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AN OPEN-LABEL, PROSPECTIVE, OBSERVATIONAL STUDY OF EFFICACY AND SAFETY OF GLIMEPIRIDE VERSUS VILDAGLIPTIN AS AN ADD-ON TO METFORMIN IN PATIENTS NOT ACHIEVING TARGET WITH METFORMIN MONOTHERAPY IN TYPE II DIABETES MELLITUS

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ABSTRACT

Introduction: Diabetes is considered nowadays a global epidemic affecting more than 8% of adult population worldwide. Glimepiride and Vildagliptin are considered as standard second line agent after metformin as per American Diabetic Association guideline for the treatment of Type-II diabetes. Few studies have been done comparing the efficacy and safety of these two well prescribed drugs. **Methodology:** It was an open-label, prospective, parallel group, observational study. Type 2 diabetic patients (in whom glycemic control not achieved by Metformin alone) were enrolled. They were divided into two groups, group 1 getting Metformin + Vildagliptin and group 2 getting Metformin + Glimepiride. Fasting Plasma glucose, Post-prandial plasma glucose and HBA1C were recorded at baseline and after 6 months. **Result and Discussion:** A total 110 patients were included in the study. A total of 100 patients could be followed having 50 patients in each treatment arm. In both groups, FPG, PPPG and HBA1C levels decreased significantly (p value <0.0001) over 6 months. Vildagliptin-Metformin treatment showed an FPG, PPPG and HbA1c reduction comparable to that of the Glimepiride-Metformin treatment over a period of 6 months. Statistically significant wt gain is noted in the Group 2. Relative Risk of developing neuro-glycopenic symptoms in Group 2 was 8 fold compared to Group 1. In each groups, only 11 patients (22%) reached target HBA1C level. **Conclusion:** Vildagliptin-Metformin combination treatment offered comparable efficacy in terms of HbA1c, FPG & PPPG reduction but significantly less weight gain, and a lower risk of hypoglycemia in comparison to Glimepiride-Metformin combination. When safety is considered along with effectiveness, the Vildagliptin has an edge over glimepiride as second line agent.

KEYWORDS: Type II Diabetes, Metformin, Vildagliptin, Glimepiride, Efficacy, Hypoglycemia, Weight gain.

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders characterized by hyperglycemia, due to reduced insulin secretion, reduced glucose utilization and increased glucose production. It will lead to both micro-vascular and macro-vascular complications leading multiple organ damage. According to International Diabetes Federation (IDF), about 451 million people worldwide are suffering from Type II DM in 2017.[1] In India, the prevalence of Type II DM reached 72 million as speculated by IDF.[2] Of the total healthcare expenditure worldwide nearly 11% is spent on diabetes. So diabetes economically hampers development of these nations and creates a significant burden on world economy.[3] Several clinical studies have demonstrated that tight glycemic control is necessary to prevent diabetic complications in type 2 as well as type 1 diabetic patients.[4-7] In general, the ADA suggests that the goal is to achieve an HbA1c as close to normal(<7%) as possible without significant hypoglycemia. Oral anti-diabetic agents are the most commonly prescribed pharmacotherapy for diabetes. Treatment algorithms by several professional societies (ADA/ European Association for the Study of Diabetes [EASD], IDF, AACE) suggest metformin as initial therapy because of its efficacy, known side effect profile, and low cost. Metformin's advantages are that it promotes mild weight loss, lowers insulin levels, and

improves the lipid profile slightly. After the failure of metformin alone to maintain target glucose control, the decision to prescribe a second-line therapy is challenging because as per the standard guidelines (ADA guideline) if the A1C target is not achieved after approximately 3 months, a combination of metformin and one of these six treatment options to be considered: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin.[8-10] Drug choice is based on patient preferences as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia.[11] Glimepiride is a second generation Sulfonylurea and Vildagliptin is an oral and highly selective di-peptidyl peptidase-4 (DPP-4) inhibitor. Although sulfonylurea is well-known as being effective in lowering blood glucose (HBA1c reduction 1.25% vs placebo)[12], it carries risk of body weight gain and severe hypoglycemia.[13] Improvements in glycemic control by Vildagliptin(HBA1c reduction 0.75% vs placebo)[12] are mediated primarily by glucose dependent increased insulin secretion and the suppression of glucagon secretion, without risk of hypoglycemia.[13] Metformin, Glimepiride & Vildagliptin all these drugs are available at free of cost in R G Kar Medical College, Kolkata. Hence both Glimepiride & Vildagliptin are widely used along with Metformin to combat hyperglycemia in the diabetic clinic of this institute. As there is lack of study in Indian population regarding efficacy and safety of vildagliptin-metformin treatment compared to those of glimepiride-metformin treatment in type 2 diabetic patients, it is thought that it is worth to do this study to assess the effect of vildagliptin versus glimepiride on glycemic control in Type 2 DM patients uncontrolled with Metformin monotherapy.

