Original Article

Comparison of Safety and Efficacy of Glimepiride-Metformin and Vildagliptin- Metformin Treatment in Newly Diagnosed Type 2 Diabetic Patients

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Abstract

Objective: To compare the safety and efficacy of glimepiride and vildagliptin as add-on therapy to metformin in newly diagnosed patients with type 2 diabetes mellitus (T2DM). **Methods:** This 24-week, prospective, comparative, observational study was conducted among newly diagnosed patients with T2DM. The primary endpoint was a change in fasting plasma glucose (FPG), postpradinal glucose (PPG), and HbA1c from the baseline to week 24. The key secondary endpoints were monitoring treatment-emergent adverse events such as hypoglycemia, overall gastrointestinal symptoms and weight gain, and electrocardiogram (ECG) findings. **Results:** A total of 100 eligible patients were divided into two groups: group A (n = 50) received vildagliptin plus metformin and group B (n = 50) received glimepiride plus metformin. The mean age of the patients was 49.98 years and 52.12 years in group A and group B, respectively. Electrocardiographic findings were within normal limits in all the patients from group A, whereas 47 patients from group B showed normal ECG findings. A significant decrease in HbA1c, fasting and post-prandial plasma glucose was observed with group A and group B from the baseline to week-24. However, at week-24, reduction in HbA1c and blood glucose parameters were comparable between the groups. Safety outcomes did not show any events of hypoglycemia with vildagliptin. Mild hypoglycemia was reported with glimepiride in five patients. **Conclusion:** Vildagliptin-metformin appeared to be equally effective to glimepiride-metformin in reducing HbA1c level and blood glucose parameters, however, resulted in better adverse event profiles with lower risks of hypoglycemia.

Keywords: DPP-4 inhibitor, glucose-lowering effect, hypoglycemia, initial combination therapy

Introduction

Type 2 diabetes mellitus (T2DM) is the most common noncommunicable disease increasing throughout Asia.[1] According to the International Diabetes Federation (IDF), India has the second-highest number of patients with diabetes aged between 20 and 79 years as of 2019.[2] Treating patients with T2DM is most challenging due to its progressive nature and increasing complication with antidiabetic agents.

The choice of antidiabetic agents is based on efficacy along with drug safety. Metformin has been the most recommended monotherapy for the initial treatment of T2DM.[3-5] However, majority of patients have advocated combined therapy in the long run to maintain glycemic control. The combined regimens are effective to minimize the dosage of antihyperglycemic agents and thereby their unwanted effects. A combination of glimepiride plus metformin is widely used in Indian clinical settings due to its cost-effectiveness and efficacy in improving glycemic control.[6,7] However, a combination of glimepiride and metformin is frequently associated with side effects such as weight gain and hypoglycemic events.[8,9] Hence, physicians and researchers are in search of a combination having better efficacy and minimal side effects as compared to the present antidiabetic formulation available in the market.

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Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, an oral antidiabetic agent, having moderate efficacy with a good overall safety profile including low risk of hypoglycemia, low risk of edema, lipid neutral effect, and weight neutrality.[10] When vildagliptin was used as add-on treatment or initial combination therapy along with metformin, good glycemic control was achieved due to their complementary mechanism of action.[11] Many randomized clinical trials have demonstrated the comparative effectiveness of glimepiride and vildagliptin as add-on therapy to metformin.[9,12-14] But their results might not always reflect what actually could be expected in clinical practice. Therefore, the present study aimed to compare the safety and efficacy of glimepiride and vildagliptin as add-on therapy to metformin in newly diagnosed patients with T2DM.

Methods

Study design and patient population

This was a 24-week, single-center, prospective, comparative, observational study conducted at the endocrinology department of Patna Medical College, Patna, India in newly diagnosed patients with type 2 diabetes (T2DM) between July 2020 and December 2020. Patients of either sex and age above 18 years, diagnosed with T2DM were included in the study. The demographic, clinical, and other investigation details were obtained from the patients. The baseline demographics details including age, sex, anthropometric measurements, blood pressure, electrocardiographic findings, and biochemical parameters were recorded. Patients having fasting plasma glucose (FPG) ≥15.0 mmol/L hepatic, renal, or cardiovascular co-morbidities, and significant laboratory abnormalities were excluded from the study. Pregnant or lactating women were excluded from the study.

