Original Research Article

Safety and efficacy of vildagliptin-metformin to glimepiride-metformin in type 2 diabetes mellitus patients - A comparative study

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Abstract

Background: Metformin and Vildagliptin have independent glucose-lowering properties and may increase GLP-1 levels by working through complementary mechanisms. The combination of metformin and glimepiride is a well-established therapy for type 2 DM. **Aim:** To compare the efficacy and safety of vildagliptin-metformin and glimepiride-metformin treatment in type 2 diabetic patients. **Material and Methods**: Patients was randomly assigned in (1:1) ratio after randomization to either of two groups (35 in each group), one group prescribed glimepiride(1mg) +metformin (500mg) twice daily half an hour before meals and other group vildagliptin(50mg)+ metformin(500mg) twice daily half an hour before meals. HbA1c, FBS, PPBS was repeated at the end of 3rd month. **Results:** The mean HbA1c levels at baseline (0 weeks) were 8.80 ±0.62and 8.99 ±0.37 in Group A and Group B respectively. Similarly, at 12 weeks mean HbA1c levels were 6.47±0.44 and 6.42±0.42 in Group A and Group B respectively. The change in percentage of HbA1c at 12 weeks was -26.06% and -27.86% in Group A and Group B respectively but no statistical significance different was found. (P=0.26). The HbA1c levels < 7 were achieved among 29 (41.43%) subjects in Group A as compared to 28 (40%) subjects in Group B. The difference between HbA1c levels among study groups was not statistically significant. (P=0.75). **Conclusion:** The efficacy and tolerability of vildagliptin, was similar, with no significant differences, when used to treat type 2 diabetic patients with inadequate blood glucose control by dual combination of metformin and glimepiride.
Key Word: Type 2 diabetes mellitus, vildagliptin, glimepiride, metformin, combination, glycemic control

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INTRODUCTION

Type 2 diabetes mellitus patients are more prone to cardiovascular complications, which can occur earlier and more frequently as compared to non-diabetic patients.[1]Early intensive glycemic control reduces the risk of diabetic complications both micro and macro vascular. According to various guidelines for T2DM treatment, metformin is recommended when diet and lifestyle interventions alone are unable to maintain blood glucose control at target levels.[2,3] Failure of monotherapy over time suggests the need for combination therapy to achieve or maintain glycemic goals.[4] Several oral therapies are approved for use in combination with metformin; however, they are not always effective and are associated with side effects.[5] Sulfonylureas are associated with hypoglycemia and weight gain. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral anti-diabetic agents that increase circulating concentrations of the glucagon-like peptide-1 (GLP-1).[6] GLP-1 released after meals but degraded by dipeptidyl peptidase-4 (DPP-4) rapidly. The DPP-4 inhibitors block the rapid inactivation of GLP-1 and improve glycaemic control.[7] Vildagliptin is a potent, oral and selective DPP-4 inhibitor for the treatment of patients with type 2 DM.[2] Metformin and Vildagliptin have

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independent glucose-lowering properties and may increase GLP-1 levels by working through complementary mechanisms. The combination of metformin and glimepiride is a well-established therapy for type 2 DM. Hence, this study was done to compare the efficacy and safety of vildagliptin-metformin and glimepiride-metformin treatment in type 2 diabetic patients.

MATERIAL AND METHODS

A Prospective randomized controlled open label comparative study for a period of 12 weeks. Patients attending the medicine out-patient department diagnosed with type 2 diabetes mellitus were included in the study for a period of 12 weeks. The study was undertaken for the span of one and a half years (18 months).

Institutional Ethical committee approval was taken to carry out the study. Informed consent was taken from the patient.

Sample Size: The sample size had been estimated in consultation with a biostatistician based on previous year's case load and the sample size is 70 [35 in each arm]. Based on previous studies, in order to establish statistical significance for change in HbA1C and FBS/PPBS- it was required to study at least 35 patients in each arm at a probability α error of 5% and keeping power of study at 80%. 70 patients diagnosed with Type 2 diabetes mellitus attending outpatient clinic were recruited based on the inclusion and exclusion criteria mentioned below.

