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

KALA P1*, JAMUNA RANI R1, KUMAR JS2

1Department of Pharmacology, SRM Medical College Hospital & Research Centre Potheri, Kattankulathur - 603 203, Kancheepuram, Tamil Nadu, India. 2Department of General Medicine, SRM Medical College Hospital & Research Centre Potheri, Kattankulathur - 603 203, Kancheepuram, Tamil Nadu, India. E-mail: ???

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.

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 285 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, prerax 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 glucoseogenesis 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 an 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 5% 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).

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 ± 2.276 ± 6.650 ± 0.120 ± 0.100 |
| With Sitagliptin | ± 0.120 ± 0.120 ± 0.120 |
| Group II (n=40) | Metformin 118.95 ± 161.93 ± 6.490 ± 3.285 ± 7.066 ± 0.110 ± 0.100 |
| With Voglibose | ± 0.110 ± 0.110 ± 0.110 |
| Group III (n=40) | Metformin 117.33 ± 167.38 ± 6.475 ± 3.173 ± 7.460 ± 0.142 ± 0.142 |
| With Glimepiride | ± 0.142 ± 0.142 ± 0.142 |

FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin A1c
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-Lim 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 Weigasser et al. which reported that glimepiride significantly reduced HbA1c [12]. Noriko et al. observed that voglibose significantly had reduced PPG 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 PPG, PPG, and HbA1c seen in all the three groups (Table 1). Hypoglycemia is the major shortcoming of oral hypoglycemic agents. Arechavala 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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