ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 10, Issue 12, 2017

Online - 2455-3891
Print - 0974-2441

Research Article

A COMPARATIVE STUDY OF EFFICACY AND SAFETY AMONG METFORMIN WITH SITAGLIPTIN, METFORMIN WITH VOGLIBOSE, AND METFORMIN WITH GLIMEPIRIDE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Received: 16 August 2017, Revised and Accepted: 11 September 2017

ABSTRACT

Objective: Type 2 diabetes mellitus (DM) is a most common metabolic disorder. The present study aimed to compare the efficacy and safety among metformin with sitagliptin, metformin with voglibose, and metformin with glimepiride in patients with type 2 DM.

Methods: This study was a prospective, randomized clinical trial study, conducted in patients attending the diabetology outpatient department of SRM Medical College Hospital and Research Center, Potheri, Kancheepuram, Tamil Nadu, from January 2013 to January 2014. The patients were randomized into three groups with 40 patients in each group. Fasting plasma glucose (FPG), 2 hrs postprandial plasma glucose (PPG), and hemoglobin A1c (HbA1c) level were assessed in all the patients before starting the treatment. In Group I, patients were prescribed metformin 500 mg with sitagliptin 50 mg, in Group II, patients were given metformin 500 mg with voglibose 0.2 mg, and in Group III, patients were put on metformin 500 mg with glimepiride 1 mg in the fixed combination. The outcome of the therapy was based on the level of improvement in the blood parameters.

Results: There was a significant reduction of FPG level seen in all three groups (p value - Group I <0.0001, Group II < 0.005, and Group III <0.0001). Group I and III showed significant reduction of PPG with p value <0.0001. There was a significant reduction of HbA1c seen in all the three groups (p<0.0001).

Conclusion: From the results of this study, it could be concluded that all the three groups were comparable in their efficacy.

Keywords: Diabetes, Fasting plasma glucose, Postprandial plasma glucose, Hemoglobin A1c Metformin, Sitagliptin, Voglibose, Glimepiride.

 DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10i12.22050

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder and a major public health issue in which the patient has high blood glucose levels either because of inadequate insulin production in the body or irresponsiveness of the cells to insulin or both. Patients with high blood glucose will often experience polyuria, polydipsia, polyphagia, and also other non-specific symptoms. It is often referred as "diabetes." Diabetes is the one of the most common non-communicable disease globally and have increased morbidity and mortality rates. It had affected 50 million in 2010 and expected 87 million in 2030 of Indian population and affected 285 million in 2010 and expected 439 million in 2030 globally [1]. India leads the world with the largest number of diabetic subjects and has become the "Diabetes Capital of the World." Reduced physical activity, increased urbanization, sedentary lifestyle, obesity, and unhealthy dietary habits are the etiological factors [2]. Even low body mass index (BMI) Indians develop diabetes at a young age due to genetic predisposition [3]. Certain genes are responsible for the development of diabetes in Indian population [4]. Hence, the prevalence rate has been increasing in Indian population. Based on insulin synthesis and secretion, DM is mainly classified into Type 1 diabetes (nil or scanty insulin secretion) and Type 2 diabetes (insulin resistance).

Since the morbidity and mortality are more in diabetes, treatment is mandatory. Treatment consists of non-pharmacologic and pharmacological therapy. Non-pharmacologic therapy includes diabetes education, exercise, weight loss, and medical nutrition therapy. In pharmacological therapy, the two broad categories are insulin and oral antidiabetic agents. Insulin is the only treatment in Type 1 diabetes and is also indicated in Type 2 diabetes. The oral hypoglycemic agents for Type 2 diabetes are insulin secretagogues, sulfonylureas and meglitinides, and insulin sensitizers such as biguanides and thiazolidinediones, α-glucosidase inhibitor is voglibose, and dipeptidyl peptidase-4 inhibitors such as sitagliptin and glucagon-like peptide-1 agonists are existing and commonly prescribed. These drugs have different pharmacokinetics and pharmacodynamics property. The United Kingdom Prospective Diabetes Study report showed that 50% of monotherapy patients required the second drug after 3 years, and 75% of patients required multiple therapies after 9 years to obtain hemoglobin A1c (HbA1c) target [5]. In action in diabetes and vascular disease, preterax and diamicron-modified release-controlled evaluation trial proved that hyperglycemia is strongly associated with major macro- and micro-vascular complications [6]. Insulin resistance is the major etiology and produces complications in Type 2 diabetes. Metformin exerts its action by reducing hepatic gluconeogenesis and increasing insulin-mediated glucose utilization in peripheral tissue (muscles and liver). Additional advantages of metformin are less hypoglycemia, weight loss, anti-ischemic to cardiac tissue, anti-neoplastic, and improvement in non-alcoholic hepatosteatosis. Metformin is evaluated as a primary drug in this study to overcome insulin resistance. Although many oral antidiabetic agents are available, we have to choose a drug with better efficacy, less adverse effects, and lower hypoglycemic property. Hence, we would like to compare the efficacy and safety of the combination of metformin with sitagliptin, voglibose, and glimepiride.