Inclusion criteria

1. Patients diagnosed with type 2 diabetes mellitus.
2. HbA1c levels between ≥ 7 and ≤10%.
3. Age ≥ 40 years and ≤ 80 years.

Exclusion criteria

1) Type 1 diabetes mellitus.
2) Patients with Known adverse reactions to Vildagliptin.
3) Cardiovascular diseases:
   A. Severe uncontrolled hypertension defined as systolic blood Pressure ≥180 mmHg and ≥110 mmHg.
   B. Any of the following within 6 months of enrolment visit: Cardiac surgery or revascularization, unstable angina, unstable congestive heart failure, [NYHA class 3 or 4], transient ischemic attack or significant cerebrovascular diseases and unstable/previously undiagnosed arrhythmias.
4) Significant Gastrointestinal diseases like intestinal obstruction, malabsorption syndromes, irritable bowel syndrome, inflammatory bowel disease etc.
5) Serum creatinine more than 1.2 mgs/dl.
6) Those with raised Alanine Transaminase (ALT), Aspartate Transaminase (AST) ≥2 times normal.
7) Pregnancy and lactation.
8) Subject with any condition which, in the judgement of the clinician, may render the subject unable to complete the study or which may pose a significant risk to the subject.
9) Concomitant medications with any other oral antidiabetic agents, chronic corticosteroids (oral or parenteral,>7 consecutive days of treatment) or any drugs which is known to alter the sugar levels are not permitted.

Investigations:

- FBS and PPBS at baseline, 6th week and 12th week.
- HbA1c, at baseline and at 12th week.

METHODOLOGY

A baseline demographic data (age, sex, weight, blood pressure, associated diseases, habits, and drug history) was collected from the included 70 patients diagnosed with type 2 DM, attending Medicine outpatient clinic. HbA1c, FBS and PPBS were done at the time of recruitment. Patients was randomly assigned in (1:1) ratio after randomization to either of two groups (35 in each group), one group prescribed glimepiride(1mg) +metformin (500mg) twice daily half an hour before meals and other group vildagliptin(50mg)+ metformin(500mg) twice daily half an hour before meals. HbA1c, FBS, PPBS was repeated at the end of 3rd month.

Group A: Patients on glimepiride(1mg) +metformin (500mg) twice daily.

Group B: Patients on vildagliptin(50mg)+ metformin(500mg) twice daily. Also, patients with fasting sugars > 200 mg/dl and/or postprandial sugars > 300 mg/dl at the 6th week of study were also withdrawn from the study and treatment was given as per the American Diabetes Association [ADA] guidelines. Primary efficacy outcome was measured as reduction in HbA1c levels from baseline to 12th week and reduction in FBS/PPBS levels from baseline to 6th and 12th week.

Statistical analysis: Quantitative data was summarized in terms of descriptive statistics like mean and standard deviation for patients who are treated for both the therapies. In order to test for statistical significance in mean values, appropriate T test oblique non-parametric test was employed. Qualitative parameters between two groups were tested by employing Chi square test of significance, oblique non-parametric test to study before and after the treatment.

RESULTS

The mean age among Group A and Group B subjects were 58.34 ±10.14 and 58.63 ±9.95 years respectively and does not show any statistical difference (P>0.05). The number of subjects in age group 50-60 years were maximum i.e. 13 (18.57%) and 14 (20%) in Group A and Group B respectively. Among 70 subjects, 38(54.28%) were male and 32 (45.72%) were females. The distribution of males and females in both the study groups were nearly similar with no statistical difference. (p>0.05). The number of subjects with diabetes in group 1-3 years were more in Group A (17) as compared to Group B (13). The difference between both groups related to duration of illness was not significant. The mean body weight of Group A subjects was 63.68±8.89 kg and Group B subjects was 64.20 ±7.48 kgs with no statistical difference (P=0.79). The mean body mass index (BMI) of Group A subjects was 24.96 ±4.65 and Group B subjects was 24.09 ±3.98 with no statistical difference (P=0.40).

