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ABSTRACT:
Anti-diabetic therapy initiated should be directed towards the target, both fasting and as well as postprandial hyperglycaemia. Despite the introduction of new agents efforts for better management of diabetes are disappointing and the control of blood glucose levels remains unsatisfactory. The aim of the present study was to evaluate the safety and efficacy of triple drug fixed dose combination (FDC) of Voglibose, Glimepiride and Metformin in type 2 diabetes mellitus. The study was post marketing surveillance (PMS) non-randomized, open, non-comparative and multi centric study. The above mentioned FDC was administered to 118 type 2 diabetic patients once daily for 3 months. Baseline values were recorded for glycated haemoglobin (HbA1c), fasting plasma glucose (FPG) and post prandial blood glucose/hyperglycaemia (PPHG) level. There was significant decrease in HbA1c value (8.69 ± 1.81 % vs. 6.475± 0.39 %, P<0.0001); FPG (206.5±73.76 mg/dl vs. 112.7 ± 25.73mg/dl, P<0.0001) and PPHG level (244.7 ± 69.95 mg/dl vs. 141.7 ± 22.64 mg/dl, P<0.0001) after 3 month of the treatment from the baseline. The triple drug FDC of Voglibose, Glimepiride and Metformin significantly decreased the HbA1c, FPG and PPHG levels at the end of the treatment. Investigators observed good clinical effectiveness without any adverse effect reported.

Keywords: Blood Glucose, Fasting, Post-prandial, HbA1c, Triple Drug Combination
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INTRODUCTION:

Diabetes mellitus (DM) is an endocrine disorder and one of the most common non-communicable diseases globally. The prevalence of type 2 diabetes across the world has been described as a global pandemic [1]. The prevalence of diabetes is steadily increasing worldwide, particularly in the developing countries like India [2]. India had 32 million diabetics in 2000 and it is expected to increase to 80 million by 2030 [3]. The predominant clinical form of DM is Type 2 DM which accounts for more than 90 % of all the cases and is responsible for developing complications which severely alters the quality

of life and gives an enormous burden on the health care system [4]. The treatment goals in Type 2 DM are the relief of acute symptoms and prevention of long term complications, whilst avoiding hypoglycaemia. Aggressive, tight control of serum glucose reduces risk of micro vascular disease [5].

According to UKPDS 38 (The UK Prospective Diabetes Study), treating other risk factors like dyslipidemia and hypertension has been shown to be effective in reducing macro vascular disease [6].

Dietary and lifestyle modifications form the mainstay of therapy for Type 2 DM [7]. Pharmacological therapy is advocated when treatment goals are not achieved with lifestyle modifications. When the lifestyle modification, diet and exercise fails to maintain the adequate glycaemic control, oral hypoglycaemic agents are introduced as a treatment approach. Several oral anti hyperglycaemic agents are available to optimize the management of Type 2 DM [8]. Despite the introduction of new agents to the armamentarium of hypoglycaemic agents, efforts for better management of diabetes are disappointing and the control of blood glucose levels remains unsatisfactory [9].

For the optimal management of type 2 DM requires a consideration on the relationships between HbA1c, FPG and PPHG (the glucose triad), and how these changes during development and progression of the disease. Early and sustained control of glycaemia remains important in the management of type 2 DM. The contribution of PPHG levels to overall glycaemic control and the role of PPHG targets in disease management are currently debated [1]. However, many patients do not reach the HbA1c targets set according to published guidelines. The landmark UKPDS showed that every reduction of 1% HbA1c reduced the risk of all microvascular and macrovascular chronic complications [10]. Guidelines for good glycaemic control have been agreed upon and a patient is generally considered to have achieved successful disease control when their HbA1C is < 7% [11-12].

To achieve optimal glycaemic control for each patient it is likely to have to consider plasma glucose levels after the overnight fast and after meals as well as the variability of glucose levels. Hence the selection of antidiabetic therapy is important to achieve target goals of both fasting and PPHG.

Glucose triad (HbA1c, FPG and PPHG) impact in the management approaches:

By combination of lifestyle modification and appropriate drug therapy [3] it is doubtful to reach the HbA1c goal [1]. Routine measurement of PPHG levels is not currently recommended or even practical for all patients with type 2 DM. International Diabetes Federation (IDF) guidelines for the management of post meal (post-prandial) glucose states that the goal of diabetes therapy should be to achieve glycaemic status as near to normal as safely possible in all three

measures of glycaemic control, namely HbA1c, FPG and PPHG [13].