METHODS

The present study was conducted in patients attending the diabetology outpatient department of SRM Medical College Hospital and Research

Centre, Potheri, Kancheepuram District from January 2013 to January 2014. The study was approved by the Institutional Ethics Committee of SRM MCH and RC.

Inclusion criteria
Patients diagnosed with type 2 DM, both male and female of age 20-65 years, and HbA1c level below 8.5% were included in the study.

Exclusion criteria
Type 1 DM, patients with known hypersensitivity to metformin, sitagliptin, voglibose and glimepiride, pregnant and lactating females, renal impairment, serum creatinine more than 1.4 mg/dl, and significant gastrointestinal diseases were excluded from the study.

Sample size
The sample size was estimated using hypothesis testing for two means (equal variances) based on the previous studies with the accuracy considered was 1% as α error, and power of 90% with sample size 40 was calculated in each group.

Study design
This study was a prospective, randomized clinical trial study. Written informed consent was obtained from the patients in English and local language. Based on the inclusion and exclusion criteria, 40 patients in each group were randomly assigned in three groups. Group I patients were instructed to receive metformin 500 mg + sitagliptin 50 mg, Group II were metformin 500 mg + with voglibose 0.2 mg, and Group III were metformin 500 mg + with glimepiride 1 mg. The drugs were administered orally for 3 months. A baseline demographic data such as age, sex, BMI, comorbid diseases, personal habits, family history, and drug history were recorded and entered in the pro forma sheet. The outcome of the therapy was based on the level of improvement in the fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c levels.

Statistical methods
Statistical analysis was done using the Statistical Package for the Social Sciences. Results were presented as a mean ± standard deviation. Results on categorical measurements were presented in number (%). Significance was assessed at 3% level of significance. They are $p<0.05$, means - suggestive significance (95%), $p<0.01$, means-moderately significant (99%), and $p<0.001$, means- highly significant (99.9%). Paired Student's t-test was used to find the significance of study parameters in the three groups (intragroup analysis). Multiple comparisons were done in between groups at the end of the 3rd month using analysis of variance. Quantitative analysis was done by Chi-square test.

RESULTS

The present study was compared the efficacy and safety among metformin with sitagliptin, metformin with voglibose, and metformin with glimepiride in patients with type 2 DM in fixed dosage form for 3 months. The biochemical parameters - FPG, PPG, and HbA1c were estimated before and after the treatment. There was a significant reduction of FPG level seen in all three groups (p value - Group I <0.0001, Group II <0.005, and Group III <0.0001) (Fig. 1). The PPG was significantly reduced in Group I and Group III ($p<0.0001$) (Fig. 2). However, Group II did not show a significant reduction in PPG. There was a significant reduction of HbA1c seen in all the three groups ($p<0.0001$) (Fig. 3).

On multiple comparisons, there was equal reduction of FPG, PPG, and HbA1c seen in all the three groups (Table 1).

There was mild hypoglycemia seen in Group I and III with 2.5%, whereas abdominal discomfort and bloating was observed in Group II with 2.5% (Table 2).

