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COMPARISON OF CLINICAL OUTCOMES OF *SITAGLIPTIN* ALONE AND *COMBINATION* OF *METFORMIN*+ GLIMEPRIDE IN THE MANAGEMENT OF UNCOMPLICATED TYPE 2 DIABETICS.

Pharmacology

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ABSTRACT

This study has evaluated two treatment antidiabetic regimens viz Sitagliptin alone and combination of *Metformin+ Glimepride* in type-2 diabetics. The most common admitting outcomes assessed were glycemia control, and the incidence of complications. The results of this study reveal that the combination regimen was more efficacious to achieve glycaemia control in comparison to monotherapy group.

Conclusion: The present study suggests that a significant difference may be existing in the clinical outcome interms of glycemia control and complications between Sitagliptin alone and combination of Metformin+ Glimepride in type-2 diabetic patients.

KEYWORDS

Type 2 DM Patients, Sitagliptin, Metformin+ Glimepride, Glycemia Control.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterised by defect in insulin secretion or insulin action, or both.[1-4] As per WHO estimation more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025.[5-7] India had 32 million diabetic subjects in the year 2000 and this number would increase to 80 million by the year 2030.[8] This high global burden is continuously on the rise with increasing incidence and prevalence of type 2 DM, due to increasing population, age, obesity, and physical inactivity as well as by the increasing longevity of patients with DM. Type 2 DM is a major risk factor for developing both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease).[9] Variable treatments focus on reducing hyperglycemia and improving insulin sensitivity. These modalities are attractive in theory, as they appear to target the primary defects associated with type 2 DM. However, despite the wide array of treatment options available, glycemic control declines over the time.[10] Unattainable glycemic control is often a result of ongoing deterioration of beta-cell function. The primary goal of treatment is to target glycemic control by maintaining the HbA1C level at 6-7% to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia.[11] Treatment with a single antihyperglycaemic agent is often unsuccessful at achieving and/or maintaining long-term glycaemic control in patients with type 2 diabetes, so many patients require combination therapies [12]. Monotherapy with metformin or a sulphonylurea is the most commonly used initial oral hypoglycaemic agent (OHA) regimen to treat patients with type 2 diabetes.

Various new drugs are introduced as monotherapy and fixed dose combinations for the treatment of type 2 diabetes. One such newly introduced class of drug is dipeptidyl peptidase-IV (DPP IV) inhibitors. Sitagliptin is a once-daily, orally active, potent and highly selective (DPP-4) inhibitor approved in many countries for the treatment of patients with type-2 diabetes. [13] It is being used as monotherapy or as an add-on to ongoing oral antidiabetic agents in patients with type 2 DM with significant reduction in glycaemic levels within a few weeks.[14] DPP IV inhibitors are being used as monotherapy or as an add-on to ongoing oral antidiabetic agents in patients with type 2 diabetes. However, there is paucity of scientific literature regarding their comparative clinical outcomes. Hence, it was found worthwhile to study and compare the clinical outcomes of DPP IV inhibitors i.e. Sitagliptin alone and combination of Metformin, Glimeride in the management of uncomplicated type 2 diabetics.

MATERIALS AND METHODS

This study was carried out in the Department of Pharmacology at Geetanjali Medical College & Hospital and other Tertiary care Hospitals on type 2 diabetes mellitus patients. The diagnostic criteria as presented by American diabetic association was followed and blood glucose estimation with history and clinical examination were undertaken to diagnose the diabetes mellitus. The uncomplicated Type-2 diabetes mellitus patients of age between 18–70 years were included into the study. However, Type -I diabetes (IDDM), pregnant women, patients with impaired renal/ liver functions and the patient with history of hypersensitivity to the study drugs were excluded. Written, informed consent of all the patients and approval of Institutional Ethics Committee (IEC) was taken before starting the study.

STUDY DESIGN

This study was a prospective, open label, observational clinical cohort study carried out on type 2 diabetes mellitus patients. It enrolled a total of 297 type 2 diabetes mellitus patients who were randomly allocated to two groups viz group A and group B respectively. Group A received sitagliptin 100mg/day and group B received a combination of Metformin, Glimepride (500+1)mg/day respectively. A day before starting the treatment, Before Breakfast (BBF) and post prandial (PP) blood sugar was measured and treatment started. The patients were advised to come after 10 days from the start of the treatment for measurement of respective blood sugar levels and HbA1c again. The data so collected on the day 10 from the start of the treatment was considered as zero month. The follow up of the patients was started and the respective blood glucose levels were measured every month upto the period of six months in each patient. In addition HbA1c was also measured & assessed after every 3 months. Blood glucose was also measured at any time if a patient experienced symptoms of hypoglycaemia (BG<60 mg/dl) or if requested by treating physician. Apart from glycaemia profile the complications attributable to the treatment regimes were also recorded in both the groups to assess the safety parameter.

