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ABSTRACT:

Present study evaluates efficacy and tolerability of fixed dose combination of Voglibose and Repaglinide in postprandial hyperglycemia (PPHG).A non-randomized, open labeled, non-comparative, multi-centric, study was conducted in 69 Type 2 diabetes mellitus (T2DM) patients, 53 (76.8%) men and 16 (23.2%) women. Each patient was administered a fixed dose combination of voglibose 0.3mg and repaglinide 1mg twice a day, just before each meal for 90 days. Fasting blood glucose (FBG) and postprandial blood glucose (PPBG) levels were measured at baseline (day zero), on day 30 and on day 90. Glycated Haemoglobin (HbA1c) was measured at baseline and on day 90. There was significant reduction in PPBG (31.2%), FBG (31.6%), and HbA1c (10.3%) on day 90 compared to baseline. Therefore fixed dose combination of voglibose 0.3mg and repaglinide 1mg has a considerable impact on PPBG control. This combination was found to be efficacious in controlling PPHG and no cases of hypoglycemia were reported.

Keywords: Diabetes mellitus; Voglibose; Repaglinide; FBG; PPBG; HbA1c.
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INTRODUCTION:

Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. WHO projects that diabetes will be the seventh leading cause of death in 2030 [1]. Largest numbers of diabetic adults among the top 10 countries are in Asian subcontinent. China tops the list with 90 million followed by India which has 61.3 million persons affected by diabetes. The numbers are estimated to rise to 129.7 million and 101.2 million, respectively by 2030 [2].

Type 2 diabetes mellitus (T2DM), which comprise more than 95% of all the diabetic populations, has an insidious onset with a lengthy and latent asymptomatic phase [3, 4]. Prandial regulation of glucose is a multifarious process. The extent and time of the peak

plasma glucose (PG) depends on different type of factors, including the timing, amount and composition of the meal.

In healthy individuals, PG peaks about 60 minutes after the start of a meal, hardly ever exceeds 140 mg/dl, and returns to pre-prandial levels within 2 – 3 hours [5].

Post-prandial hyperglycemia (PPHG) appears to be the rate limiting factor for achieving optimal glycemic control in T2DM. In people with postprandial hyperglycemia, initial insulin release after food is decreased and there is fewer declines in glucagon secretion, resulting in improper glucose production in the liver leading to increased PPBG levels [6].

To accomplish optimal glycemic control, the consensus statement of the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) recommends a patient-centered approach to incorporate individual factors such as lifestyle, cost, motivation, and need to lose weight [7]. Further, the latest guidelines from the International Diabetes Federation recognize the importance of PPBG control in mitigating cardiovascular risks and include strategies for cardiovascular risk reduction as a major focus of therapy [8].

Drugs targeting post-meal hyperglycemia are essential to control the post prandial glucose level. These drugs may be used in combination or as a mono-therapy. Combinations that specifically target PPBG can prove to be a beneficial approach in the management of PPHG.

This study was designed to investigate effectiveness and safety of fixed dose combination of Voglibose and Repaglinide (Prandin) in controlling PPHG in patients with type 2 DM.

METHODOLOGY:

Design and participants

This was a non-randomized, open labeled, non-comparative, multi-centric study to determine the effectiveness and safety of the fixed dose combination of voglibose 0.3mg and repaglinide 1mg twice daily for 90 days. A total of 69 T2DM patients, made up of 53 (76.8%) men and 16 (23.2%) women. The combined mean Age of all the patients was 55.1 ± 1.4 years and their age range was 26 to 81 years. All of them reporting to diabetologist, were screened for FBG and PPBG at baseline (day zero) and those fulfilling the criteria of FBG ≥126 mg/dl (7.0mmol/L) and/or PPBG ≥200 mg/dl (11.1mmol/L) were enrolled in the study. The study was conducted, at outpatient departments of diabetologists in Telangana, Malda and Thiruvananthapuram in India.

Patient characteristics:

Inclusion and Exclusion criteria

Informed consent in the vernacular language was obtained from each of the 69 patients with T2DM included in this study. Eligible patients were already diagnosed to have diabetes (T2DM) assessed as per FBG and PPBG were enrolled. The exclusion criteria included patients with any of the several conditions listed as follows: Subjects with planned surgery during the treatment course or undergone surgery prior to 3 months of enrollment. Patients with Type-1 diabetes, female type-2 diabetes patients who were pregnant or planning to conceive and lactating mothers were excluded from the study.