Treatment regimen

After screening, the eligible patients were divided into two groups: group A (n = 50) received vildagliptin plus metformin, and group B (n = 50) received glimepiride plus metformin. At initial 6 weeks, the patients from group A received metformin only (500 mg BID), followed by metformin (500 mg BID) and vildagliptin (50 mg BID) for up to 24 weeks. Similarly, the patients from group B received metformin (500 mg BID) for initial 6 weeks, followed by metformin (500 mg BID) and glimepiride (2 mg BID) for up to 24 weeks. The total duration of the study was 6 months. The fasting plasma glucose (FPG), postpradinal glucose (PPG) levels, and body weight were measured after every 6 weeks.

Endpoints

The primary efficacy endpoints were changes in FPG, PPG, and HbA1c from the baseline to week 24. Safety assessments included recording and monitoring of treatment-emergent adverse events such as hypoglycemia, overall gastrointestinal symptoms and weight gain, biochemical parameters, ECG findings, and blood pressure. Newly diagnosed diabetes was defined by fasting glucose ≥126 mg/dL or/and a 2 h post-load glucose ≥200 mg/dL of less than 1 year duration without treatment.

Hypoglycemia was defined by symptoms indicative of hypoglycemia and a self-monitored plasma glucose level of <3.1 mmol/L. Severe hypoglycemia was defined as an event requiring the support of another person to administer carbohydrate or hospitalization with or without a plasma glucose measurement <3.1 mmol/L.[15]

Statistical analysis

The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software. Continuous variables were expressed as mean (standard deviation [SD]), and the significance between the two groups was calculated using a parametric and nonparametric test. Categorical variables were expressed as frequency and percentages, and the significance was assessed using Chi-square test. A P value of <0.05 was considered statistically significant.

Ethical conduct of study

This trial was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of Patna Medical College, Patna (Ref. No: MF/873). Informed consent was obtained from participants before enrolment in the study.

Results

A total of 100 patients newly diagnosed with T2DM were included in this prospective observational study. The demographic characteristics are summarized in Table 1. The mean age of the patients did not vary significantly ($P > 0.05$) in group A (49.98 years) and group B (52.12 years). The proportion of men was higher than women in both the groups (group A, n = 30 and group B, n = 33). The mean duration of diabetes was comparable between both the groups (group A: 5.12 vs. group B: 4.78 months, $P > 0.05$).

At the baseline, biochemical analysis including blood glucose parameters, serum urea, serum creatinine, lipid profile, aspartate transaminase (AST), alanine transaminase (ALT), and thyroid-stimulating hormone (TSH) were comparable between the groups ($P > 0.05$) [Table 1]. Symptoms such as polyuria and thirst, both were observed in 19 patients from group A and 30 patients from group B, whereas 10 and 6 patients from group A and B, respectively showed only polyuria symptom. Electrocardiographic findings were within normal limits in all the patients from group A, whereas 47 patients from group B showed normal ECG findings. Two patients from group B presented with left ventricular hypertrophy, and one presented with central left ventricular hypertrophy.

Fasting and PPG levels were evaluated at the baseline, after 6 weeks with metformin only followed by vildagliptin with metformin and glimepiride with metformin at 12 weeks and 24 weeks. A significant decrease in FPG and PPG levels were observed within group A as well as group B ($P < 0.0001$). In group A, the baseline FPG decreased from 188.40 mg/dL to 145.36 mg/dL with metformin only that further decreased to