FPG and PPHG both contribute to HbA1c. Treatment of both FPG and PPHG should be initiated simultaneously at all levels of HbA1c above agreed levels. Based on hypoglycaemic mechanism of action, they are subdivided into agents that increase insulin secretion like sulfonylureas, meglitinides, GLP-1 (Glucagon-like peptide-1) agonists, DPP-4 (Dipeptidyl peptidase) inhibitor, reduce glucose production like biguanides, increase insulin sensitivity like thiazolidinediones and reduce carbohydrate absorption like α-glucosidase inhibitors. Voglibose is a competitive inhibitor of α - glucosidase enzyme present in the brush border of small intestine. It inhibits the cleavage of complex carbohydrates into simple sugars and inhibits their absorption from small intestine [14]. The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of glimepiride. Glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin [15].

Metformin improves the glucose tolerance in patients with type 2 DM, lowering both the basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [16].

Current recommendations of the American Diabetes Association include a trial of diet and exercise as first line therapy for the treatment of patients with type 2 DM [17]. If glycemic control is not achieved with diet and exercise within a three-month period, pharmacologic intervention is required. Moreover if adequate control is not obtained with the use of a single agent, combination therapy is an option. Several of the available oral agents have been studied in combination and have been shown to further improve glycemic control when compared to monotherapy [18]. Some physicians now advocate the therapy combining three oral agents (sulfonylurea, metformin, alpha-glucosidase inhibitor or sulfonylurea, metformin, thiazolidinedione) in the management of type 2 DM [19]. This study was conducted to find the efficacy of triple drug combination (i.e. Voglibose, Metformin and Glimepiride) in the management of type 2 DM based on its effect on all the three parameters of glucose triad FPG, PPHG and HbA1c levels.

MATERIALS AND METHODS:

This study was a non-randomized, open, non-comparative, multi centric and post marketing surveillance study. The fixed dose combination (FDC) of Voglibose, Glimepiride and Metformin was orally administered as once daily to type 2 diabetic patients for 3 months. An approval from ethics committee was not obtained since

this was a post marketing surveillance study and the investigational product is already in market and approved by regulatory authorities. Informed consent was obtained from the patients and the post marketing surveillance was done in accordance with the clinical principles laid down in declaration of Helsinki [20]. A total of 118 type 2 diabetic patients were enrolled from the diabetic clinic and completed the treatment. At the time of entry into the study, base-line demographics were recorded. Patients were observed on 1st month of treatment, then subsequently 2nd and 3rd month of the treatment. Evaluation of FPG and PPHG were carried out regularly at the interval of each month for all the enrolled patients. The HbA1c level was examined only before the treatment and after 3 months of treatment. The HbA1c determination was carried out by using BIORAD Micromat II HbA1c instrument [21], while FPG and PPHG were determined by using Microplate reader [22].

Inclusion Criteria:

Both male and female patients over 32 years of age, HbA1c >7%, FPG level >200 mg/dl and PPHG >240 mg/dl were included in the study. Clinical criteria for the evaluation included FPG, PPHG and HbA1c value. After informed consent was obtained, patients were prescribed to receive the FDC of Voglibose, Glimepiride and Metformin tablet once daily for three months.

Exclusion Criteria:

Patients with current insulin therapy or received insulin for more than six weeks in last 3 months, who had known hypersensitivity to biguanides and sulphonylurea, who were on chronic medication known to affect glucose metabolism were excluded from the study. In addition, patients with renal disease or renal dysfunction, with congestive heart failure, hepatic insufficiency, alcoholics, pregnant and lactating women were excluded from the study.

Efficacy and Safety Evaluations:

The primary efficacy variable was the change in HbA1c from baseline to 3 month. Secondary efficacy outcomes included changes in FPG and 2-hour PPHG levels from baseline to the subsequent month of the treatment up to 3 month. Safety outcomes included adverse events, particularly hypoglycaemic symptoms. The patients were interviewed and asked for any type of adverse events throughout the study. The patients were specially asked for the hypoglycaemic symptoms during each visit to the study centre. The daytime hypoglycaemic episodes are usually recognized by sweating, nervousness, tremor, and hunger while night-time hypoglycaemia may be without symptoms or manifest as night sweats, unpleasant dreams, or early morning headache [23].

Statistical Analysis:

The analysis of HbA1c and FPG and PPHG was carried out by using graph pad prism 6.

Comparison between the baseline values with the value on the 1st, 2nd and 3rd month of treatment were made, as well as comparison in between these months was done by applying one way analysis of variance and the Turkeys multiple comparison test. Values of P <0.001 were considered significant.

RESULTS:

A total of 118 patients were screened and completed the study. The baseline characteristics of all patients at randomization are summarized in table 1.

