COMPARATIVE STUDY OF METFORMIN AND VILDAGLIPTIN FOR MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

Diabetes mellitus is a major health problem which increases the rate of morbidity and mortality. Cheap Metformin and costlier vildagliptin are the frequently used oral hypoglycaemic agents. The comparative effectiveness of metformin and vildagliptin has not been studied earlier. So, this study was conducted to compare the antidiabetic efficacy of metformin and vildagliptin and their effects on renal function in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

It was a prospective, open-labelled, non-randomised, phase IV clinical trial which was carried out over the duration of 12 weeks. The patients attending the medicine outpatient department of Tripura Medical College (TMC) hospital were enrolled in the study. Patients, who fulfilled the selection criteria, were allocated in two treatment groups. Group A was treated with metformin (Sustained release preparation) 500 mg once daily and group B was treated with vildagliptin 50 mg once daily. Measurement of body weight, fasting blood glucose (FPG), postprandial blood glucose (PPG), glycated haemoglobin (HbA_{1c}), serum urea, creatinine and urine albumin/creatinine ratio was performed at the initial visit and at the end of 12 weeks of treatment.

RESULTS

Metformin and vildagliptin significantly reduced the levels of FPG, PPG & HbA_{1c} at week #12 from their respective baseline values. There was similar reduction in the level of HbA_{1c} in both groups. Vildagliptin significantly reduced urine ACR at week #12 from baseline value.

CONCLUSION

The study shows that metformin and vildagliptin have similar effect on glycaemic control, but vildagliptin exerts better renoprotective effect and there were no reports of serious adverse events.

KEYWORDS

Diabetes Mellitus, Metformin, Vildagliptin.

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BACKGROUND

Diabetes mellitus (DM) is a chronic disorder emerging as major health problem which increases the rate of morbidity and mortality.¹ At present over 415 million people are living with diabetes across the globe, by 2040 this will rise to 642 million.² A survey on Indian population showed that 4% of the adults suffered from DM in the year 2000 and it is expected to rise to 6% by the year 2025.³

Nephropathy has been reported to occur in 20-40% of patients with diabetes and is the single leading cause of end stage renal disease, accounting for >40% of patients requiring renal replacement therapy each year in developed countries.⁴ There are nearly 30% of chronic renal failure patients in India because of diabetic nephropathy.⁵

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The major epidemiological studies support that glycosylated haemoglobin (HbA_{1c}) levels should be maintained as close to normal which may give longterm beneficial effects on the risk of diabetes complications.⁶

The cost of antidiabetic drugs is the major deciding factor for the patients' compliance. There exists a wide range of variation in the prices of drugs marketed in India and other countries of the world.⁷ Medical bankruptcy is a common phenomenon in India, as in other resource-challenged countries, where patients have to pay from pocket.

Metformin and vildagliptin are commonly used oral hypoglycaemic agents (OHAs). The comparative effectiveness of cheap OHA metformin and costlier OHA vildagliptin has not been studied earlier.⁸

So, the present study was conducted to evaluate the effectiveness of metformin with vildagliptin on glycaemic control and renal function in type 2 DM patients.

MATERIALS AND METHODS

Objectives/Primary

To compare the antidiabetic efficacy of metformin and vildagliptin in type-2 diabetes mellitus.

Secondary

1. To analyse the adverse drug reactions (ADRs) of metformin and vildagliptin.
2. To compare the effects of metformin and vildagliptin on renal function in the study subjects, if any.

A prospective, open-labelled, non-randomised, phase IV clinical trial was carried out over the duration of 12 weeks. The patients attending the medicine outpatient department of TMC hospital were enrolled in the study after explaining the aim of the study. Written informed consent was obtained from each patient. Prior approval of Institutional ethics committee was obtained [Permission Ref No.F.3 (PO-75)/Inst. Ethical Com./SFTMC/2010-11/123284-123301 dated 05/08/2016].

Inclusion Criteria

- Adults of either gender aged between 18 to 60 years.
- Newly diagnosed type-2 diabetes patients with FPG <200 mg/dL, PPG < 300 mg/dL and HbA_{1c} level from 6.5 to 10.
- Patients with normal renal function.

Exclusion Criteria

- Patients with any complication of diabetes mellitus like retinopathy, neuropathy or nephropathy, etc.
- Patients with impaired liver function tests.
- Pregnant or lactating women.
- Patients taking medications that could affect blood glucose level, i.e. patients on non-selective β -blockers, diuretics and corticosteroids.
- Any contraindication to metformin/vildagliptin.
- Patients with known psychiatric illness.