Table 1: Demographic characteristics

Parameters	Group A (vildagliptin + metformin) *n*=50	Group B (glimepiride + metformin) *n*=50	*P*
Age (years)	49.98 (10.63)	52.12 (9.24)	0.190
Age group (years)			
30-50	31	22	-
>50	19	28	
Sex *n* (%)			
Men	30 (60.00)	33 (66.00)	-
Women	20 (40.00)	17 (34.00)	
Anthropometric measurements			
Height (cm)	164.36 (7.49)	164.92 (6.83)	0.201
Weight (kg)	70.18 (5.60)	70.92 (5.97)	0.522
BMI (kg/m^2)	25.96 (2.02)	26.13 (1.82)	0.901
Duration of diabetes (months)	5.12 (2.19)	4.78 (2.09)	0.777
Blood pressure			
SBP (mmHg)	141.28 (22.45)	143.72 (19.85)	0.311
DBP (mmHg)	83.20 (6.50)	84.96 (6.85)	0.572
Biochemical analysis			
FPG (mg/dL)	188.40 (22.45)	206.68 (24.71)	0.527
PPG (mg/dL)	395.64 (28.23)	410.50 (25.86)	0.923
HbA1C (%)	8.14 (0.26)	8.33 (0.29)	0.191
Serum urea (mg/dL)	20.78 (5.17)	20.62 (4.11)	0.219
Serum creatinine (mg/dL)	0.61 (0.08)	0.61 (0.09)	0.639
eGFR (mL/min/1.73 m^2)	112.66 (12.74)	112.94 (12.56)	0.707
ACR (mg/L)	26.32 (5.47)	26.08 (5.96)	0.302
Total cholesterol (mg/dL)	179.29 (44.45)	175.37 (44.03)	0.712
HDL (mg/dL)	51.53 (13.36)	50.71 (13.18)	0.794
Triglyceride (mg/dL)	205.61 (141.34)	226.09 (75.25)	0.842
LDL (mg/dL)	103.36 (14.11)	99.33 (34.28)	0.334
VLDL (mg/dL)	39.54 (26.85)	38.47 (15.68)	0.421
AST (IU/L)	26.10 (7.89)	26.06 (7.78)	0.870
ALT (IU/L)	29.04 (8.14)	30.78 (7.46)	0.274
TSH (µIU/mL)	3.14 (2.51)	3.60 (3.11)	0.434
Symptoms, *n* (%)			
Polyuria	10 (20.00)	06 (12.00)	
Polyuria and thrust	19 (38.00)	30 (60.00)	-
No symptoms	21 (42.00)	14 (28.00)	
Electrocardiographic findings			
Within normal limits	50 (100.00)	47 (94.00)	
Left ventricular hypertrophy	-	2 (4.00)	-
Central left ventricular hypertrophy	-	1 (2.00)	

Data are shown as mean (SD) unless specified. ACR, albumin to creatinine ration; AST, aspartate aminotransferase; ALT, alanine transaminase; BMI, body mass index; DBP, diastolic blood pressure; eGFR; estimated glomerular filtration rate; FPG, fasting blood glucose; HbA1c; glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPG; postprandial glucose; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone, VLDL, very low-density lipoprotein

109.60 mg/dL with vildagliptin added to metformin, and it was sustained up to 24 weeks as FPG value was 110.46 mg/dL. Likewise, the baseline PPG levels in group A decreased from 395.64 mg/dL to 262.24 mg/dL with metformin only that further decreased to 136.76 mg/dL with vildagliptin added to metformin, and it was sustained up to 24 weeks as PPG value was 133.32 mg/dL. In group B, the baseline FPG decreased from 206.68 mg/dL to 159.52 mg/dL with metformin only that further decreased to 112.20 mg/dL with glimepiride added to metformin, and it was sustained up to 24 weeks as FPG value was 110.52 mg/dL. Furthermore, the baseline PPG levels in group B decreased from 410.50 mg/dL to 277.62 mg/dL with metformin only that further decreased to 144.68 mg/dL with glimepiride added to metformin, and it was sustained up to 24 weeks as PPG value obtained was 136.66 mg/dL [Table 2].

