Efficacy and Tolerability of Oral Triple Drug Combination (Voglibose, Glimepiride and Metformin) in the Management Type 2 Diabetes Mellitus

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Abstract
The prevalence of diabetes is rapidly rising across the globe at an alarming rate. Despite the introduction of new agents efforts for better management of diabetes are disappointing and the control of blood glucose levels remains unsatisfactory. Material and method: The study was a post marketing surveillance (PMS) non-randomized, open, non-comparative, mono centric study. The triple drug fixed dose combination of Voglibose, Glimepiride and Metformin was administered to 20 Type 2 diabetic patients once daily for 4 months. Observation: Baseline value was recorded for glycated haemoglobin (HbA1c), fasting blood glucose and post prandial blood glucose level. There was a significant decrease in glycated haemoglobin value (9.07 ±0.346 to 6.51±0.129, p < 0.0001), fasting (181±10.2 mg/dl to 116±2.97 mg/ml P < 0.0001) and post prandial blood glucose level (239±11.2 mg/dl to 140±4.42 mg/dl P < 0.0004) after 4 months of treatment from the baseline. The combination was found to be effective in controlling both fasting and post prandial glucose level and was well tolerated. Conclusion: Fixed dose triple drug combination of voglibose plus metformin plus glimepiride significantly reduces the HbA1c value, fasting and post prandial blood glucose level with an excellent tolerability.
Keywords- HbA1c; Fasting blood glucose; Post Prandial Blood Glucose;Fixed Dose Triple drug

INTRODUCTION

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Over the past 30 years, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people too. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. The International

Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025[1]. Despite the introduction of new agents to the armamentarium of hypoglycemic agents efforts for better management of diabetes are disappointing and the control of blood glucose levels remains unsatisfactory[2].The American diabetes association (ADA) 2013 recommends the target HbA1c less than 6.5%[3]. Blood glucose levels that correspond to HbA1c level of 6.5% are a fasting level <110 mg/dL and a 2-hour postprandial level <140 mg/dL[4]. Despite the significant improvement in health outcomes associated with aggressive management of type 2 diabetes, current treatment often fails to achieve desirable therapeutic targets of glycemic control. The importance of early and optimal control of glycemia in diabetes is well known. The need for multiple drugs, focusing on the various pathophysiologic mechanisms that cause diabetes, is also well understood. Of the nearly 300 million people with diabetes worldwide, over half are unable to achieve glycemic target[5]. 85% of them are overweight or obese[6], and 75% are hypertensive[7]. Many have dyslipidemia and other comorbid conditions. All these require multidrug therapy which is daunting and complex for both patient and physician.

Most of the time inability to achieve desired glycemic goals is due to poor adherence with the suggested antidiabetic therapy. Adherence can be improved by using appropriate fixed dose combination (FDC) preparations. Early and proactive use of appropriate FDCs is a simple and effective way of achieving glycemic targets.

Current Management Strategies

The American Association of Clinical Endocrinologists (AACE), created a ground by categorizing patients according to their initial HbA1c. Patients with an initial HbA1c of 7.6-9.0%, who form the majority in every practice, are recommended initial dual therapy. Those with an HbA1c > 9% can start triple therapy. Thus, the logic of early, aggressive combination therapy has received expert backing, based on pathophysiological logic and clinical evidence[8]. Now some physicians are advocating the therapy combining three oral agents (sulfonylurea, metformin, alpha-glucosidase inhibitor or sulfonylurea, metformin, thiazolidinedione) in the management of type 2 diabetes[9]. This study was conducted to evaluate the efficacy and tolerability of triple drug combination (i.e. Voglibose, Metformin and Glimepiride) in the management of type 2 diabetes.

MATERIALS AND METHOD

This was a post marketing non-randomized, open, non-comparative, mono centric study. The triple fixed dose combination of Voglibose 0.2 mg, Glimepiride 1mg/2mg and Metformin (SR) 500 mg, was administered to type 2 diabetic patients for 4 months. Informed consent was obtained from the patients & the post marketing surveillance was in accordance with the clinical principles laid down in declaration of Helsinki. A total of 20 type 2 diabetic patients were enrolled and completed the treatment. At the time of entry into the study, base-line data were recorded. After informed consent was obtained,

patients were prescribed to receive triple drug fixed dose combination of Voglibose, Glimepiride and Metformin tablet once daily for four months. Patients were followed up on 1st month of treatment, than subsequently on 2nd, 3rd and 4th month of the treatment. The patients were asked for the determination of FBG, PPBG and HbA1C level regularly at the interval of each month. The HbA1C determination was carried out by using BIORAD Micromat II HbA1C instrument, while FBG and PPBG were determined by using Microplate reader.

