Research Article

Comparative Study of Glycemic Control and Adverse Effect Profile of Metformin and Vildagliptin Vs Metformin and Glimepiride in Patients of Type-2 Diabetes Mellitus with Poor Glycemic Control.

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ABSTRACT

Diabetes Mellitus is a heterogenous, chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin action and or insulin secretion that affects about 240 million people globally. The aim of the experiment is to compare the efficacy, safety and adverse effect profile of glimepiride 1 mg bid and vildagliptin 50 mg bid when added to metformin 500mg bid in patients of type-2 diabetes mellitus with poor glycemic control. Totally 60 patients were enrolled in the study and divided into two groups, each group containing 30 patients. These patients were already receiving metformin 500mg bid with poor glycemic control. Group 'A' patients received glimepiride 1 mg bid in addition to metformin 500mg bid. Group 'B' patients received vildagliptin 50 mg bid in addition to metformin 500mg bid. The total period of the study was three months. The study was done in type 2 DM patients attending Government General Hospital, Vijayawada. The blood glucose levels and HbA$_{1C}$ were estimated by GLUCOSE OXIDASE METHOD and AUTOANALYSER METHOD respectively. After 90 days of treatment, both the groups showed a significant decrease in fasting and postprandial blood sugars. There was a significant difference between the two groups in decreasing the fasting blood sugar levels (p<0.05) and postprandial blood sugars (p>0.10). After 3 months of therapy there was no reduction in HbA$_{1C}$ in A group. There was a reduction in HbA$_{1C}$ in B group. The reduction of HbA$_{1C}$ was not statistically significant between the two groups. There was a significant difference in the incidence of adverse effects between both the groups.('p'<0.001.). The new approach for treatment of diabetes mellitus achieved by DPP-IV inhibition has the potential to reduce and may even normalize both fasting and postprandial glucose concentrations without adverse effects such as weight gain. The DPP-IV inhibitors have not been associated with any incidence of severe hypoglycemia even when given in combination with existing oral antidiabetic agents. In future long term safety studies are required on these drugs especially on vildagliptin particularly in halting the progression of the disease, which has not been possible till now with any other antidiabetic agents.

Keywords: Diabetes mellitus, HBA$_{1C}$, DPP-IV inhibitors.

INTRODUCTION

Diabetes Mellitus is a chronic metabolic disorder that affects about 240 million people globally[1]. It is defined as a heterogenous chronic metabolic disorder principally characterized by persistent hyperglycemia resulting from defects in insulin action and or insulin secretion. In course of time prolonged hyperglycemia and associated metabolic aberrations result in tissue toxicity manifested as accelerated atherosclerosis, reno-retinal microangiopathy, neuropathy leading to a variety of vascular, neurological and focal complications.

India is currently experiencing an epidemic of diabetes mellitus. According to WHO, India has the unique distinction of being the country with largest number of diabetic patients (47 millions) in the world[2].

In India prevalence of diabetes in semi urban area was found to be 5.9% in comparison with the prevalence of 2.4% in rural and 11.5% in the urban population[3]. Prevalence of diabetes mellitus is similar in both genders. NIDDM accounts for 85-95% of patients with diabetes in various populations of the world. Among patients clinically diagnosed as Type-2 diabetes around 10% may have maturity onset diabetes in the young (MODY).

The pathogenesis of 80-88%, patients of NIDDM is based on following two factors[4,5].

1. Impaired insulin action / sensitivity i.e., insulin resistance.

2. β cell defect–insulin secretory dysfunction.

Table 1: ADA guidelines for the diagnosis of Type-2 diabetes[6].

	Normal Glucose Tolerance	IGT	D.M.
FBS	<110mg/dl	110-125mg/dl	≥126mg/dl
PPBS	<140mg/dl	140-199mg/dl	≥200mg/dl

- Symptoms of diabetes plus random blood glucose concentration ≥ 200 mg/dl or

- Fasting plasma glucose ≥126 mg/dl or

- Two hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test.

- HbA$_{1C}$ ≥ 6.5%.

Patients with persistent hyperglycemia and those with inadequate glycemic control despite regular diet and

exercise regimen should be treated with oral hypoglycemic agents. Sulfonylureas are usually the first line drugs of choice in non obese, metformin is first choice in obese diabetics. Most often the first line drug is either a insulin secretogogue (sulfonylureas and glinides) or insulin sensitizers (metformin and thiazolidinediones). Combining two types of OHAs is effective in situations where the first OHA is not able to achieve adequate glycaemic control despite maximal dosage. For combination usually we choose one drug from the secretogogue group and another from the sensitizer group.

In spite of well planned dosage regimens consisting of different OHAs, in Type 2 diabetes mellitus, glycemic control is poor in some patients. In addition, many OHAs produce adverse effects like weight gain, hypoglycemia etc. In this situation the search is going on for better OHAs.