The analysis did not show any significant differences in FPG, PPG levels, and body weight at 6 weeks and 12 weeks ($P > 0.05$) [Figure 1]. The biochemical analysis showed a decrease in efficacy endpoints such as FPG, PPG, and HbA1c within the group, but there were no

Table 2: Comparison of fasting and postprandial glucose levels at 6, 12, and 24 weeks

Group	Anti-diabetic agent	Fasting glucose (mg/dL)	*P*	Post-prandial glucose (mg/dL)	*P*
Group A (vildagliptin + metformin) *n*=50	Baseline	188.40 (22.46)	<0.0001	395.64 (28.24)	<0.0001
	Metformin only (6 weeks)	145.36 (14.54)		262.24 (26.64)	
	Vildagliptin + Metformin (12 weeks)	109.60 (11.34)		136.76 (19.33)	
	Vildagliptin + Metformin (24 weeks)	110.46 (5.35)		133.32 (8.21)	
Group B (glimepiride + metformin) *n*=50	Baseline	206.68 (24.72)	<0.0001	410.50 (25.86)	<0.0001
	Metformin only (6 weeks)	159.52 (25.48)		277.62 (31.22)	
	Glimepiride + Metformin (12 weeks)	112.20 (13.57)		144.68 (20.53)	
	Glimepiride + Metformin (24 weeks)	110.52 (7.10)		136.66 (8.10)	

Data are presented as mean (SD)

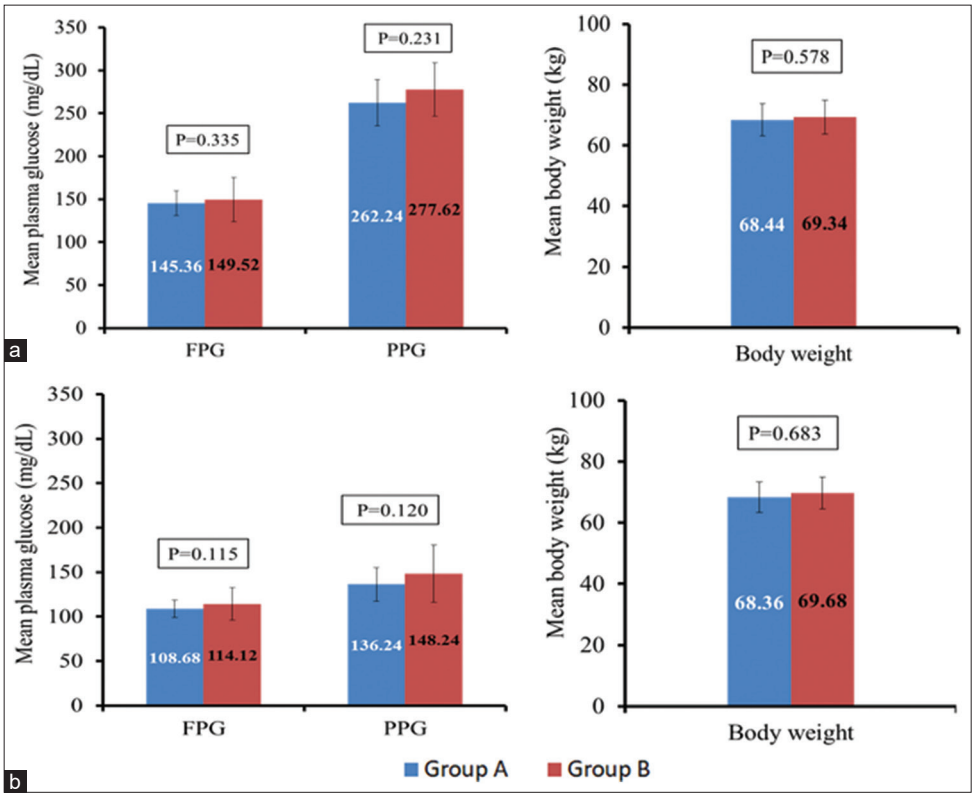

Figure 1: Comparison of FPG, PPG, and body weight between group A and B after (a) 6 weeks and (b) 12 weeks. FPG, fasting plasma glucose; PPG, postprandial glucose