Table 1: Baseline characteristics of all patients

Number of patients	118 (54% Male; 46% Female)
Age (yrs)	32 - 85
HbA1c (%)	8.69 ± 1.81
FPG (mg/dl)	206.5±73.76
PPHG (mg/dl)	244.7 ± 69.95
Body weight (kg)	69.91±12.55

Evaluation of Glycaemic Control:

Glycated haemoglobin (HbA1c):

HbA1c level was significantly reduced from the baseline after using the triple combination of voglibose, glimepiride and metformin. During the study there was significant differences found in the value of HbA1c at the baseline to the value observed after the completion of the treatment, respectively (8.69 ± 1.81 vs.6.475± 0.39, P< .0001) as shown in table 2.

Table 2: FPG, PPHG, and HbA1c values from the baseline and after 30, 60 and 90 days (Mean±SD)

Parameters	Baseline	Day 30	Day 60	Day 90
FPG (mg/dl)	206.50±73.76	155.70±46.77***	133.30±29.29***#	112.70±25.73***
PPHG(mg/dl)	244.70±69.95	193.50±44.5***	169.60±40.0***#	141.70±22.64***
HbA1c (%)	8.69±1.81	8.06±1.35***	7.07±0.89***	6.47±0.39***$

*** P< 0.0001 vs. Baseline, # P< 0.01 vs Day 30, $ P< 0.01 vs. Day 60

Evaluation of Fasting Plasma Glucose (FPG) level:

The FPG level was reduced throughout the study period of 3 month. The FPG level was measured at baseline and then subsequently at 1st, 2nd and 3rd month of the treatment. The FPG level was 206.5±73.76 mg/dl at baseline. The FPG level was significantly reduced just after 1 month of the treatment from the baseline value (206.5±73.76 mg/dl vs. 155.7 ± 46.77 mg/dl, p=0.01). The level of significance was highest between the FPG at baseline and on 3rd months of the treatment (206.5±73.76 mg/dl vs. 112.7 ± 25.73 mg/dl, P< .0001). There was no significant change between the 1st month and 2nd month of the treatment (155.7 ± 46.77 mg/dl vs. 133.3 ± 29.29 mg/dl, P=0.01) and between 2nd and 3rd month of the treatment (133.3 ± 29.29 vs. 112.7 ± 25.73, P=0.01). Overall the FPG level was significantly (P<0 .0001) decreased by 93.8± 48.03 mg/dl from the baseline after the completion of the study of 90 days (Table 3). The decrease in FPG level from the baseline to the subsequent month of treatment is presented in table 3.

Table 3: Reduction in FPG, PPHG and HbA1c from the baseline (Mean±SD)

Parameters	Day 30	Day 60	Day 90
ΔFPG (mg/dl)	-50.8±26.99***	-73.2±44.47***	-93.8±48.03***
ΔPPHG(mg/dl)	-51.2±25.45***	-75.1±29.93***	103.0±47.31***
ΔHbA1c (%)	-0.62±0.46***	-1.62±092***	-2.22±1.42***

*** P<0 .0001 vs. Baseline

Evaluation of Post Prandial Blood Glucose (PPHG) level:

The PPHG level was reduced throughout the study period of 3 month. The PPHG level was measured at baseline and then subsequently at 1st, 2nd and 3rd month of the treatment. The PPHG level was 244.7 ± 69.95 mg/dl at baseline. The PPHG level was significantly reduced on 2nd month of the treatment vs. baseline (244.7 ± 69.95 mg/dl vs. 169.6 ± 40.02 mg/dl, P=0.01). But the level of significance was highest between the PPHG at baseline and to that on the 3rd month of the treatment (244.7 ± 69.95 mg/dl vs.141.7 ± 22.64, P< 0.0001). By applying the turkey's multiple comparison it was observed that there was no significant changes in PPHG level between the1st month of treatment to the 2nd month of treatment (193.5± 44.5 mg/dl vs. 169.6 ± 40.02mg/dl, P=0.01) and also in

between 2nd and 3rd month of the treatment (169.6 ± 40 mg/dl vs. 141.7 ± 22.64 mg/dl, P= 0.01). Overall the PPHG level was significantly decreased by 103 ± 47.31 mg/dl from the baseline after the completion of the study period of 90 days (Table 3).

Evaluation of body weight variation during the study period:

There were no significant changes observed in body weight during the whole treatment period. Body weight was recorded as mean average (±SD) at the entry of the study, and then subsequently on 1st , 2nd and on 3rd month of the treatment (69.91±12.55 vs70±12.53, 69.7± 12.27 and 69.25± 12.57 kg respectively).

Evaluation of Hypoglycaemic and other adverse effect:

The patients were interviewed during each visit and at the end of the study for the detection of any hypoglycaemic episode and about other side effects like nausea, vomiting, headache. No patient complained about the side effects including nausea, vomiting, headache or GIT side effects at the given doses of medication.