Recently, the role of 'incretins' particularly that of glucagon like peptide (GLP-1) has been firmly established. The peptide GLP-1 increases insulin secretion while decreasing that of glucagon in response to rise in plasma glucose[7]. But this peptide hormone cannot be used orally as such because of very short plasma half life (2 min)[8-10] and chemical nature. Hence, to prolong the duration of action of endogenous GLP-1, compounds have been synthesized which inhibit DPP-4 (Dipeptidyl peptidase-4) the enzyme responsible for metabolic degradation of GLP-1[8,11,12]. DPP-4 inhibitors are a new class of anti diabetes that target DPP-4 and appear to offer an improved benefit risk profile over traditional drugs.

Vildagliptin, sitagliptin, saxagliptin are the DPP-4 inhibitors now available for the treatment of type 2 diabetes mellitus[13,14]. Vildagliptin is a potent, selective and reversible inhibitor of DPP-4 that improves glycemic control in patients with Type 2 diabetes mellitus by increasing both α and β cell responsiveness to glucose[15-17]. When Type 2 diabetes mellitus progresses, it is often necessary to combine antidiabetic agents from different classes to control hyperglycemia. So, in patients of Type 2 diabetes mellitus with poor glycemic control a combination of metformin and vildagliptin were used and its efficacy and safety compared with metformin and glimepiride in improvement of glycemic control.

MATERIALS AND METHODS

Study Design

This is a longitudinal interventional study. The study protocol was approved by the institutional ethics committee and a written consent was taken from all patients included in the study in their local language. The study was done in diabetic OP in Government General Hospital, Vijayawada. Totally 60 patients were enrolled in the study. These patients were already receiving metformin 500mg bid with poor glycemic control. These

60 patients were divided into two groups, each group containing 30 patients. Group 'A' patients received glimepiride 1 mg bid in addition to metformin 500mg bid. Group 'B' patients received vildagliptin 50 mg bid in addition to metformin 500mg bid. The total period of the study was three months. Clinical examination findings, investigations and relevant history were obtained and entered in the proforma. Periodical blood sugar levels (both fasting and postprandial) were measured at the end of every month. Blood glucose and HbA_{1c} levels were estimated before and at the end of the study.

Inclusion Criteria

1. Males and females of age between 40-70 years

2. Type-2 diabetes already on treatment with metformin 500mg bid but with uncontrolled blood sugars i.e., (FBS > 126 mg/dl and PPBS > 200 mg/dl)

3. Type-2 diabetes with hypertension and on treatment with ACE inhibitors.

Exclusion Criteria

1. Males and females of age below 40 years and above 70 years

2. Newly diagnosed cases of Type-2 diabetes

3. Type-2 diabetics with hypertension and on treatment with β blockers.

4. Type-2 diabetics with other endocrinological disorders like hypo or hyper thyroidism, cushing's syndrome and acromegaly.

5. Type-2 diabetics with acute complications of diabetes mellitus

6. Type-2 diabetics on drugs like thiazide diuretics, corticosteroids, oral contraceptive pills, protease inhibitors.

7. Type-2 diabetics with pancreatic disorders like pancreatitis.

8. Other specific types of diabetes like MODY.

9. Type-2 diabetics with severe renal failure, heart failure and hepatic failure.

10. Pregnant and lactating woman.

MATERIALS

Blood Glucose Estimation

Estimated by GLUCOSE OXIDASE METHOD[18].

Principle: The aldehyde group of glucose is oxidized by glucose oxidase to give gluconic acid and hydrogen peroxide. The overall reaction is

Glucose + H_2O + O_2 → gluconic acid + H_2O_2.
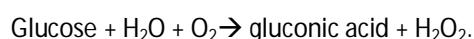
The hydrogen peroxide is broken down to water and oxygen by peroxidase.

Peroxidase H_2O_2--------------------→ H_2O+O_2
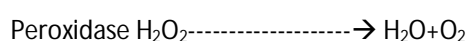
The oxygen reacts with 4-aminophenazone in the presence of phenol to form a pink coloured compound and intensity of which can be determined at 530nm.

Sample material–serum/plasma. Fluoride plasma or serum collected within 30 minutes of blood collection.

HbA$_{1c}$ - Auto Analyser Method[18]

Principle: The interfering substances are removed by washing the red blood cells 4-6 times with normal saline.

Hemolystate is prepared by using carbon tetrachloride.

Hexoses bound to haemoglobin are quantitatively hydrolysed by heating the hemolysate at 100 °C in the presence of oxalic acid. Resultant chromogen is measured at 443nm.

The data were analyzed using statistical package for social sciences (SPSS) for windows version 12.

Chi square test and Unpaired 't' test were applied. P value < 0.05 was considered to be significant (0.01).

RESULTS

Total number of patients enrolled in the study were 60. Maximum number of patients belonged to the age group of 50-54 years i.e., 66% (n=20). There were no patients below the age of 40 years.

Out of 60 patients 47% (n=28) patients were males and 53% (n=32) patients were females. Among the total 60 patients 47% (n=14) were males in both group A and group B and 53% were females in both groups.