Assay of glucose and HbA1c:

The level of glucose in blood was assayed by the Glucose Oxidase Peroxidase (GOD-POD) method [9]. The HbA1c level in blood was assayed using the HPLC Biorad Variant II Turbo, National Glycohemoglobin Standardization Program (NGSP) certified [10].

Ethical clearance:

This was a post marketing surveillance study for already marketed formulation of the fixed dose combination of Voglibose & Repaglinide, hence only consent was taken from the patients for sharing their personal details and blood sugar reports.

Statistical Analysis:

All results were expressed as mean ± SEM. Statistical Analysis was assessed using Graph Pad prism 6 and $P < 0.05$ was considered as statistically significant.

RESULTS:

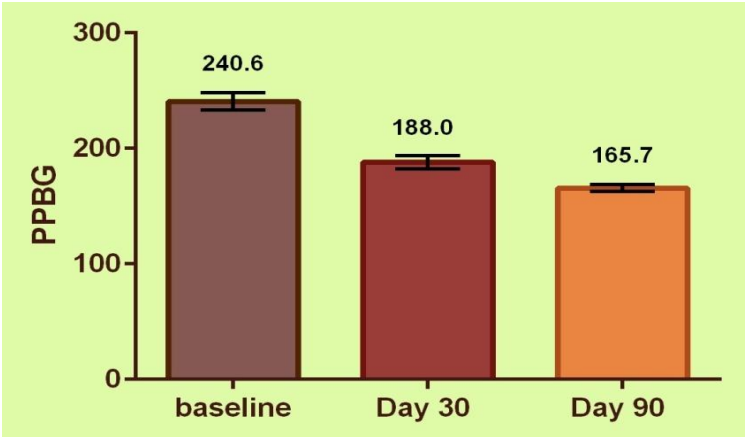
At the end of day 90, data was available for all 69 patients. At day 90 PPBG level was 165.7 ± 2.9 mg/dl; and day 30 level was (188.0 ± 5.864 mg/dl), both were significantly ($P< 0.0001$) lower compared to glucose level at baseline (240.7 ± 7.586 mg/dl) (Figure 1).

Percent (%) reduction in PPBG, FBG and HbA1c from baseline to day 30 and day 90 was statistically significant (Figure 2).

Similar trend was also seen with FBG which was significantly ($P< 0.0001$) reduced from baseline 158.0 ± 5.3 mg/dl to 129.2 ± 3.6 mg/dl at day 30 and 108.1 ± 2.5 mg/dl at day 90 (Figure 3). At the same time HbA1c after day 90 was 7.1 ± 0.13% when compared with 8.0 ± 0.17% at baseline ($P< 0.0001$) (Figure 4).

On 90th day there was no significant change in body weight compared to baseline. In the present study no adverse events including hypoglycemia were reported.

Figure 1: Mean Postprandial blood glucose level (PPBG) (mg/dl) at baseline, at day 30 and at day 90



NB: Divide mg/dl by 18.01 to convert to mmol/L

Figure 2: Percent (%) Reduction in PPBG, FBG and HbA1c from baseline

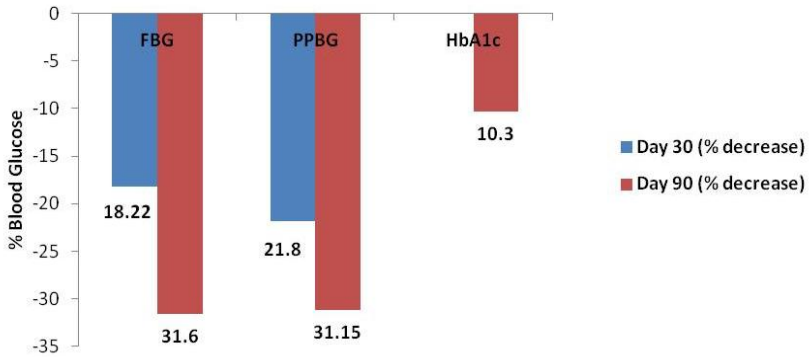


Figure 3: Mean fasting blood glucose levels (FBG) (mg/dl) at baseline, at day 30 and at day 90