significant differences between the groups. Estimation after 24 weeks showed a significant decrease in FPG levels in both the groups (P = 0.012). In group A, FPG decreased from 188.40 mg/dL to 110.46 mg/dL and in group B from 206.68 mg/dL to 110.52 mg/dL. There was a decrease in PPG and HbA1c levels after 24 weeks in both the groups as compared to the baseline. In group A, PPG levels decreased from 395.64 mg/dL to 133.32 mg/dL and in group B from 410.50 mg/dL to 136.66 mg/dL. Further, HbA1c levels in group A decreased from 8.14% to 6.98% and in group B, 8.33% to 6.99%. [Table 3]. Safety outcomes did not show any events of hypoglycemia with vildagliptin. Mild hypoglycemia was reported with glimepiride in five patients.

Discussion

The early combination therapy with glimepiride and metformin is the most commonly used combination, whereas DPP-4

Table 3: Comparison of efficacy endpoints after 24 weeks

Parameters	Group A (vildagliptin + metformin) *n*=50	Group B (glimepiride + metformin) *n*=50	*P*
FPG (mg/dL)	110.46 (5.34)	110.520 (7.10)	0.012
PPG (mg/dL)	133.32 (8.21)	136.66 (8.10)	0.505
HbA1c (%)	6.98 (0.26)	6.99 (0.24)	0.412
BMI (kg/m^2)	25.28 (2.05)	25.64 (1.83)	0.691
Serum Urea (mg/dL)	19.34 (3.97)	19.02 (3.55)	0.457
Serum creatinine (mg/dL)	0.57 (0.07)	0.59 (0.07)	0.943
eGFR (mL/min/1.73 m^2)	115.04 (11.42)	113.26 (9.35)	0.131
ACR (mg/L)	24.30 (4.50)	23.46 (4.92)	0.176
AST (IU/L)	23.38 (6.40)	23.76 (5.93)	0.554
ALT (IU/L)	29.06 (7.50)	30.30 (6.39)	0.062

Data are presented as mean (SD). ACR, albumin to creatinine ration; AST, aspartate aminotransferase; ALT, alanine transaminase; BMI, body mass index; eGFR; estimated glomerular filtration rate; FPG, fasting blood glucose; HbA1c; glycated hemoglobin; PPG; post-prandial glucose

inhibition is the new approach of treatment for T2DM which has the potential to reduce and may even normalize both FPG and PPG concentrations without adverse effects such as weight gain and hypoglycemia. Few studies have reported conflicting results of both vildagliptin and glimepiride added to metformin regarding the efficacy of antidiabetic agents and safety outcomes.[9,12,13,16]

In the present study, the vildagliptin-metformin treatment showed a reduction in HbA1c and blood glucose parameters comparable to that of the glimepiride-metformin treatment over a 24-week period. Electrocardiographic findings were within normal limits in the vildagliptin plus metformin group, whereas 6% of the patients from the glimepiride plus metformin group showed abnormal ECG findings. Furthermore, vildagliptin-metformin and glimepiride-metformin treatments did not induce weight gain, whereas vildagliptin-metformin provided definite advantages in terms of hypoglycemia incidence reduction.

In the present study, HbA1c was done at 3 months as the measurement of HbA1c provides an estimate of plasma glucose level over a period of 2 to 3 months preceding the test. The use of this indicator of glycemic control not only facilitates clinical trials but also assists routine management. When treatment is established and glycemic control appears stable, testing one or two times in a year is usually sufficient. In our study, at the end of the study period (6 months), satisfactory results were obtained for the glucose triad. All three parameters (HbA1c, FPG, and PPG) remained significantly lowered compared to the baseline in both the groups. These findings were consistent with the previous studies which evaluated early initiation of vildagliption or glimepiride add-on to metformin associated with durability in glycemic control.[12] This indicates both treatments were effective in antihyperglycemic effects and early initiation of this combination therapy would be a good approach to manage T2DM in drug naïve patients.

