

Original Research Article

A comparative study of efficacy and safety of vildagliptin against metformin in newly diagnosed patients of type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus is a progressive disease characterised by declining β -cell function. Cornerstone of effective management of T2DM is maintaining strict glycaemic control through agency of various oral hypo-glycaemic agents (OHAs). Metformin (a biguanide) currently forms the preferred treatment in newly diagnosed patients of T2DM. Vildagliptin is a potent, orally administered, competitive and reversible inhibitor of DPP-4, which was launched in 2006 and is now approved in more than 70 countries worldwide.

Methods: The study was a single blinded study conducted in a district level tertiary care hospital attached to a medical teaching institute. Newly diagnosed patients were screened and randomised in two groups. Group 1 received metformin (500 mg) twice daily and group 2 received vildagliptin (50 mg) twice daily. FPG, PPPG, HbA1c and Weight were assessed on week 0 and week 12.

Results: At the end of 12 weeks, Δ FPG was 39.33 ± 4.72 mg/dL and 37.84 ± 6.58 mg/dL with metformin and vildagliptin respectively. Δ PPPG was 73.88 ± 13.80 mg/dL and 65.08 ± 13.00 mg/dL with metformin and vildagliptin. Δ HbA1c was 1.12 ± 0.46 and 0.95 ± 0.32 with metformin and vildagliptin. Δ Weight was 1.02 ± 0.90 Kg with metformin and 0.69 ± 1.33 Kg.

Conclusions: Vildagliptin offers an alternative mode of therapy for newly diagnosed, obese patients of type 2 DM, especially those with impaired fasting plasma glucose.

Keywords: Metformin, HbA1c, Obesity, T2DM, Vildagliptin

INTRODUCTION

Diabetes mellitus is a chronic non-communicable disease resulting in increased blood glucose levels. Type 2 diabetes mellitus (T2DM) is a heterogeneous syndrome characterized by abnormalities in carbohydrate and fat metabolism. The causes of T2DM are multi-factorial and include both genetic and environmental elements that affect beta-cell function and tissue (muscle, liver, adipose tissue, and pancreas) insulin sensitivity.¹ It is a progressive disease characterised by declining β -cell function that, in concert with insulin resistance, leads to loss of glycaemic control and eventual diabetic complications.²

Diabetes is fast gaining the status of a potential epidemic in India, with more than 62 million diabetic individuals diagnosed with the disease. India has been called “the diabetes capital of the world,” and it is estimated that “every fifth diabetic in the world is an Indian”.³⁻⁵

Cornerstone of effective management of T2DM is maintaining strict glycaemic control through agency of various oral hypo-glycaemic agents (OHAs). Metformin (a biguanide) currently forms the preferred treatment in newly diagnosed patients of T2DM.^{6,7} However, gastrointestinal disturbances like anorexia, nausea, lactic acidosis and vitamin B12 malabsorption, which may

increase the risk of developing vitamin B12 deficiency, are seen with metformin therapy.^{8,9}

New studies have given us an insight into physiological role of Incretin hormones like glucagon like peptide-1 (GLP-1) in regulating insulin release and subsequent regulation of blood glucose levels.¹⁰ Native GLP-1 stimulates β -cell proliferation in animal models and inhibits apoptosis in vitro, which may increase β -cell mass and function.¹¹ GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4) in human body. Vildagliptin is a potent, orally administered, competitive and reversible inhibitor of DPP-4, which was launched in 2006 and is now approved in more than 70 countries worldwide.¹² Clinical trials have shown that vildagliptin is effective in significantly lowering glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), and post prandial plasma glucose (PPPG) levels.¹³ Beta-cell function may also be improved.¹⁴ Vildagliptin is also one of the few weight neutral oral hypoglycaemic agents and may actually promote weight loss.¹⁵ Vildagliptin's potential for drug-drug interaction is also very low.¹⁶ Vildagliptin also provides a favourable adverse effect profile. Commonly encountered adverse events are headache, nasopharyngitis, cough, constipation, dizziness and increased sweating.¹⁷

Various studies have been conducted to assess the efficacy and safety of vildagliptin as an add-on to metformin in the patients of T2DM mellitus.¹⁸⁻²⁰ However, not many studies have been conducted to assess the safety and efficacy of vildagliptin versus metformin in newly diagnosed patients of T2DM. Keeping in view the various advantages of vildagliptin and its favourable safety profile, it was considered prudent to conduct a study to compare its efficacy and safety with currently acceptable first line oral hypoglycaemic agent metformin. The proposed study aimed to do the same.