DISCUSSION

DM is a group of heterogeneous disorders in which carbohydrate metabolism is altered. The estimated prevalence rate of diabetes in India is 87 million by 2030. Uncontrolled DM is one of the most common risk factors for many diseases. Diet and exercise is the cornerstone for the treatment of diabetes. When these fail, the patients are usually treated with sulfonylurea and also by other groups of drugs. The overall therapeutic goal of type 2 DM is to achieve and maintain target FPG, PPG, and HbA1c levels. The primary defect in type 2 DM is insulin resistance,

Table 1: Multiple comparisons of plasma glucose parameters in post-treatment groups

Groups	FPG	PPG	HbA1c
Group I (n=40)			
Metformin	120.0	157.9	6.603
With	±	±	±
Sitagliptin	2.276	6.650	0.120
Group II (n=40)			
Metformin	118.95	161.93	6.490
With	±	±	±
Voglibose	3.285	7.066	0.110
Group III (n=40)			
Metformin	117.33	167.38	6.475
With	±	±	±
Glimepiride	3.173	7.460	0.142

FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin A1c

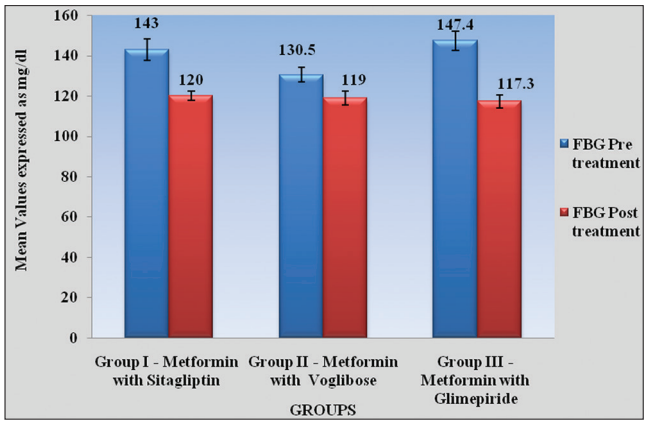

Fig. 1: Comparison of fasting plasma glucose in three groups

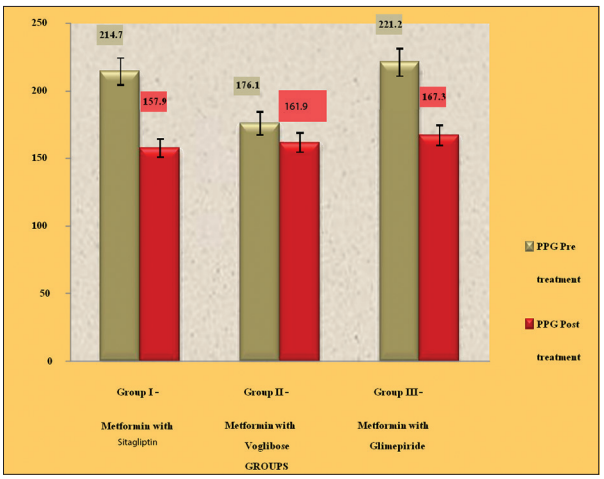

Fig. 2: Comparison of postprandial plasma glucose in three groups

Table 2: Safety parameters observed in three groups

Safety parameters	Group I Metformin with sitagliptin (n=40)	Group II Metformin with voglibose (n=40)	Group III Metformin with glimepiride (n=40)
Hypoglycemia (%)	1 (2.5)	0 (0)	1 (2.5)
Flatulence (%)	0 (0)	1 (2.5)	0 (0)
Abdominal bloating/discomfort (%)	0 (0)	1 (2.5)	0 (0)
Pharyngitis (%)	0 (0)	0 (0)	0 (0)
Giddiness (%)	0 (0)	0 (0)	0 (0)