The mean HbA1c level was 8.14% and 8.33% in viltagliptin-metformin and glimepiride-metformin group at the baseline which was reduced to 6.98% and 6.99% at 24-weeks follow-up, respectively. There was no significant difference in HbA1c reduction between treatment groups. This is in accordance with the previous studies where both treatment groups showed similar efficacy in reducing HbA1c.[9,16] Contrast to this Sarkar BS *et al*.,[14] in a prospective observational comparative study in West Bengal, India, found significantly more reduction in HbA1c when glimepiride was added to metformin than vildagliptin and metformin at 4- month follow-up. However, another previous study reported superiority of vildagliptin-metformin combination compared to glimepiride-metformin in reducing HbA1c.[13] This indicates the lower incidence of treatment failure associated with vildagliptin and metformin combination therapy compared to glimepiride and metformin combination.

A significant decrease in FPG and PPG levels were observed within vildagliptin-metformin group as well as glimepiride-metformin group. In vildagliptin-metformin group, the baseline FPG decreased from 188.40 mg/dL to 145.36 mg/dL with metformin only that further decreased to 110.46 mg/dL with vildagliptin and metformin at week-24. Likewise, the baseline PPG levels in vildagliptin-metformin treatment decreased from 395.64 mg/dL to 262.24 mg/dL with metformin only that further decreased to 133.32 mg/dL with both vildagliptin and metformin at week-24. Similarly, in glimepiride-metformin group, FPG and PPG values were significantly reduced from the baseline to week-6 with metformin only and add-on glimepiride with metformin showed drastically reduced FPG and PPG values which were within the normal range. However, these values were comparable between the groups. Sarkar *et al*.[14] and Jeon HJ *et al*.[9] in accordance with the results of the present study, showed that vildagliptin added to metformin is inferior to glimepiride plus metformin in reducing blood glucose parameters. Conversely, a longitudinal interventional study by Gullapalli H. and Desai S. compared vildagliptin and glimepiride combination with metformin in patients who were already on metformin with poor glycemic control. After 3 months of treatment, FPG and PPG levels were 120.97 mg/dL and 199.67 mg/dL in vildagliptin metformin group and 132.5 mg/dL and 203.47 mg/dL in glimepiride metformin group, respectively. The FPG and PPG levels were

significantly reduced in the vildagliptin plus metformin group compared to the glimepiride plus metformin group.[12]

When safety outcomes were considered, there were no hypoglycemia events observed with vildagliptin metformin, whereas mild hypoglycemia was reported with glimepiride added to metformin. Similarly, a previous randomized comparative study of vildagliptin and glimepiride add on to metformin showed better adverse events profile with a 10-fold lower incidence of hypoglycemia in the vildgliptin group.[9] A real-life study from Asia reported 9% adverse events including one hypoglycemic event in drug naïve patients with T2DM. The initial combination therapy with vildagliptin and metformin was well tolerated in these patients associated with high HbA1c and cardiovascular risk factors.[17] This attributed to glucose-dependent nature of vildagliptin with insulinotropic polypeptide-mediated effect that helps to lower the incidence of hypoglycemia.[18] Moreover, vildagliptin has weight neutral activity. As the risk of hypoglycemia is more often associated with weight gain, previous studies reported no weight gain with vildagliptin metformin therapy.[17,19,20] This is confirmed by the present study findings. However, the mean body weight was comparable between both the groups at 6-weeks and 12-weeks follow-up. In contrast to this, a previous comparative study of vildagliptin and glimepiride showed glimepiride along with metformin is prone to weight gain and severe hypoglycemia.[9,12,13]

The present study was limited by a small sample size. This was a prospective comparative study from a single institution. Randomized trials with a larger sample size and longer follow-up are necessary to conclude robustly which treatment modality is better for diabetes management in long-term care.

Conclusion

Vildagliptin-metformin appeared to be equally effective to that of glimepiride-metformin in reducing HbA1c level and blood glucose parameters, however, resulted in better adverse event profiles with lower risks of hypoglycemia.

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Conflicts of interest

There are no conflicts of interest.

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