Patients, who fulfilled the selection criteria, were allocated in two treatment groups (Group A & Group B) by nonrandomised manner. In both groups, age and sex matched study subjects were selected. The decision to prescribe metformin or vildagliptin was made by the treating physician according to his/her normal medical practice, and patients were enrolled in the study only after the treatment decision had been made. Group A was treated with metformin (sustained release preparation) 500 mg once daily and group B was treated with vildagliptin 50 mg once daily.

Measurement of body weight, fasting blood glucose (FPG), postprandial blood glucose (PPG), HbA_{1c}, serum urea & creatinine and urine albumin/creatinine ratio (ACR) was performed at initial visit and at the end of 12 weeks of treatment. Patients were monitored continuously throughout the study for any adverse event (AE). Adverse drug reaction form of Pharmacovigilance Programme of India (PvPI) was filled up in case of any AE. World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria⁹ was used for causality assessment of AE.

Sample Size

Based on an effect size of 0.5, standard deviation of 0.7, significance level α of 0.05 and power of the study as 80% power, the target number of evaluable subjects was 30 per group.

Outcome

Overall assessment was done at the end of the study period. The assessment of metformin/vildagliptin antidiabetic efficacy was done as follows-

1. Three-point scale HbA_{1c} assessment-
 - a. Excellent control: HbA_{1c} <6.5
 - b. Good control: HbA_{1c} =6.5 to 8
 - c. Poor control: HbA_{1c} >8
2. Blood glucose levels-FPG & PPG.

The Role of Metformin and Vildagliptin on Renal Function was assessed at the End of the Study by the following Parameters

1. Serum urea.
2. Serum creatinine.
3. Urine albumin-creatinine ratio.

Statistical Analysis

The data were analysed by SPSS version 17. P value of < 0.05 was considered significant. For intragroup comparison paired t test and for intergroup comparison unpaired t test were used. The data collected at 0 week will be used as the baseline against which changes during therapy will be compared. Chi-square test will be used to compare adverse effects between the groups. All statistical tests were two sided, and the results were presented as mean $\pm$ standard deviation.

RESULTS

Out of 84 patients screened, 74 were enrolled for the study. Of the 74 patients, 39 (52.7%) were male and 35 (47.3%) were female. The patients were divided into two groups (group A & group B) consisting 37 patients in each group. Out of 74 patients, 62 completed the study. Out of 12 patients who did not complete the study, 5 patients were lost during followup period and 7 patients discontinued treatment due to AEs (Figure-1). The mean age of the patients was 51 and 49 years in the groups A and B respectively.

There was no statistical difference in the baseline FPG, PPG, HbA_{1c}, serum urea, serum creatinine, urine ACR and body weight between two groups.

Hypoglycaemic Effect of Metformin and Vildagliptin

Metformin & vildagliptin significantly reduced ($p < 0.0001$) the levels of FPG, PPG & HbA_{1c} at week #12 from their respective baseline values. In both groups there was good glycaemic control (HbA_{1c}=6.5-8) at the end of the study. The reduction in blood glucose level by vildagliptin was statistically significant ($p < 0.001$) as compared to metformin. But there was no significant change in the level of HbA_{1c} between the groups. (Table-1)

Role of Metformin and Vildagliptin on Renal Function

There was significant decrease ($p < 0.05$) in serum urea level in vildagliptin group as compared to baseline value, but there was no such significant change in metformin group. In both the groups there was no significant change in serum creatinine levels at the end of 12 weeks as compared to baseline values. Vildagliptin significantly reduced urine ACR at week #12 from baseline value ($p < 0.05$), but in metformin group there was no significant change of urine ACR after 12 weeks of therapy. (Table-1).

Role of Metformin and Vildagliptin on Body Weight

Metformin significantly reduced body weight (~ 3.31 kg) at week #12 as compare to baseline value ($p < 0.001$), but in vildagliptin group there was no change in the body weight. (Table-1)

Safety Analysis of Drug Therapy

As per modified intention to treat (ITT), safety analysis of both metformin and vildagliptin was carried out. All patients who were receiving treatments were considered for safety

analysis. Total seventeen patients developed AEs. The reported AEs were nausea, vomiting, abdominal bloating, epigastric pain, anorexia & dizziness. Ten Patients in group A and seven patients in group B reported AEs. There were no significant difference of AEs between the groups (Chi square value = 0.6873, $p = 0.407$). These AEs were mild in nature. These lasted for about 2 weeks. Four (10.81%) patients in group A and three (8.11%) patients in group B discontinued the study due to AEs. Causality assessment showed that they were in the "possible" category.