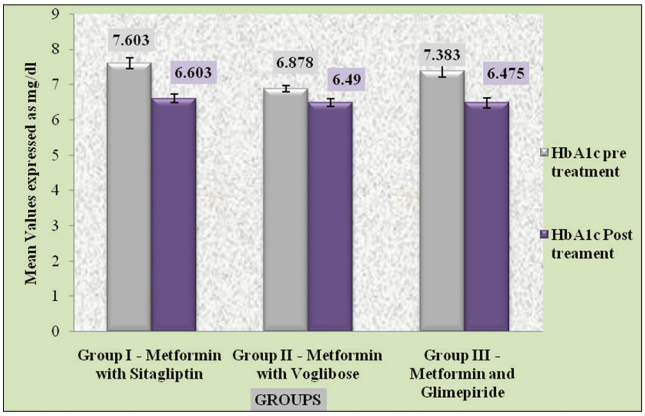

Fig. 3: Comparison of hemoglobin A1c in three groups

which decreases the response to target tissues to insulin. Insulin resistance enhances the glucose production by the liver and impairs the glucose uptake by the peripheral tissues. Inhibition of α-glucosidase, a key enzyme in carbohydrate digestion in the small intestine, is useful in postprandial hyperglycemia and hyperinsulinemia, thus in improving insulin sensitivity [7]. In the early stages of the disease, the pancreas is able to overcome insulin resistance by producing more insulin. As the disease progresses, the pancreas is unable to overcome the insulin resistance, leading to the development of type 2 DM. Metformin reduces the blood glucose levels by lowering hepatic glucose production and increasing the peripheral utilization of glucose. Metformin has regulatory actions on lipid metabolism, improves endothelial function, decreases hypercoagulation, and has a protective effect on the cardiovascular system. Since insulin resistance is the most common pathology in Type 2 diabetes, metformin is the most commonly used drug to treat Type 2 diabetes along with glimepiride [8]. ADA and EASD also recommend metformin as the first-line drug in type 2 DM. Hence, in our study, we have taken metformin as the primary drug.

The present study compared the efficacy and safety among metformin with sitagliptin, metformin with voglibose, and metformin with glimepiride in patients with type 2 DM. In this study, 40 patients were taken in each group. The mean age in metformin with sitagliptin (Group I) was 50.8 years, metformin with voglibose (Group II) was 47 years, and metformin with glimepiride (Group III) was 52 years. The male:female ratio was 17:23 in Group I, 26:14 in Group II, and 19:21 in Group III. Lim *et al.* reported in their study that early initial combination therapy of sitagliptin and metformin in drug-naïve Type 2 diabetic patients with low β-cell function has produced a significant reduction in FPG, PPG, and HbA1c (13%) at 12 weeks [9]. In another study by Williams-Herman *et al*., the combination of sitagliptin with metformin showed significant reduction of FPG and PPG level [10]. Jeon *et al*. reported in their study that there was a well comparable statistically significant reduction of FPG, PPG, and HbA1c seen in vildagliptin-metformin and glimepiride-metformin groups [11]. There was a study by Weitgasser *et al.* which reported that glimepiride significantly reduced HbA1c [12]. Noriko *et al*. observed that voglibose significantly had reduced FPG and PPG levels [13]. There was a study in voglibose by Takami *et al.* which showed a significant reduction of FPG and HbA1c level. It also showed a beneficial effect on acute insulin response and less effect on BMI [14]. Ismail *et al*. demonstrated that voglibose showed a significant reduction of FPG, PPG, and HbA1c level [15].

In this study, there was a significant reduction of FPG level seen in all the three groups (p value - Group I <0.0001, Group II <0.005, and Group III <0.0001) (Fig. 1). The PPG was significantly reduced in Groups I and III (p<0.0001) (Fig. 2). There was reduced PPG level in Group II also, but it was not statistically significant. There was a significant reduction of HbA1c level seen in all the three groups (p<0.0001) (Fig. 3). When multiple comparisons was done, there was an equal reduction of FPG, PPG, and HbA1c seen in all the three groups (Table 1). Hypoglycemia is the major shortcoming of oral hypoglycemic agents. Arechavaleta *et al*. described in their study that hypoglycemia was reported for 114 (22%) patients treated with glimepiride and 36 (7%) patients treated with sitagliptin [16]. In this study, there was mild hypoglycemia seen in Groups I and III with 2.5%, whereas abdominal discomfort and bloating were observed in Group II with 2.5% (Table 2).

CONCLUSION

DM is a metabolic disorder with an increase in prevalence, morbidity, and mortality rate worldwide. The available treatment focuses on reducing hyperglycemia and increasing insulin sensitivity. The primary goal of treatment is to reduce and maintain the target HbA1c level at 6-7%, which can reduce the micro- and macro-vascular complications. The currently available drugs act by different mechanisms to lower the blood glucose level. Each of the drugs has its own efficacy and tolerability. The main aim of this study is to compare the efficacy and safety among metformin with sitagliptin, metformin with voglibose, and metformin with glimepiride in patients with type 2 DM. The results of this study were analyzed, and it could be concluded that all three groups had equal efficacy in controlling the FPG, PPG, and HbA1c level. Only a few cases of metformin with glimepiride combination had mild hypoglycemia, which subsided after food intake.

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