METHODS

The study was a single blinded study conducted in a district level tertiary care hospital attached to a medical teaching institute. The approval for conducting the said study was obtained vide letter no: IEC/0019/2013. Patients were recruited from the Medicine Out-patient department (OPD), Cardiology OPD, Diabetes OPD and Dental OPD. They were screened for participating in the study.

Patients were diagnosed on the basis of history and biochemical investigation as per the American Diabetic Association, 2001.²¹ Patients who were found fit to be included into the study were explained the aims and objectives of the study in detail. They were informed about the benefits of the study along with possible risks. After explaining the entire scope of the study, a written informed consent was obtained from them. The written informed consent was based on the specimen informed

consent document. The patients were randomly allocated to either group I or group II of the treatment group based on chit method. Patients were blinded, and were not informed about the drug they were to receive.

On the first visit, patients characteristic such as age, sex, registration no, a brief medical history was noted on the case record form. Baseline investigations such as complete blood count, renal function test, and liver function test were performed. Patients were counselled regarding their diet and encouraged to have regular exercise. They were provided with a drug diary to record consumption of medicines and any adverse event. Patients were encouraged to maintain a log of all the medicines consumed in the drug diary along with the side effects experienced, if any. Patients from group I received metformin (1000 mg) twice a day, and patients from group II received vildagliptin (50 mg) twice daily. Tests to determine FPG, PPPG and HbA1c along with weight measurement, were performed on the first visit (Week 0) and on 12 week, and analysed (Figure 1).

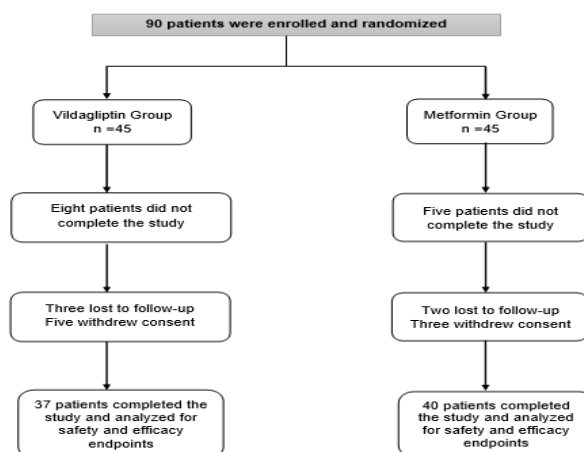


Figure 1: Flowchart of the study.

The primary efficacy end point was the mean percentage change in HbA1c concentration from baseline to final assessment. Along with it, the secondary efficacy end points included the mean change in FPG, PPPG and Weight from baseline to final assessment. At each visit patients were interviewed for occurrence of any adverse effect and physically examined during the study period. Patients were also encouraged to enter any side effect they experienced in the drug diary provided to them. These drug diaries were also evaluated for occurrences of side effects.

Statistical analyses of the collected data was performed using Statistical Package for the Social Sciences (SPSS), version 21.22. Continuous variables between the two treatment groups were analysed by unpaired t-test. Safety parameters were analysed using 'Z' test for difference between two proportions. A 'p' value < 0.05 was considered statistically significant.

RESULTS

A total 90 patients were included in the study, of which 45 patients were allocated to metformin group and 45 patients to vildagliptin group. During the study period, three patient from vildagliptin and two patients from metformin group were lost to follow up. Five patients

from vildagliptin group and three patients from metformin group withdrew consent. Hence, eight patients from vildagliptin group and five patients from metformin group were excluded from analysis. Thus 37 patients from vildagliptin group and 40 patients from metformin group completed the study and were considered for the analysis of data.

Table 1: Baseline plasma glucose profile.

Drug Group	Vildagliptin	Metformin	#p value
Fasting Plasma Glucose (Mean \pm SD)	176 \pm 19.67	182.9 \pm 12.51	0.067
Post-prandial Plasma Glucose (Mean \pm SD)	268.89 \pm 15.7	262.38 \pm 22.58	0.174
HbA1c (Mean \pm SD)	8.56 \pm 0.38	8.67 \pm 0.47	0.244

#Unpaired t test.

Table 2: Plasma Glucose profile at the end of 12 weeks.

Drug and Parameters	Vildagliptin	Metformin	p value
Fasting Plasma Glucose (Mean \pm SD)	139 \pm 25.75	144.15 \pm 14.6	0.279#
Post-prandial Plasma Glucose (Mean \pm SD)	203.81 \pm 17.62	188.18 \pm 21.33	0.001#
HbA1c (Mean \pm SD)	7.635 \pm 0.37	7.4 \pm 0.67	0.067#

#Unpaired 't' test.