	Baseline Value		Value at the end of 12 th Week	
	Metformin Group	Vildagliptin Group	Metformin Group	Vildagliptin Group
FPG (mg/dL)	171.31 $\pm$ 7.37	169.86 $\pm$ 9.02	125.47 $\pm$ 5.89*	117.93 $\pm$ 10.32* Φ
PPG (mg/dL)	225.7 $\pm$ 6.71	228.03 $\pm$ 6.49	171.75 $\pm$ 8.78*	159.8 $\pm$ 13.28* Φ
HbA _{1c} (%)	8.27 $\pm$ 0.39	8.1 $\pm$ 0.33	6.98 $\pm$ 0.1*	6.96 $\pm$ 0.15*
Serum urea(mg/dL)	32.33 $\pm$ 5.68	33.07 $\pm$ 8.72	31.98 $\pm$ 5.03	28 $\pm$ 5.92 Δ
Serum Creatinine (mg/dL)	0.66 $\pm$ 0.18	0.8 $\pm$ 0.1	0.64 $\pm$ 0.12	0.77 $\pm$ 0.06
Urine ACR (mg/g)	18.66 $\pm$ 3.06	22 $\pm$ 5.69	18.22 $\pm$ 1.52	17.53 $\pm$ 3.41**
Body weight (kg)	68.31 $\pm$ 4.97	66.33 $\pm$ 4.61	65 $\pm$ 3.61 Ψ	66.33 $\pm$ 4.30

Table 1. Effect of Metformin and Vildagliptin on Glycaemic Parameters, Kidney Function and Body Weight

Values are expressed in mean standard $\pm$ deviation.

* $p < 0.0001$ as compare to baseline value.

** $p = 0.0003$ as compare to baseline value.

$\Delta p = 0.0156$ as compare to baseline value.

$\Psi p = 0.0076$ as compare to baseline value.

$\Phi p < 0.001$ as compare to metformin group at the end of 12th week.

DISCUSSION

In this study, metformin significantly reduced the levels of FPG, PPG & HbA_{1c} after 12 weeks of therapy. These findings are similar to that of ADAM CR et al.¹⁰ Metformin improves hyperglycaemia primarily by suppression of hepatic gluconeogenesis¹¹ In addition to suppressing hepatic gluconeogenesis, metformin increases insulin sensitivity, enhances peripheral glucose uptake and increases fatty acid

oxidation.¹² Vildagliptin also significantly reduced the levels of FPG, PPG & HbA_{1c} after 12 weeks of therapy. It acts by increasing the levels of GLP-1 and GIP by inhibiting DPP IV enzyme which is responsible for degradation of GLP-1 and GIP.¹³ Vildagliptin caused more reduction of FPG & PPG but similar reduction of HbA_{1c} after 12 weeks of therapy as compared to that of metformin.

Both metformin and vildagliptin protected renal function. Vildagliptin in addition improves kidney function as there was improvement in serum urea and urinary albumin excretion. Liu et al¹⁴ reported that vildagliptin attenuates kidney injury in streptozotocin-induced diabetic rats. In this same model, vildagliptin also significantly decreased proteinuria, albuminuria & urinary ACR.

Metformin significantly reduced body weight (~3.31 kg) which is comparable with the finding of Jack A. Yanovski et al¹⁵ But Overall weight neutrality has been seen with vildagliptin which is similar with findings of other studies.^{16,17,18,19} The overall weight neutrality seen with vildagliptin appears to be a class effect because the DPP-4 inhibitors, saxagliptin and sitagliptin have also been shown to produce improvements in glycaemic control, both as monotherapy and as add-on therapy to other oral agents, without significant change in body weight in most clinical trials.^{20, 21}

Safety analysis showed that there were no serious AEs, although 10.81% patients in group A and 8.11% patients in group B discontinued treatment due to AEs.

CONCLUSION

The study shows that metformin and vildagliptin have similar effect on glycaemic control, but vildagliptin exerts better renoprotective effect and there were no reports of serious adverse events.

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