Inclusion Criteria

Patients with age more than 35 yrs, of either sex, glycosylated hemoglobin > 9% were included in the study.

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, or the patients who were on chronic medication known to affect glucose metabolism were excluded from the study. Also the patients with renal dysfunction, congestive heart failure, hepatic insufficiency, alcoholic person and 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 4 month. Secondary efficacy outcomes included changes in fasting blood glucose and 2-h postprandial blood glucose levels & body weight from baseline to the subsequent month of the treatment up to 4 months. Safety outcomes included adverse events, particularly hypoglycaemic

symptoms recognized by sweating, nervousness, tremor, and hunger and night time hypoglycaemia manifesting as night sweats or early morning headache. The patients were interviewed and asked for any type of adverse events throughout the course of treatment.

Statistical analysis

The analysis of Glycosylated hemoglobin and fasting and post prandial glucose was carried out by using graph pad prism 6. Comparison between the baseline values with the value on the 1st, 2nd, 3rd and 4th month of treatment were made, as well as comparison in between these months was done by applying one way analysis of variance & the Turkeys multiple comparison test. Value of $P<0.001$ were considered significant.

RESULTS AND DISCUSSION

A total of 20 patients were screened & included in the study. Enrolled patients were prescribed with triple drug fixed dose combination of voglibose, metformin and glimepiride for 4 months and & were evaluated at the end of 1st, 2nd, 3rd and 4th month of treatment. The baseline characteristics of all patients are summarized in table 1.

Table. 1 Baseline characteristics of patients	
Sex (Male/Female)	07/13
Age (yrs)	38-75
HbA1c (%) (Mean±SEM)	9.07 ± 0.346
FBG (mg/dl) (Mean±SEM)	181 ± 10.2
PPBG (mg/dl) (Mean±SEM)	239 ± 11.2
Weight (Kg) (Mean±SEM)	65.6 ± 3.41

3.1 Evaluation of Glycosylated hemoglobin

Glycated haemoglobin value was significantly reduced from the baseline after using the fixed dose triple drug combination of voglibose, glimepiride and metformin. During the study there was significant (p<0.001) difference found in the value of HbA1c at the baseline to the value observed at the subsequent month of the treatment as shown in the Table 2. & Figure 1.

Table. 2

HbA1c (%) level at baseline and subsequent month

	Baseline	Day 30	Day 60	Day 90	Day 120
Mean ± SEM	9.07 ±0.346	7.68±0.194**	7.33±0.257***	6.64±0.17*** $	6.51±0.129***$$

** p<0.001vs Baseline, *** p<0.0001 Vs. Baseline, $ p<0.05 Vs 30th Day, $$ p<0.001 Vs. 30th Day
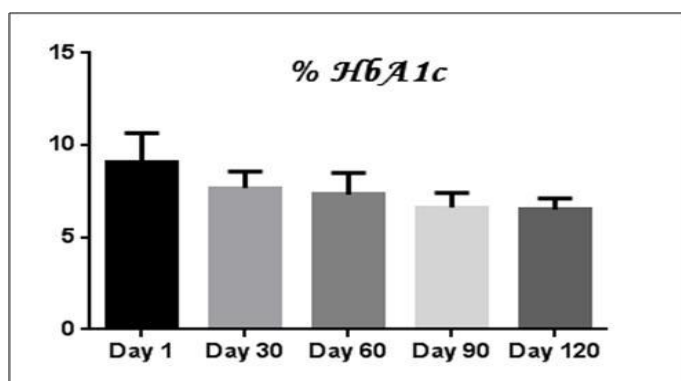

Figure 1: Effect of triple drug combination on Glycosylated haemoglobin

3.2 Evaluation of Fasting Blood Glucose (FBG)

The FBG level was reduced throughout the study period of 4 month. The FBG level was measured at base line and then subsequently at 30th, 60th, 90th and 120th day of the treatment. The FBG level

(±SEM) was 181±10.2 mg/dl at baseline. The Fasting blood glucose level was significantly reduced after 60 days of the treatment from the baseline value (181±10.2 mg/dl vs. 144 ± 6.79 mg/dl). There was insignificant change between the 1st and 2nd month of the treatment and between 2nd and 3rd month of the treatment. Overall the fasting blood glucose level was significantly (p<0.0001) decreased by 65 ± 7.23 mg/dl from the baseline after the completion of the study (Fig. 2). The comparative decrease in fasting blood glucose level from the baseline to the subsequent month of treatment has been depicted in the Table 3. & Figure 2 and 3.