The baseline characteristics of the patients of both the groups were comparable with respect to glycaemic parameters and weight. Table 1 and 2 show the plasma glucose profile at baseline and at the end of 12 weeks. The mean reduction in FPG (Table 3) at the end of 12 weeks was 37.84 \pm 6.58 mg/dL with vildagliptin and 39.33 \pm 4.72mg/dL with Metformin.

Table 3: Mean reduction in FPG from baseline values after 12 weeks treatment.

Drug	Vildagliptin	Metformin	#p value
Mean Change (mean \pm SD)	37.84 \pm 6.58	39.33 \pm 4.72	0.256

#Unpaired 't' test.

The difference in the reduction of FPG was not statistically significant ($p>0.05$). The mean reduction in PPPG at end of 12 weeks (Table 4) with vildagliptin was 65.08 \pm 13.00 mg/dL and that with Metformin was 73.88 \pm 13.80 mg/dL.

Table 4: Mean reduction in PPPG from base line values after 12 weeks of treatment.

Drug	Vildagliptin	Metformin	#p value
Mean Change (Mean \pm SD)	65.08 \pm 13	73.88 \pm 13.8	0.005

#Unpaired 't' test.

The reduction in PPPG was better with metformin as compared to vildagliptin and this difference was statistically significant ($p<0.05$). The mean reduction of HbA1c (Figure 2) achieved by vildagliptin was 0.95 \pm 0.32%.

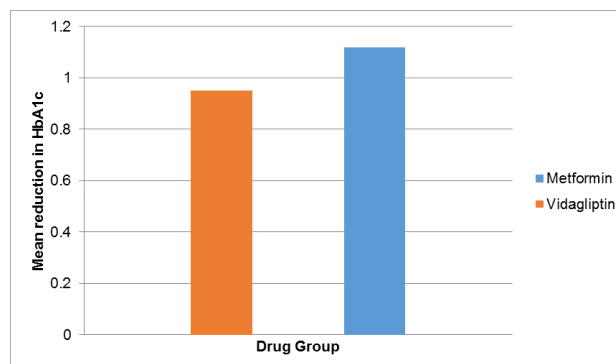


Figure 2: Mean reduction in HbA1c after 12 weeks of treatment.

Mean reduction of HbA1c in patients of metformin group was 1.12 \pm 0.46%. The differences in reductions of HbA1c achieved by both the drugs was comparable ($p=0.062$). The weight loss achieved by vildagliptin (0.69 \pm 1.33 Kg) was comparable to that achieved by Metformin (1.02 \pm 0.9Kg). The difference in weight reduction (Table 5) achieved at the end of 12 weeks was not statistically significant ($p=0.218$). Gastrointestinal side effects such as diarrhoea and nausea and/or vomiting were reported in both the treatment groups (Figure 3). Metformin group

reported incidence of headache and generalized weakness, which was not seen in vildagliptin group. None of the treatment groups reported any life threatening adverse drug reactions. None of the adverse drug reactions were serious enough to warrant discontinuation of the drugs under investigation.

Table 5: Mean reduction in weight of patients at the end of 12 weeks.

Drug	Vildagliptin	Metformin	#p value
Reduction in Weight (in Kg) (Mean \pm SD)	0.689 \pm 1.33	1.02 \pm 1	0.218

#Unpaired 't' test.

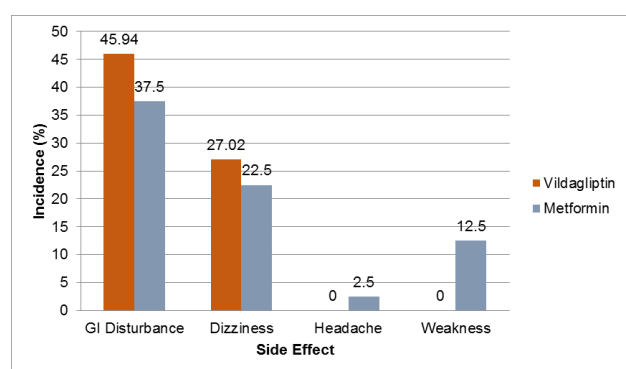


Figure 3: Incidence of adverse effects in the treatment groups.

DISCUSSION

In the present study, the efficacy of vildagliptin in lowering plasma blood glucose and its tolerability was compared with that of metformin. Patients in vildagliptin group were administered vildagliptin 50 mg twice daily (100 mg daily) orally. Similar doses of vildagliptin were used in many studies such as those conducted by Schweizer et al, Goke et al, Iwamoto et al, Schweizer et al and Pan et al.²³⁻²⁷ Patients in metformin group were administered metformin tablet 1000 mg twice daily (2000 mg daily) orally. Similar doses of metformin were used in studies conducted by Schweizer et al, Goke et al, Bosi et al, Schweizer et al conducted a study comparing 100 mg of vildagliptin daily versus 1500 mg of metformin daily, in drug naïve elderly patient of T2DM mellitus.^{23,24,26,28} The mean reductions of FPG in vildagliptin and metformin groups were 37.84 mg/dL and 39.33 mg/dL respectively (Table 3).