Table 1: Distribution of subjects according to baseline blood sugar levels

Variable	Group A	Group B	P value
FBS	179.06 ±32.56	174.03 ±19.19	0.43*
PPBS	270.86 ±43.82	277.94 ±28.41	0.42*
HbA1c	8.80 ±0.62	8.99 ± 0.37	0.12*

(* p>0.05; Statistically not significant)

In the study the mean fasting blood sugar levels at baseline (0 weeks) were 179.06 ±32.56 and 174.03 ±19.19 mg/dl in Group A and Group B respectively. The difference between two groups was not statistically significant. (P=0.43). The mean post prandial blood sugar levels at baseline (0 weeks) were 270.86 ±43.82 and 277.94 ±28.41 mg/dl in Group A and Group B respectively. The difference between two groups was not statistically significant. (P=0.42). The mean glycated haemoglobin (HbA1c) levels at baseline (0 weeks) were 8.80 ±0.62 and 8.99 ± 0.37in Group A and Group B respectively. The difference between two groups was not statistically significant. (P=0.12)

Table 2: Effect of treatment on Fasting Blood Sugar levels in study groups

Time	Group A (Mean ±SD)	Group B (Mean ±SD)	P value*
0 week	179.06 ±32.56	174.03 ±19.19	0.43
6 week	115.60±14.01	109.54±12.53	0.06
12 week	109.80±12.41	104.57±11.52	0.07
Change from baseline to 12 week (%)	-36.84 ±12.43	-39.33±8.54	0.33

(*p<0.05; Significant)

The mean fasting blood sugar levels at baseline (0 weeks) were 179.06 ±32.56 and 174.03 ±19.19 mg/dl in Group A and Group B respectively. The fasting blood sugar levels at 6 weeks were 115.60±14.01and 109.54±12.53 mg/dl in Group A and Group B respectively. Similarly, at 12 weeks mean fasting blood sugar levels were 109.80±12.41and 104.57±11.52 mg/dl in Group A and Group B respectively. The change in percentage of fasting blood sugar at 12 weeks was -36.84% and -39.33% in Group A and Group B respectively but no statistical significance different was found. (P=0.33).

Table 3: Effect of treatment on Post-prandial Blood Sugar levels in study groups

Time	Group A (Mean ±SD)	Group B (Mean ±SD)	P value
0 week	270.86 ±43.82	277.94 ±28.41	0.42
6 week	168.31±18.42	158.82 ±15.64	0.02*
12 week	159.03 ±15.99	154.45 ±13.91	0.21
Change from baseline to 12 week	-39.73±11.51	-43.88±7.42	0.07

(*P <0.05; Statistically Significant)

The mean Post prandial sugar levels at baseline (0 weeks) were 270.86 ±43.82 and 277.94 ±28.41 mg/dl in Group A and Group B respectively. The Post prandial blood sugar levels at 6 weeks were 168.31±18.42 and 158.82 ±15.64mg/dl in Group A and Group B respectively. The difference between two groups shows statistical significance. (P=0.02). Similarly, at 12 weeks mean Post prandial blood sugar levels were 159.03 ±15.99 and 154.45 ±13.91 mg/dl in Group A and Group B respectively. The change in percentage of Post prandial blood sugar at 12 weeks was -39.73% and -43.88% in Group A and Group B respectively but no statistical significance different was found. (P=0.07)

Table 4: Effect of treatment on HbA1c levels in study groups

Time	Group A (Mean ±SD)	Group B (Mean ±SD)	P value*
0 week	8.80 ±0.62	8.99 ±0.37	0.12
12 week	6.47±0.44	6.42±0.42	0.92
Change from baseline to 12 week	-26.06±7.47	-27.86±5.96	0.26

(*P <0.05; Statistically Significant)

The mean HbA1c levels at baseline (0 weeks) were 8.80 ±0.62and 8.99 ±0.37 in Group A and Group B respectively. Similarly, at 12 weeks mean HbA1c levels were 6.47±0.44 and 6.42±0.42 in Group A and Group B respectively. The change in percentage of HbA1c at 12 weeks was -26.06% and -27.86% in Group A and Group B respectively but no statistical significance different was found. (P=0.26). The HbA1c levels < 7 were achieved among 29 (41.43%) subjects in Group A as compared to 28 (40%) subjects in Group B. The difference between HbA1c levels among study groups was not statistically significant. (P=0.75). The mean BMI at baseline (0 weeks) were 24.96 ±4.65 and 24.09 ±3.98 in Group A and Group B respectively. Similarly, at 12 weeks mean BMI levels were 25.20 ±4.51 and 23.56 ±3.80 in Group A and Group B respectively. It was observed that mean BMI in Group A subjects was slightly more than baseline while that in Group B subjects was slightly lower than baseline at 12 weeks but not statistically significant.