Objectives

1. To compare the Glycosylated Hemoglobin (HbA1c), Fasting Plasma Glucose (FPG) & 2-hrs Post Prandial Plasma Glucose (PPPG) reduction between two groups
2. To compare weight gain & incidence of hypoglycemia between two groups.

MATERIALS AND METHODS

It was an open-label, prospective, parallel group, observational study. The participants of the study were type 2 diabetic patients diagnosed by attending physician (in whom glycemic control not achieved by Metformin alone) getting Metformin + Vildagliptin or Metformin + Glimepiride who will attend the Diabetic Clinic under Department of Medicine of R.G. Kar Medical College & Hospital in this tertiary care hospital between 1/7/15 to 31/12/15 & who fulfill the inclusion criteria. Sample size was not calculated - Patients attended the Diabetic Clinic in specified time & fulfilled the inclusion criteria were taken as study population. After obtaining approval from the IEC & after taking written consent from the patients they were followed up for 6 months. These patients were divided into two groups:

Group 1: Getting Vildagliptin 50mg twice daily as an add-on to Metformin (at least 1000mg/day)
Group 2: Getting Glimepiride (1 -4 mg) once daily as an add-on to Metformin (at least 1000mg/day)

As per the protocol followed in the Diabetic Clinic of this hospital, the patients who were on Metformin monotherapy (for at least 4 wks) were considered as having uncontrolled plasma glucose level, who fulfill any of these following criteria:

1. FBS greater than 120mg/dL
2. PPBS greater than 180mg/dL
3. HbA1c greater than 7%

Fasting Plasma Glucose (FPG) & Post Prandial Plasma Glucose (PPPG) & Glycosylated Hemoglobin (HbA1c) values were noted at the beginning of the study. Then FPG, PPPG were measured monthly for 6 months & HbA1c value was measured 3 monthly after starting the second oral hypoglycemic agent. Data collection for this study was done at Diabetic Clinic, R.G. Kar Medical College & Hospital, Kolkata & data processing done at Department of Pharmacology, R.G. Kar Medical College & Hospital, Kolkata. The total study duration for the present was 01.07.2015 to 30.06.2016. Patient recruitment was done in first six months i.e. from 1/7/15 to 31/12/15. Those patients were followed up for next six months till the date of recruitment. This study was conducted in accordance with the Declaration of Helsinki Principles. The study was started only after obtaining permission from the Institutional Ethics Committee. Informed consent was taken from each subject before inclusion into the study. Personal data of the patients were obtained and recorded. Patients were screened for the following inclusion & exclusion criteria before recruitment.

Inclusion Criteria

T2DM patients (of both sexes & all ages) not achieving glycemic control with Metformin monotherapy (at least 1000mg/day) for at least past 4 weeks & getting Glimepiride or Vildagliptin as second drug.

Exclusion Criteria: Type1 DM patients, Diabetes in pregnancy, Patients with renal (Creatinine Clearance less than 50ml/min) or hepatic impairment (pre-treatment ALT/AST greater than 3 times UNL), Patients with COPD or Moderate or severe persistent Asthma, CHF (NYHA Class 3 & 4), Patient allergic to Metformin, Vildagliptin or Glimepiride.

The medicines were prescribed by the physicians of diabetes clinic in R.G. Kar Medical College & Hospital. Doses were adjusted at regular follow-ups by them with an aim to achieve euglycemia.

For measurement of FPG blood samples were collected from patients after 8 – 10 hours fasting & for measurement of PPPG blood samples were collected from patients 2 hours after lunch. Blood sample for

measurement of HbA1c were taken at any time as per patients' & investigator's convenience. The tests were carried out by following methods:

1) FPG-by endpoint assay and kinetic assay-GODPOD method[14]
2) PPPG - by endpoint assay and kinetic assay-GODPOD method[14]
3) HbA1c - by Ion Exchange Resin method[15]

Data have been analyzed by GRAPHPAD PRISM V 7.0 software. Categorical data have been analyzed by Chi-Square test whereas; numerical data have been analyzed by Paired t test, unpaired t test and Mann Whitney U Test. P value less than 0.05 have been considered significant.

RESULTS

A total 110 patients were included in the study. Out of them, 54 patients received Metformin plus Vildagliptin (Group 1) and rest received Metformin plus Glimepiride (Group 2). A total of 100 patients could be followed having 50 patients in each treatment arm. The demographic profile of the patients is given in Table 1.

Table 1: Patients' demographic profile.