STUDY PROTOCOL

As the patient turned out to be diabetic, routine investigation of fasting, random and post prandial blood glucose was done twice for confirmation. After being educated on diet, importance of treatment regimen with special emphasis on need to adhere to treatment, the patient was started with one of the two regimes. The blood glucose estimation was done by glucose oxidase test in the central laboratory of the concerned hospital by using Olympus AU 640 auto-analyser. A blood sample of 10µl for estimation of blood glucose was done within half an hour after the sample collection. HbA1C was also used as a comparative criteria for the assessment of glycaemia control in each patient. A proforma was developed for collecting the data required for this study. Face to face interview technique was used for interviewing the patients and / or their closest attendants. The other technique applied was that of retrospective analysis of the records. It was done

with an intention to provide supplementary information on the data collected. In this study, it was contemplated to analyze the records of previous treatment with the history of diabetes mellitus to test the reliability about the duration of disease and compliance to treatment. The patient sample for this study was calculated as per the incidence of Type 2 Diabetes mellitus in the projected area and the power of study is more than 80%. Unpaired t-test was employed for statistical analysis of the data. A probability value of less than 0.05 ($p<0.05$) was considered to be statistically significant.

RESULTS:

A total of 297 Type 2 Diabetes Mellitus patients have completed the study. The patients were allocated to two groups Viz group A and B received Sitagliptin alone and combination of Metformin, Glimeride respectively. Both the treatment groups had more or less similar clinical and demographic characteristics. The most common admitting outcomes assessed were glycemia control, and the incidence of complications. Comparison for assessment of glycemia control was done between zero and six month within group and at six month between groups.

Mean fasting blood glucose obtained a day Before Treatment (BT) has significantly reduced ($p<0.001$) when compared to mean fasting blood glucose levels obtained on zero month till a period of six months within and between groups after the treatment. A significant difference ($p<0.01$) exists in all the mean blood glucose levels between treatment groups (Fig-1 &2).

While assessing the glycemia control a significant ($p<0.05$) but gradual decrease was noted in all the mean blood glucose levels recorded for a period from zero month to six month when compared with the mean fasting and postprandial blood glucose levels recorded before starting the treatment in group A (Fig-1). However, an adequate significant control in mean fasting and mean post prandial blood glucose levels was not achieved even at a period of six month therapy with sitagliptin alone.

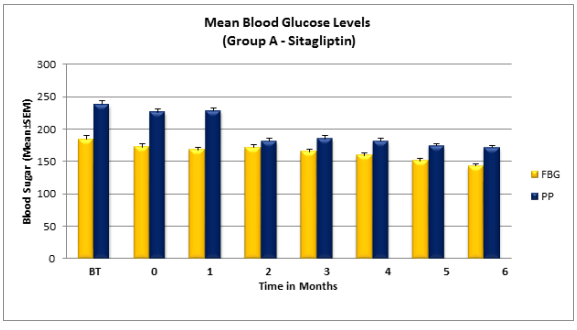

FIG.1: Comparison of mean fasting and post prandial blood glucose levels. FBG= Fasting Blood glucose, PP= Post prandial, BT= Fasting Blood Glucose Before Treatment.

On the contaray a significant ($p<0.001$) decrease was recorded in all the mean blood glucose levels for a period from zero month to six month when compared with mean blood glucose levels obtained a day before starting the treatment in group B. Interstingly a significant ($p<0.001$) control in mean fasting and post prandial levels was recorded with combination therapy of Metformin+ Glimepride in group B (Fig-2).

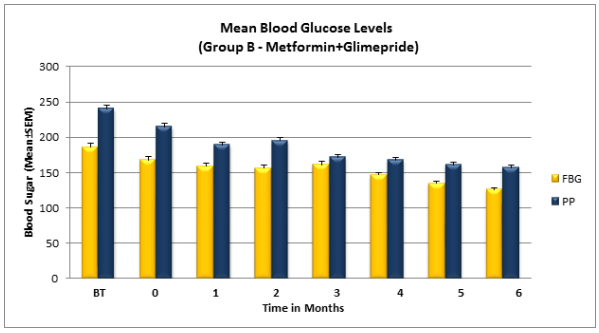

FIG.2: Comparison of mean fasting and post prandial blood glucose levels. FBG= Fasting Blood glucose, PP= Post prandial, BT= Fasting Blood Glucose Before Treatment.

While assessing the overall comparative glycemia control achieved in both the treatment groups, a significant ($p< 0.001$) glycemia control was noted in within and between group mean blood glucose level in group B than group A (Fig-1 Vs Fig-2).

In addition each patient was assessed for the HbA1c and used as a comparative criteria for the assessment of glycaemia control in both the groups. A significant difference existed in HbA1c values recorded after the three and six months period when compared to HbA1c value recorded on zero month period in group- B who were treated with combination of Metformin+Glimepride. However, no significant difference was noted in HbA1c values recorded before or after treatment in a group who were treated with sitagliptin alone (Fig-3).