Evaluation of Global efficacy and tolerability:

As per investigators assessment about efficacy and tolerability of Voglibose, Metformin and Glimepiride tablet, all (100%) the patient tolerated the treatment and benefitted. Moreover investigator showed the interest that it would be the good choice in the management of diabetes when there is need to control both FPG and PPHG level.

DISCUSSION:

The management of DM includes diet control, exercise and pharmacological therapy. PPHG, similar to post-challenge glucose, was related to cardiovascular disorders (CVD) than FPG [24-26]. However, higher fasting hyperglycaemia was not significantly associated with CVD risk. Previous analyses suggested that fasting hyperglycaemia tended to be associated with beta cell dysfunction, whereas post-challenge hyperglycaemia tended to be more strongly related to insulin resistance, higher blood pressure, obesity, and dyslipidemia [27]. The drug therapy is generally initiated either with sulfonylurea or metformin as monotherapy. In the present study patients with DM whose glycaemic status were not controlled with two oral hypoglycaemic agents (metformin and glimepiride) were given third drug voglibose as FDC. The effect of add on therapy with voglibose as a third agent was observed on various parameters. Among the clinical parameters, there was no significant change observed in body weight at the end of study. A significant reduction in FPG, PPHG and HbA1c was found with FDC.

For the optimal management of type 2 DM there is the requirement to understand the relationships between HbA1c, FPG and PPHG level (the glucose triad), and how these change

takes place during development and progression of the disease. Early and sustained control of glycaemia remains important in the management of type 2 DM. When antidiabetic therapy is initiated, physicians may need to consider selection of agents that target both fasting and PPHG levels. M. John et al [28], in a review article reported that, triple FDCs provide effective glycemic control in a safe, well tolerated, and economic manner. They also stated that, the components of FDC acts by different mechanisms thereby targeting multiple pathophysiological targets. Similar results were also reported by C Rao et al [29], concluding their findings as triple drug combination of voglibose, metformin and glimepiride reduces HbA1c, FPG and PPHG level in type 2 DM patients. In the same study, they reported that, the above mentioned triple drug FDC was safe and well tolerated in their clinical trial. Jindal et al [30] in another trial studied the effect of addition of voglibose to the combination of glimepiride and metformin and observed changes on various parameters i.e. FPG, PPHG, HbA1c and lipid profile (Total cholesterol, triglycerides, low density cholesterol, and very low density cholesterol and high density lipoprotein) in type 2 DM patients. At the end of the study it was found that there was a significant reduction in FPG, PPHG and HbA1C was found with the addition of voglibose. The reduction in these parameters was observed in chronological sequence with duration of study i.e. at 1st, 2nd, 3rd, 4th, 5th and 6th months. Addition of voglibose was reported to have an influence on serum lipids, which include total cholesterol, triglycerides, low density cholesterol and very low density cholesterol; these were reduced significantly with voglibose [30]. Derosa et al [31] also observed significant reduction in FPG, PPHG and HbA1c with combination of sulfonylurea, metformin and acarbose.

In this post marketing surveillance study, HbA1c value was significantly reduced from the baseline after using the FDC of voglibose, glimepiride and metformin. During the study there was significant differences found in the value of HbA1c at the baseline to the value observed after the completion of the treatment (8.69 ± 1.81 to 6.475± 0.39, P< 0.0001).

The FPG level was reduced throughout the study period of 3 months. FPG level was significantly (P< 0.0001) decreased by 93.8 ± 48.03 mg/dl from the baseline after the completion of the study of 3 months. After 3 month the FPG level was reduced to 112.7 ± 25.73 mg/dl. Moreover the PPHG level was also reduced throughout the study period of 3 month. Overall the PPHG level was decreased significantly by 103 ± 47.31 mg/dl from the baseline after 3 months of treatment and the PPHG level lowered down to the value 141.7 ± 22.64 mg/dl.

Overall this combination is highly effective and safe in controlling all the glycemic parameters like HbA1c, FPG and PPHG for optimal management of type 2 DM. Regarding the

tolerability and safety of the FDC of Voglibose, Metformin and Glimepiride, 100% of patients tolerated the treatment very well without the need for discontinuing the therapy due to adverse effect.

CONCLUSION:

The FDC of Voglibose, Metformin and Glimepiride significantly decreased the HbA1c value, FPG and PPHG level after 3 months of treatment from the baseline. Investigators observed that the therapy was safe and well tolerated. Investigators commented that this is a good option to control the FPG and PPHG level for the optimal management of type 2 DM.

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Competing Interests:

All authors had access to the data and vouch for the veracity and completeness of the data and the data analysis. Authors have declared that no competing interests exist.

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