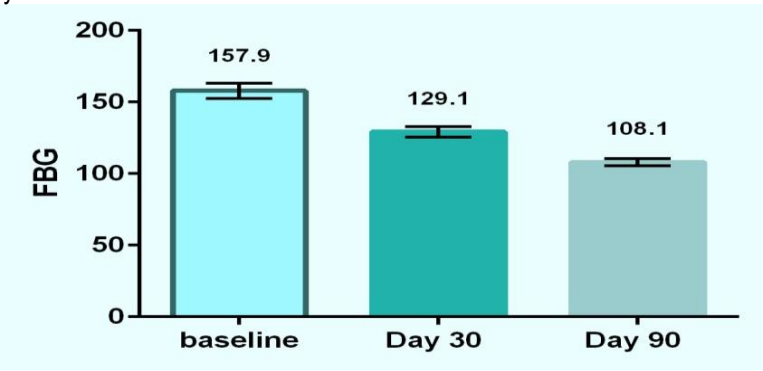
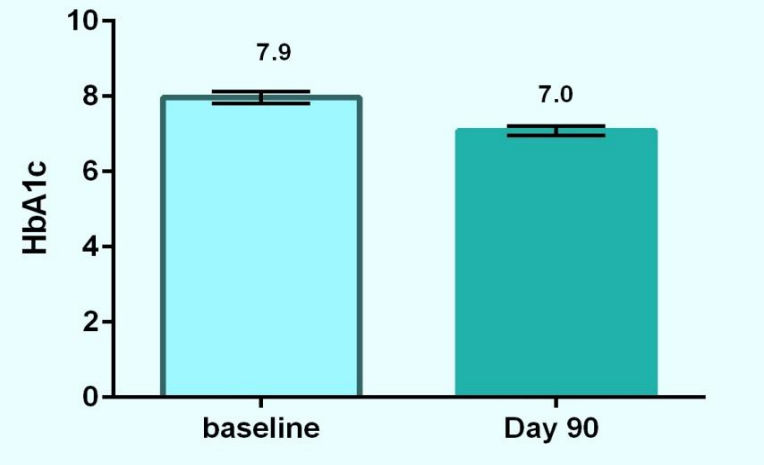


Figure 4: Mean change in percent HbA1c level from baseline to day 90



DISCUSSION:

In the present study effectiveness and safety of fixed dose combination of repaglinide and voglibose was evaluated in 69 T2DM patients. Voglibose is an alpha-Glucosidase inhibitor that delays the absorption as well as digestion of dietary polysaccharides by reversibly inhibiting carbohydrate digestive enzymes like sucrase, maltase, zomaltase; resulting in reduction in PPBG level [11]. At the same time Repaglinide mimics the physiological release of insulin and thus ameliorates PPBG [12].

When voglibose 0.3mg and repaglinide 1mg was combined and administered twice daily for 90 days there was significant reduction in PPBG at the end of 90 days which represents significant effect of combination therapy on PPBG control (Figures 1 and 2).

Fasting hyperglycemia is a phenomenon that has been observed in all individuals with diabetes and may be due to dysregulation of the normal circadian hormonal patterns resulting in increased hepatic glucose output. Normalization of the fasting blood glucose reduces the risk of the complications of diabetes [13].

In this study voglibose combination with repaglinide also has shown significant effect on FBG at the end of 90 days (Figure 3). PPBG contributes more to HbA1c levels than fasting hyperglycemia when HbA1c levels approach target values and, therefore, becomes the rate-limiting factor for achieving optimal glycemic control [14]. This can be interpreted as when PPBG is high or its control is poor it is more likely to get HbA1c above the recommended 6.5% In the present study, when compared to the baseline there was a statistically significant

reduction (P<0.0001) in %HbA1c at the end of 90 days study period (Figure 4).

CONCLUSION:

The fixed dose combination of Voglibose and Repaglinide showed statistically significant reduction in FBG, PPBG and HbA1c over 90 days compared to the baseline. No cases of hypoglycemia were reported during the study period.

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Conflict of Interest: Author declares no conflict of interest.

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