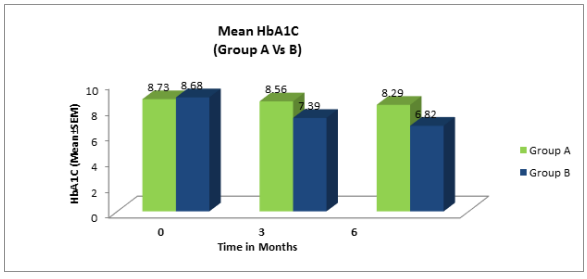

FIG-3: Comparison of HbA1C between group A and B. Group A= Sitagliptin, Group B= Metformin+Glimepride

2.04 percent hypoglycaemic episodes were recorded in patients who were treated with sitagliptin alone. Whereas 16.66 percent hypoglycaemic episodes were recorded in patients who were treated with combination of Metformin+ Glimepride. However, this difference in hypoglycaemic episodes was statistically significant. 4.76 and 11.33 percent of the patients treated with sitagliptin alone and combination Metformin+Glimepride respectively suffered GIT complications like nausea,vomiting and abdominal discomfort. Weight loss was recorded in 8.16 percent patients who were treated with sitagliptin alone. It was also noted that 3.33 percent patients lost weight who were treated with combination of Metformin+ Glimepride whereas 6 percent patients suffered weight gain who were treated with combination of Metformin+ Glimepride.

DISCUSSION

Diabetes mellitus is the most common endocrine disorder which is characterised by relative or absolute deficiency of insulin. The incidence of diabetes is alarming globally. India is leading the world as rank one in diabetics, thus has earned a dubious distinction of being termed as *Diabetic Capital* of the world. As per WHO estimation, India is going to receive 80 million diabetics in the year 2030. Though there is no permanent treatment available for diabetes till date, however, the current treatment modalities can only control but cannot cure it. Therefore, number other new drugs are introduced as monotherapy and fixed dose combinations for the treatment of type 2 diabetes. One such newly introduced class of drug is DPP IV inhibitors. DPP IV inhibitors are being used as monotherapy or as an add-on to ongoing oral antidiabetic agents in patients with type 2 diabetes. However, there is paucity of scientific literature regarding their comparative clinical outcome. Hence, it was found worthwhile to study and compare the clinical outcomes of DPP IV inhibitors i.e. Sitagliptin alone and in combination of Metformin, Glimepride in terms of glycaemia control achieved and incidence of complications.

A total of 297 Type 2 Diabetes Mellitus patients have completed the study. The patients were allocated to two groups Viz group A and B received Sitagliptin alone and combination of Metformin, Glimepride respectively. The most common admitting outcomes assessed were glycemia control, and the incidence of complications. When comparing the mean fasting and post prandial blood glucose obtained before starting the treatment with mean fasting and post prandial blood glucose levels recorded after zero month a statistically significant ($P<0.001$) difference existed in both the groups (Fig-1). These results are in support of a study mentioning that a significant decrease was noted in mean blood glucose levels in patients who were treated with sitagliptin alone and combination of metformin+Glimepride[15,16]. When comparing the glycemia control achieved by combination therapy of metformin+Glimepride a statistically significant difference was recorded among mean blood glucose levels for a period from zero month to six month (Fig-2). The results of this study are similar to a

study mentioning similar glycemia control achieved by metformin+ Glimepride combination[17,18,19]. A gradual decrease in mean blood glucose was noted in a group who was treated with sitagliptin alone (Fig-1). However, this difference was statistically insignificant. In addition a significant difference (P<0.001) was also noted in HbA1c after starting the treatment in group B when compared with HbA1c recorded before treatment. However, this difference in HbA1c values recorded before and after treatment in group A was insignificant. In addition a significant difference existed in HbA1c values recorded after the three and six months period when compared to HbA1c value recorded on zero month period in group- B who were treated with combination of metformin+Glimepride. These results are in accordance to a study mentioning the significant decrease in HbA1c values in patients treated with sitagliptin+ Glimepride combination[20,21,22]. While comparing the adverse effects 2.04 percent hypoglycaemic episodes were recorded in group A and 16.66 percent hypoglycaemic episodes were recorded in patients in group B respectively. 4.76 percent patient from group A and 11.33 percent patient from group B suffered GIT complications like nausea, vomiting and abdominal discomfort. Weight loss was recorded in 8.16 percent patients in group A. It was also noted that 3.33 percent patients lost weight whereas 6 percent patients suffered weight gain group B.

The results of this study reveal that the combination regimen was more efficacious to achieve glycaemia control in comparison to monotherapy group. Therefore, Sitagliptin as monotherapy regimen for control of hyperglyacemia in type 2 diabetics did not result superior to combination therapy. Time and resource constraint was the major limitation of this study therefore more short and long term studies are warranted to investigate the significance and causal relationships of the differences in the outcomes with the treatments.

CONCLUSION

The present study suggests that a significant difference may be existing in the clinical outcome interms of glycemia control and complications between Sitagliptin alone and combination of metformin+Glimepride in type-2 diabetic patients. The combination of metformin+ Glimepride resulted comparatively in better glycemia control.

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