The difference was not statistically significant ($p > 0.05$). The mean reduction in FPG achieved by metformin was similar to those achieved by metformin in studies conducted by Schweizer et al, and Bosi et al.²³ Schweizer et al, reported a reduction of 34.52 mg/dL at the end of 52 week study.²⁸ Bosi et al, reported a reduction of 35 mg/dL at the end of 24 week study.²⁸ The reduction in the

FPG achieved by vildagliptin was slightly higher in the present study, than that observed in studies conducted by Schweizer et al, Iwamoto et al, and Bosi et al.^{23,25,28} Schweizer et al, reported a mean reduction of 16.36 mg/dL, Bosi et al, reported a reduction of 23 mg/dL in FPG.^{23,28} In the present study, the effect of vildagliptin in reducing PPPG was also compared with that of metformin. At the end of 12 weeks, mean reductions achieved by vildagliptin was 65.08 mg/dL, while that achieved by metformin was 73.88 mg/dL (Table 4).

The difference in the mean reduction of PPPG between two group was statistically significant ($p < 0.05$). Metformin was significantly better in reducing of PPPG as compared to vildagliptin. The mean reduction achieved by vildagliptin in the present study was comparable to the mean reduction achieved in a study conducted by Iwamoto et al.²⁵ Iwamoto et al, reported a mean reduction of 51.5 mg/dL in PPPG at the end of 12 weeks with vildagliptin. The difference in the mean reductions of HbA1c in vildagliptin group and metformin group was not statistically significant ($p > 0.05$). The mean reduction in vildagliptin group was comparable to that observed in studies conducted by Schweizer et al, Goke et al, and Schweizer et al.^{24,26} Schweizer et al and Goke et al reported a reduction in HbA1c of 1% with vildagliptin at the end of 52 week study and 104 weeks study, respectively.^{23,24} Schweizer et al reported a reduction of 0.64% in HbA1c with vildagliptin at the end of 24 weeks in drug naïve elderly population.²⁶ The mean reduction of HbA1c observed in metformin group (1.12%) was comparable to those reported by Schweizer et al, Goke et al and Schweizer et al.^{23,24,26} Schweizer et al and Goke et al reported a reduction of 1.4% and 1.5% respectively, with metformin.^{23,24} Schweizer et al, reported a reduction of 0.75% in HbA1c with metformin. The weight reduction observed with vildagliptin group was similar to those observed by Pan et al, Schweizer et al and Goke et al.^{24,26,27} Schweizer et al reported a reduction of 0.3 Kg at end of 52 weeks with vildagliptin.²³ The weight reduction in the present study with metformin group (1.02 Kg) was similar to the weight reduction by the same drug in study conducted by Schweizer et al, which reported a reduction of 1.25 Kg in metformin group at the end of 24 weeks.²⁶ However, other studies, such as those conducted by Schweizer et al and Goke et al, reported much higher reductions in body weight with metformin, the reductions being 1.9 Kg and 2.5 Kg respectively.^{23,24}

The modest reductions observed with metformin in the current study as compared to other studies can be attributed to the short duration of the present study. In present study, adverse events reported in the vildagliptin group were 72.97% and in metformin group were 75% of the patients. The reported adverse events in the present study were similar to those observed in other studies.^{23,24,26} Schweizer et al observed that 70.1% of patients of vildagliptin group and 75.4% of patients of metformin group reported at least one adverse event.²³ Goke et al observed that 82.2% patients in vildagliptin

group and 87.3% patients in metformin group reported at least one adverse event.²⁴ None of the adverse events reported in the study was life threatening. None of the adverse event in both the groups necessitated stoppage of the drug.

CONCLUSION

The present study was one of the initial studies conducted to explore the scope of vildagliptin versus metformin as a first choice OHA in newly diagnosed obese patients of T2DM. The study showed that vildagliptin was acceptable alternative to patients for control of disturbed FPG, HbA1c and body weight profile. The present study could not, however, record and compare the long term efficacy and safety of vildagliptin versus metformin as it was only of 12 weeks duration. The present study was carried out at a single centre - a district level tertiary care hospital in Maharashtra, and hence, large scale multi-centric studies are required to validate the findings of the present study.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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