	Group 1	Group 2	P value
Age (in yrs)	49.36 ± 9.52 (mean ±SD)	51.4 ± 9.46 (mean ±SD)	0.29
Sex Male female	 27 (54%) 23 (46%)	 24 (48%) 26 (52%)	0689
Body wt (in kg)	69.38 ± 9.21 (mean ±SD)	70.82 ± 9.05 (mean ±SD)	0.43

The groups were comparable in respect of their age, gender and BMI values. Figure 1 shows the change of mean Fasting plasma glucose and Post-prandial plasma glucose in both groups.

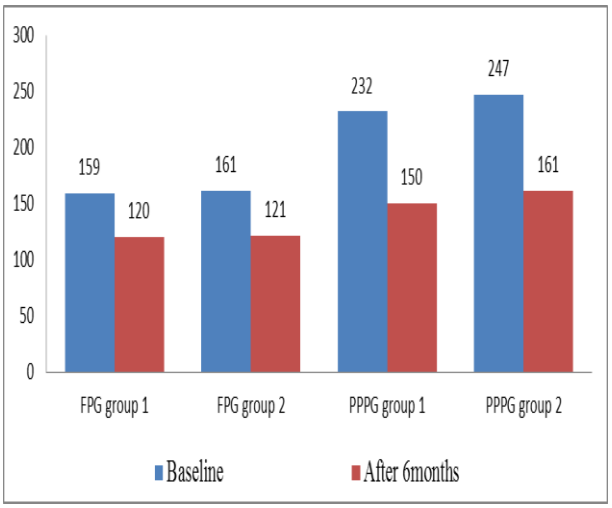

Figure 1: Change of mean FPG & PPPG level.

It is clearly evident that in both groups, FPG levels and PPPG levels decreased significantly (p value <0.0001) over 6 months. Similarly, figure 2 shows the change of mean HBA1C level in both groups.'

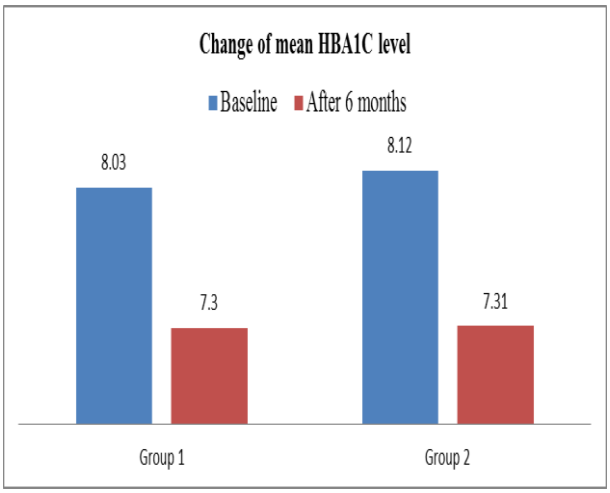

Figure 2: Change of mean HBA1C level.

In both groups, mean HBA1C level decreased significantly (p value <0.0001 in both groups). Regarding between group comparisons, table 2 shows the reduction of FPG and PPPG level in two groups. Baseline FPG levels and HBA1C levels were comparable between groups (p value 0.644 and 0.20 respectively). However baseline PPPG levels were not comparable (p value 0.005). Mean PPPG levels were higher in Glimepiride groups than Vildagliptin group. After 6 months, mean FPG and HBA1C level were also comparable. (p value 0.816 and 0.88 respectively). Mean PPPG levels were not comparable also at the end of follow up among two groups (p value 0.001). However mean reduction of FPG and PPPG were comparable between groups as shown in Table 2.

Table 2: Comparison of FPG & PPPG reduction between groups.

	Reduction (Mean ± SD) Group 1	Reduction (Mean ± SD) Group 2	P value (unpaired t test)
FPG	38.42±14.41 mg/dl	39.68± 16.44 mg/dl	0.6845
PPPG	82.56 ± 21.92 mg/dl	86.42 ± 25.42 mg/dl	0.4181

Reduction in HbA1c level in the Metformin + Vildagliptin group is 0.7(0.5,0.9) (Median, interquartile range) which is comparable to that of Metformin + Glimepiride group i.e. 0.8(0.6,0.9)(Median, interquartile range) (p value = 0.12) (Mann Whitney test applied), as shown in Table 3.

Table 3: Comparison of HbA1c reduction between groups.

Group 1	Group 2	P value (Mann Whitney U test)
0.7(0.5,0.9) (Median, interquartile range)	0.8(0.6,0.9) (Median, interquartile range)	0.12

Table 4 shows the mean Body weight levels in two groups over the 6 month follow up. There is no statistically significant wt gain in the Metformin + Vildagliptin group. On the other hand, statistically significant wt gain is noted in the Metformin + Glimepiride group. Wt gain in the group 2 is 2(1,2)(Median, interquartile range), where Wt gain in the group 1 is 0(0,0)(Median, interquartile range) 23– the difference is statistically significant (p value <0.05) (Mann Whitney test applied).

