insulin therapy in patients with T2DM. The aim of this observational study was to assess the efficacy and safety of basal regimen insulin glargine (BASALOG®, BIOCON) in T2DM patients who were inadequately controlled with oral antidiabetic drug (OAD) therapies or other insulin regimen.

Objectives

The primary objective is to describe the proportion of T2DM patients with HbA1c < 7% after 6 months of realistic treatment with insulin glargine. The secondary objective was to find the number of hypoglycemic events.

Study design

This study was conducted between April 2016 and March 2017. A total of 125 patients with T2DM were enrolled if they fulfilled the following inclusion criteria: adults (male or female) aged ≥ 18 years with uncontrolled T2DM, HbA1c between 7.5% and 9.5% despite antidiabetic treatment in addition to lifestyle and dietary measures conducted for at least 6 months, and basal insulin therapy initiated. All eligible patients gave their signed informed consent to take part in the study. Patients aged < 18 years, those with known hypersensitivity to glargine, pregnant or breastfeeding women were excluded from the study. Taking into account 20% dropout, the calculated sample size was 125 patients. Only patients given basal therapy with insulin glargine were included in the analysis. Patients were treated with insulin glargine (100 IU/mL subcutaneous injection) as per the physician's requirements were included. According insulin glargine is administrated subcutaneously once a day at any time but at the same time each day. The dosage and timing of insulin glargine dose is titrated and individually adjusted to achieve fasting blood glucose (FBG) levels of < 130 mg/dL. Data for each patient were collected by the participating physicians using a standardized performa at each visit. All patients had three visits: an initial inclusion (baseline) visit and two follow-up visits at week 12 and week 24 after inclusion. Total duration of the study for each patient was 6 months. The following data were collected at baseline: age, sex, weight, height, waist circumference, duration of diabetes, previous treatments, duration of insulin therapy, doses of insulin FBG and HbA1c level; and at the two follow-up visits: BMI, HbA1c level, FBG, dose of insulin glargine administered, addition of another insulin dose, oral medications and their doses (if applicable), hypoglycemic events and their characteristics (symptomatic, severely symptomatic, and nocturnal).

Statistical analysis

A descriptive analysis was performed on the socio-demographic, clinical and therapeutic characteristics of the patients. Student's t-test was used to compare qualitative and quantitative variables between baseline and each visit. A P value of < 0.05 was considered statistically significant. SPSS version 17.0 was used for all statistical analyses.

RESULTS

A total of 125 patients were enrolled. Data were available for 110 (88%) of these patients. Mean age was 55.5 ± 10 years, 68 % of the patients were male and mean duration of diabetes was 8.5 ± 6 years (Table 1). Using the WHO body mass index (BMI) classification, 83.4% of patients were overweight or obese.

Table 1. Characteristics of the Study Population at Inclusion

Male/ Female	75/35
Age (years)	55.5 ± 10
Duration of diabetes	8.5 ± 6
Body mass index	
< 25 kg/m^2	18/110(16.1)
25 - 30 kg/m^2	75/110(68)
> 30 kg/m^2	17/110(15.4)
Insulin therapy	
Initiation of insulin glargine	85(77.2%)
Change to insulin glargine	25(22.7%)

All values shown are n (%), or mean ± SD

Antidiabetic treatments

At baseline, 88 patients (80%) were being treated with OADs alone and 22 (20%) were receiving insulin other than insulin glargine (12 on insulin + OADs and 8 on insulin alone). Among the 22 patients receiving insulin, 12 (54.5%) patients were on a basal regimen, 4 (18.1%) were on a basal + prandial regimen and 6 (27.2%) were being treated with premixed insulins. All patients were started on a basal insulin glargine

regimen at a mean dose of 18.6 ± 6.4 IU/day. The treatment changes in these patients over the 6-month follow-up period are shown in Table 2. OAD treatment was changed in 20% of patients at visit 2 and in 10% of patients at visit 3. Insulin glargine doses were changed in 75.5% of patients at visit 2 and in 51% at visit 3. The mean daily dose of insulin glargine was increased significantly (P < 0.001) during follow-up (18.6± 6.4IU at baseline, 22 ± 6.5 IU at visit 2 and 24.4 ± 6.3 IU at visit 3). Short acting insulin was added to the basal regimen in 13.6% of patients at visit 2 and in 8.0% of patients at visit 3 (Table 2).