Table. 3

Fasting blood glucose (FBG) level at baseline and subsequent month

	Baseline	Day 30	Day 60	Day 90	Day 120
Mean± SEM	181±10.2	155±10.6	144±6.79**	126±4.58***	116±2.97***$$

** p<0.001vs Baseline, *** p<0.0001 Vs. Baseline, $$ p<0.001 Vs. 30th Day
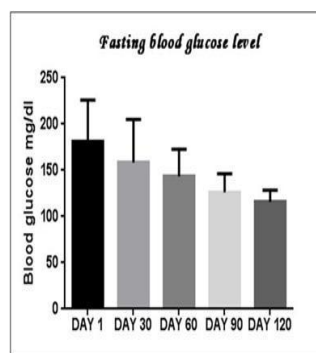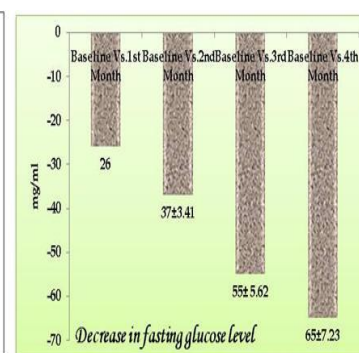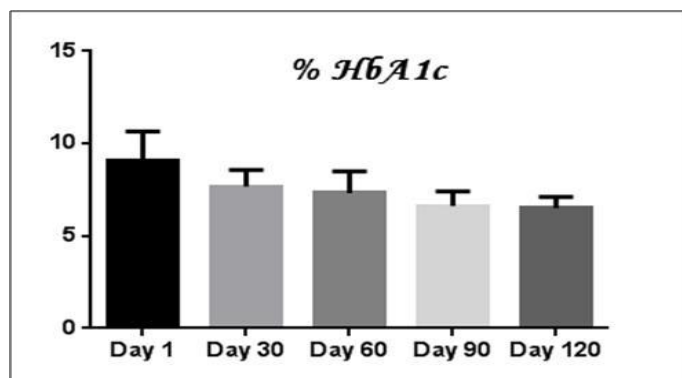

Figure 2: Effect of triple drug combination on fasting blood glucose

Figure 3: Effect of triple drug combination on reduction in fasting blood glucose

3.3 Evaluation of Post Prandial Blood Glucose (PPBG)

The post prandial blood glucose (PPBG) level was reduced throughout the study period of 4 month. The post prandial blood glucose level was measured at base line and then subsequently at 1st , 2nd, 3rd and 4th month of the treatment. The PPBG level was 239 ± 11.2 mg/dl at baseline. The PPBG level was significantly reduced starting from 1st month but decrease was highly significant (p<0.001) from 2nd month and onwards. By applying the turkey's multiple comparison; it was observed that there was insignificant change in post prandial blood glucose level between the 1st and 2nd month of treatment (203 ± 8.41 mg/dl vs. 187 ± 8.55 mg/dl) and also in between 2nd and 3rd month of the treatment (187 ± 8.55 mg/dl vs. 168 ± 9.07 mg/dl). Overall the post prandial blood glucose level was significantly decreased by 99 ± 6.68 mg/dl from the baseline after the completion of the study period of 120 days. The comparative post prandial blood glucose level at baseline and the subsequent months of treatment is shown in Table 4 & Figure 4. and 5.

Table. 4

Post prandial blood glucose (PPBG) level at baseline and subsequent months

	Day 1	Day 30	Day 60	Day 90	Day 120
Mean ± SEM	239 ± 11.2	203 ± 8.41*	187 ± 8.55**	168 ± 9.07***$	140 ± 4.42***$$

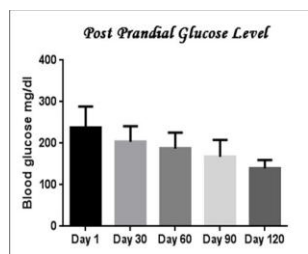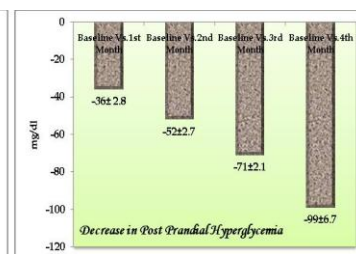* p<0.01vs Baseline, ** p<0.001vs Baseline, *** p<0.0001 Vs. Baseline, $ p<0.01 Vs. 30th, $$ p<0.001 Vs. 30th Day

Figure 4:Effect of triple drug combination on postprandial blood glucose

Figure 5:Effect of triple drug combination on reduction in postprandial blood glucose

3.4 Evaluation of body weight during the study period

Insignificant changes have been observed in weight during the whole treatment period. Weight was recorded as mean average (±SEM) at the entry of the study, and then subsequently on 1st, 2nd, 3rd and 4th month of the treatment (Table 5).