Table 4: Comparative evaluation of Wt gain in group 1 and group 2.

	Baseline	After 6 Months	Wt Gain	95 % CI	P value
Group 1 (in kg)	70.82 ± 9.05 (mean ± SD)	70.94 ± 9.11 (mean ± SD)	0(0,0) (Median, interquartile range)	-0.06 to 0.34	0.18
Group 2 (in kg)	69.38 ± 9.21 (mean ± SD)	70.86 ± 9. (mean ± SD)	2(1,2) (Median, interquartile range)	1.27 to 1.85	<0.05

Among 50 patients in group 1, 1 patient suffered from neuro-glycopenic symptoms suggestive of hypoglycemia & in group 2, among 50 patients 8 patients suffered from neuro-glycopenic symptoms (Table 26). It is calculated from Fisher's exact test that Relative Risk of developing neuro-glycopenic symptoms in group 2 is 8 fold compared to group 1.

In each groups, only 11 patients (22%) reached target HBA1C level (≤ 7%).

DISCUSSION

Present prospective, parallel group, observational study was conducted to compare the effect of Vildagliptin versus Glimepiride as add-on in type 2 diabetic patients uncontrolled with Metformin monotherapy.

In the present study, the Vildagliptin-Metformin treatment showed an FPG, PPPG and HbA1c reduction comparable to that of the Glimepiride-Metformin treatment over a period of 6 months, which is in line with the observation made by Hyun Jeong Jeon et al. (2011), who found FPG, PPPG and HbA1c reduction in Vildagliptin-Metformin was comparable to that of the Glimepiride-Metformin treatment over a period of 32 wks.[16]

The finding in the present study also corroborates with the result of the study conducted by Ferrannini E. et al (2009), which showed non-inferiority of vildagliptin (97.5% confidence interval 0.02%, 0.16%) with a mean (SE) change from baseline HbA1c (7.3% in both groups) to week 52 endpoint of -0.44% (0.02%) with vildagliptin and -0.53% (0.02%) with glimepiride. The study by Ferrannini E et al. (2009) showed FPG reductions were comparable between Vildagliptin-Metformin & Glimepiride-Metformin groups (mean [SE] -1.01 [0.06] mmol/l and -1.14 [0.06] mmol/l respectively). This result also is in line with the result obtained in present study.[17]

Regarding safety, the Vildagliptin-Metformin treatment has a favourable hypoglycemic profile. In the present study, there is 8-fold increased incidence of hypoglycemia with Glimepiride-Metformin as compared to Vildagliptin -Metformin. This observation supports the finding of the study by Hyun Jeong Jeon et al (2011)[16], which demonstrated 10-fold increased incidence of hypoglycemia with Glimepiride-Metformin in comparison to Vildagliptin-Metformin. Several papers have recently been published regarding the association between hypoglycemia and adverse clinical outcome.[18,19] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive blood glucose control did not produce any benefits with regard to CV events but did provoke unanticipated excess mortality: 19 of the 41 deaths were attributed to unexpected CV disease, which may have been related to severe hypoglycemia.[20]

In the present study, changes in body weight differed between the treatment groups. After 6 months, weight gain was significant in Glimepiride-Metformin group in comparison to Vildagliptin-Metformin group. This observation is in line with the finding by Hyun Jeong

Jeon et al.(2011),[16] which demonstrated at 32 weeks, body weight did not change in the vildagliptin-metformin treatment group, whereas the patients treated with glimepiride-metformin evidenced weight increase (2.35 kg) relative to baseline. The result is also consistent with the finding by Ferrannini E. et al (2009).[17] These results were consistent with findings reported in other studies involving vildagliptin or sitagliptin in combination with metformin.[21] In another study by Matthews et al.[21] reported results similar to the present study.DPP-4 inhibitors have been shown to improve glycemic control and measures of pancreatic β-cell function in clinical trials in the Asian population, including patients from China, India, and Korea.[22] Deterioration in the early insulin responses is frequently observed in patients with type 2 diabetes, particularly in the Asian population. DPP-4 inhibitors improved pancreatic β-cell dysfunction and may be associated with more improved responses in Asian than in Caucasian patients.[23]

CONCLUSION

Although the present study had several limitations e.g. small sample size, unicentric short duration study, and it is an observational study, the results demonstrated that Vildagliptin-Metformin combination treatment offered comparable efficacy in terms of HbA1c, FPG & PPPG reduction but significantly less weight gain, and a lower risk of hypoglycemia in comparison to Glimepiride-Metformin combination therapy in type 2 diabetic patients. When safety is considered along with effectiveness, the Vildagliptin-Metformin combination treatment may constitute a better therapeutic option than does the glimepiride-metformin combination treatment. However, as Vildagliptin is costlier than glimepiride, a cost-effectiveness study is planned to find out any superiority of either treatment regimen.

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