Table 5: Distribution according to adverse effects among study groups

Adverse Effects	Group A (n=35)	Group B(n=35)	P value*
Edema	4	3	0.50
Headache	3	5	0.35
Elevated liver enzymes	1	3	0.30
Symptomatic hypoglycemia	5	2	0.23
Abdominal discomfort	1	2	0.55
Diarrhea	2	8	0.04#
Chest discomfort and dyspnea	2	3	0.51
Others	3	5	0.35

(* P value calculated by Fisher Test and # P <0.05; significant)

The adverse effects in Group A subjects was maximum with related to hypoglycemia. 5 subjects suffered symptomatic hypoglycemia in Group A as compared to 2 subjects in Group B. Elevated liver enzymes was seen more in group B subjects along with diarrhea which shows statistical significance.

DISCUSSION

Based on the comparison of the treatment we conclude that combination of metformin + vildagliptin significantly reduced the values of FPG, PPG and HbA1c after 3 months. This might be due to the additive effect of these two drugs (metformin + vildagliptin). These results were in agreement with other studies[8,9] results that also indicate effectiveness of additive effect of metformin and vildagliptin. The combination therapy with Vildagliptin and metformin lower glucose via enhancement of insulin secretion, suppression of glucagon secretion, and insulin sensitization by adipose tissue. The use of this combination in diabetes management will provide a greater degree of glycosylated hemoglobin – lowering than that seen with use of either drug as monotherapy.[10] Sulfonylurea drugs as a group had been on the market for a long time and were relatively low price. Sulfonylureas had the advantage of being quite effective in blood glucose lowering, with an almost instant onset of the effect after start of therapy. Drops in HbA1c of 1–2% can be expected as a mean, with the higher the baseline HbA1c, the bigger the drop. The synergistic effects were seen when Sulfonylureas are combined with metformin, and the different mechanisms of action of these two agents – one stimulating insulin secretion, the other increasing insulin sensitivity – make them the obvious couple in the dual activity in type 2 diabetes.[11] Vildagliptin should be used to its maximum potential, started early in the disease process to maintain and preserve beta cell function[10] and preferably used in combination with Metformin in order to achieve the maximum reduction in HbA1c.[12,13] All recent clinical trials hint to the benefit of the early use of vildagliptin, alone or in combination, of any antidiabetic medication. The adverse effects in Group A subjects was maximum with related to hypoglycemia. Five subjects suffered symptomatic hypoglycemia in Group A as compared to 2 subjects in Group B. Elevated liver enzymes was seen more in group B subjects along with diarrhea which shows statistical significance. In the present study, vildagliptin therapy appears to be safe and well tolerated by most, as outlined in the previous sections. When administered in combination with other agents vildagliptin therapy appears unlikely to cause hypoglycemia and is generally weight-neutral. Other adverse effects noted to occur in clinical

trials of DPP-4 inhibition have included increased reports of nasopharyngitis, upper respiratory infection, and headache – these were not likely to be severe or result in discontinuation of the medication. The main disadvantage of Sulfonylurea is the risk of hypoglycaemia, and increase weight which rises with advanced age, poor nutrition, alcohol consumption, liver or kidney disease and polypharmacy[14]and is higher than with other oral medications.[15] The combination of Vildagliptin and metformin in type 2diabetes management has been shown in clinical trials to be effective in blood glucose lowering, with very low associated rates of hypoglycemia and no attenuation in the potential weight loss effects seen with metformin monotherapy.[14]

CONCLUSION

The efficacy and tolerability of vildagliptin, was similar, with no significant differences, when used to treat type 2 diabetic patients with inadequate blood glucose control by dual combination of metformin and another traditional oral hypoglycemic agent (glimepiride). Vildagliptin in combination with metformin also had good safety with low risk of hypoglycaemia and weight gain.

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