Table. 5

Post prandial blood glucose (PPBG) level at baseline and subsequent month

	Day 1	Day 30	Day 60	Day 90	Day 120
Mean ± SEM (Kg)	65.6± 3.41	64.2 ±3.3 5	63.1 ±3.0 3	62.3 ±3.2 5	60.4 ±3.0 9

3.5 Evaluation of Hypoglycaemia and other adverse effect

The patients were interviewed during every visit to know about any hypoglycaemic episode and other side effects like nausea, vomiting, headache abdominal pain or flatulence. None of the patient reported these adverse effects.

3.6 Evaluation of Global efficacy and tolerability

As per investigators assessment about efficacy and tolerability of fixed dose triple drug combination of Voglibose, Metformin and Glimepiride, all the patients tolerated the combination without any safety concern. Regarding the global efficacy by the investigator 85% of patient reported good, 15% reported excellent efficacy while only 5% of the patients reported poor efficacy.

DISCUSSION

In general type 2 diabetes mellitus is often treated in a stepwise manner like starting with a regimen of nutrition counselling to monotherapy and then combination therapy. As hyperglycemia worsens, combinations of oral agents are often required[10].

Early and sustained control of glycaemia remains important in the management of type 2 diabetes. When antidiabetic therapy is initiated, physicians may need to consider selection of agents that target both fasting and postprandial hyperglycaemia (as both are responsible for the development of complications in diabetes). Since multiple drugs are required to tackle the various pathophysiologic mechanisms that causes diabetes, non adherence to the therapy due to pill burden creates the difficult situation to achieve desired glycemic target. By using appropriate fixed dose combination (FDC) adherence to the therapy can improved.

The most commonly prescribed antidiabetic FDC in India is Metformin +Sulphonylurea targeting both insulin resistance and deficiency[11]. Metformin suppresses hepatic gluconeogenesis to reduce fasting hyperglycemia, and also increases peripheral glucose uptake. Sulfonylurea increase insulin release from the β-cells, and work as long as some amount of β-cell residual function is present. This therapy has been shown to provide synergistic effect in many studies and meta- analysis. The addition of the second agent usually lowers the mean HbA1c level 1.0 to 1.4% more than monotherapy when the baseline value is between 8.5% and 9.5%[12]. Thus by using dual therapy and when the HbA1C is >9 it is not possible to achieve the desired HbA1C target i.e. <6.5%. It is proposed that a third agent with different mechanism of action can be added to the existing dual therapy if the HbA1c level achieved with two agents is 8.0% or less[4]. It has been observed that post prandial glucose level plays major role in complications, thus besides controlling the fasting glucose it is very important to control the post prandial glucose level aggressively. In this triple drug combination voglibose specifically controls post prandial hyperglycemia by reducing intestinal glucose absorption. Thus all the

three drugs acts by different mechanism and controls both fasting and post prandial glucose level. Moreover some physicians advocate therapy combining three oral agents (sulfonylurea, metformin, alpha-glucosidase inhibitor or sulfonylurea, metformin, thiazolidinedione), although this approach has not been extensively studied [13]. Results of this study are in accordance to the previous study in which patients were additionally prescribed with acarbose (alpha glucosidase inhibitor) to the dual therapy of sulfonylurea and metformin. Results had shown a significant decrease ($P < 0.001$) in Glycosylated hemoglobin level and postprandial blood glucose level[14]. Flatulence which was reported in previous study is not observed in this study. It is thought that voglibose has lesser incidence of GI side effects than the acarbose.

In this study glycated haemoglobin value was significantly reduced from the baseline after using the triple combination of voglibose, glimepiride and metformin. During the study there were significant differences found in the value of HbA1c at the baseline to the value observed after the completion of the treatment (9.07 ±0.346 to 6.51±0.129, p < 0.0001).

The FBG level was reduced throughout the study period of 4 month. Fasting blood glucose level was significantly (p<0.0001) decreased by 65 ± 7.23 mg/dl from the baseline after the completion of the study of 120 days. After 4 month the fasting blood glucose level was reduced to 116±2.97 mg/dl. Similarly the post prandial blood glucose (PPBG) level was also reduced throughout the study period of 4 month. Overall the post prandial blood glucose

level was decreased significantly by 99 ± 6.68 mg/dl from the baseline after 4 months of treatment and the post prandial glucose level lowered down to 140±4.42 mg/dl from the baseline value of 239±11.2 mg/dl. All the patients tolerated the therapy well and none of the patients reported any side effects.

CONCLUSION

Fixed dose triple drug combination of Voglibose, Glimepiride and Metformin is safe and effective in the management of type 2 diabetes uncontrolled with dual therapy.

Acknowledgments

Author Contributions

Author 2 conceived the study & prepared the protocol , Case Record Form & manuscript. Author 1 conducted the study as per the protocol.

Conflicts of Interest

The authors declare no conflict of interest.

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