Table 2. Changes in Antidiabetic Treatments over the 6-Month Study Period

Total number of Oral antidiabetic drugs changes	22/110 (20)	11/110(10)
Sulphonylureas stopped	12/110(10.9)	5/110(4.5)
Biguanides stopped	5/110(4.5)	3/110(2.7)
Insulin glargine		
Dose changed	82/110(75.5)	56/110(51)
Short acting insulin added	15/110(13.6)	9/110(8)

Results are shown as n (%)

Efficacy outcome measures

HbA1c levels after initiation of insulin glargine in insulin-naive patients or continuing/changing insulin therapy to insulin glargine in patients previously treated with insulin is shown in Table 3. Regarding the primary endpoint, 16.3% (18/110) of patients reached the target HbA1c of < 7% after 12 weeks of treatment and 36.3% (40/110) after 24 weeks.

DISCUSSION

This observational study showed the efficacy and safety of insulin glargine in T2DM patients who were inadequately controlled with other antidiabetic treatments and required optimal basal insulin therapy. The results show that, a basal regimen with insulin glargine is associated with a significant reduction in mean HbA1c levels and in mean FBG. After 12 weeks of treatment, 16.3% of patients reached the target HbA1c of < 7% and 36.3% after 24 weeks. Mean HbA1c decreased significantly from 9.25±1.07% to 8.2±1.05% after 12 weeks of treatment with insulin glargine and to 7.46±0.92% after 24 weeks. Overall, mean HbA1c was reduced by 1.79±1.4% from baseline to the last visit at week 26 .A recent real-life study conducted in France (Charbonnel *et al.,* 2010) reported that the mean HbA1c level decreased from 8.3% at baseline to 7.8% a month after the initiation of insulin glargine and to 7.5% at the end of followup (12 months). The proportion of patients with HbA1c < 7% increased from 19.9% to 33.4% after the initiation of insulin glargine in patients previously treated with insulin and from 13.9% to 39.1% in insulin-naive patients. Similar results observed in clinical studies with insulin glargine conducted in other countries, treatment of T2DM patients with insulin glargine for 6 months was associated with a reduction in HbA1c of 1.9±1.2% and a reduction in FBG of 108.1 ± 69.8 mg/dL (Abdelmjid Chraibia, 2015). The safety of insulin glargine has been assessed in several studies in patients with T2DM. In the present study, 13.6% of patients reported hypoglycemic episodes. This compares with 12% hypoglycemic episode seen in Chraibia *et al* study.

Table 3. Efficacy Outcome Measures during the 24-week Study Period

	Inclusion	Week 12	Week 24	P value-W12	Pvalue-W24
HbA1c ≤ 7%	0	18(16.3)	40(36.3)		
HbA1c (%)	9.25± 1.07	8.2± 1.05	7.46±0.92	< 0.001	< 0.001
FBG (mg/dL)	247± 55.6	162.4 ± 47.7	129.7 ± 38.1	< 0.001	< 0.001

Mean HbA1c decreased significantly from 9.25±1.07% to 8.2±1.05% (P < 0.001) after 12 weeks of treatment with insulin glargine and to 7.46±0.92% (P < 0.001) after 24 weeks. Overall, mean HbA1c was reduced by 1.79±1.4% from baseline to the last visit at week 26 (P < 0.001). Mean FBG also decreased significantly from 247+ 55.6mg/dL at baseline to 129.7 ± 38.1 mg/dL at week 26 (P < 0.001), which represented an overall reduction of 118.1 ± 65.3 mg/dL Table 3.

Safety

A total of 110 patients were included in the safety analysis. Twelve patients (10.9%) reported episodes of hypoglycemia between inclusion and visit 2, 15 (13.6%) between visit 2 and visit 3. Nocturnal hypoglycemia episodes were reported by 10 patients respectively at visit 2 and 8 patients respectively at visit 3. Symptomatic hypoglycemia was reported by 13 patients at visit 2 and 15 patients at visit 3.

Three patients reported severe episodes of hypoglycemia at visit 3 but no severe hypoglycemia was reported during visit 2. No adverse event other than hypoglycemia was reported during the study period. The mean body weight of the patients increased significantly from 74.2 ± 9.5 kg at inclusion to 75.7 ± 11.9 kg at visit 3, an increase of 1.5 ± 3.6 kg (P < 0.001).

Insulin glargine treatment is often associated with a minor gain in body weight as well. In conclusion, this study shows the basal insulin regimen with insulin glargine significantly improves glycemic control in patients with T2DM who are poorly controlled with OAD medications or other insulin regimens. An acceptable hypoglycemic episode and weight gain profile seen in insulin glargine regimen.

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