Table 2: Distribution of Cases according to Age

Age group	Group A		Group B	
	Number	Percentage	Number	Percentage
<40 Yrs	0	0	0	0
40-44 yrs	0	0	1	3%
45-49 yrs	8	27%	5	17%
50-54 yrs	10	33%	10	33%
55-59 Yrs	4	13%	6	20%
60-64 yrs	7	24%	6	20%
65-70 yrs	1	3%	2	7%
Total	30		30	

Table 3: Sex wise distribution

Gender	Group A		Group B	
	Number	Percentage	Number	Percentage
Males	14	47%	14	47%
Females	16	53%	16	53%
Total	30		30	

After 90 days of treatment, both the groups showed a significant decrease in fasting blood sugar. There was a significant difference between the two groups in decreasing the fasting blood sugar levels (p<0.05).

Table 4: Fasting Blood Sugar Levels

FBS	Group A		Group B		't' value	'p' value	Inference
	Mean	SD	Mean	SD			
At the starting of Therapy	204.13	41.39	215.07	37.6	1.071	0.289	Not Significant
At the end of 1st month	150.2	24.17	144.77	11.34	1.115	0.271	Not Significant
At the end of 2nd month	141.7	16.24	131.67	12.5	2.681	0.010*	Significant
At the end of 3rd month	132.5	11.66	120.97	7.35	4.584	<0.0001*	Significant

After 3 months of treatment both the groups showed a significant decrease in the postprandial blood sugar levels. There was no significant difference between the two groups in decreasing the postprandial blood sugar levels (p>0.10).

Table 5: PostPrandial Blood Sugars

PPBS	Group A		Group B		't' Value	'p' Value	Inference
	Mean	SD	Mean	SD			
At the starting of Therapy	288.57	49.56	303.33	39	-1.282	0.205	Not significant
At the end of 1st month	226.47	24.95	218.8	28.9	1.100	0.276	Not significant
At the end of 2nd month	210.9	25.43	202.03	21.46	1.459	0.150	Not significant
At the end of 3rd month	203.47	18.74	199.67	21.78	0.725	0.472	Not significant

After 3 months of therapy there was no reduction in HbA$_{1c}$ in A group. There was a reduction in HbA$_{1c}$ in B group. The reduction of HbA$_{1c}$ was not statistically significant between the two groups.

Table 6: HbA$_{1c}$ Levels

HbA$_{1c}$	Metformin & Glimepiride Group		Metformin & Vildagliptin Group		t value	P value	Inference
	Mean	SD	Mean	SD			
At the Starting of Therapy	8.49	0.81	8.83	0.74	-1.663	0.102	Not Significant
At the End of IIIrd Month	8.53	0.81	8.79	0.72	-1.297	0.200	Not Significant

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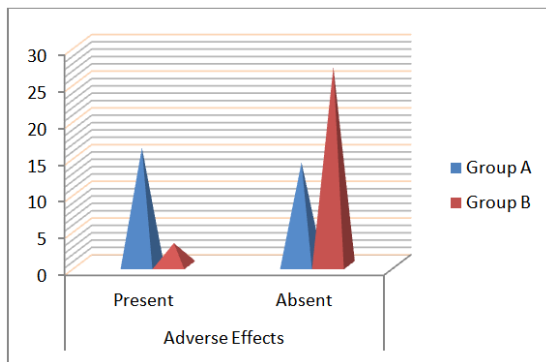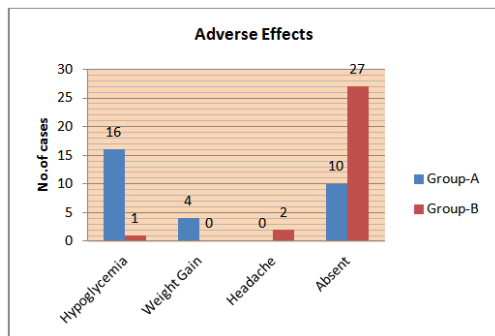**Figure 7:** Incidence of Adverse Effects in Groups A & B

Figure 8: Incidence of Adverse Effects in Groups A & B

DISCUSSION

Type 2 diabetes mellitus is at present one of the most challenging health care problems, which require optimum management. Current treatment for Type 2 diabetes mellitus is often associated with inadequate glycemic control (especially with sulfonylureas, metformin & thiazolidinediones), weight gain (sulfonylureas, glinides, thiazolidinediones and insulin) and loss of efficacy over time (a problem with all current oral agents). Inadequate glycemic control contributes to diabetic microvascular and macrovascular complications. Usually we initiate therapy as first choice with sulfonylureas or metformin in patients with Type 2 diabetes mellitus. In patients of inadequate glycemic control with metformin or sulfonylureas, a combination of two classes of drugs may be effective. Hence, the study was aimed to estimate efficacy and safety of glimepiride Vs Vildagliptin in glycemic control when added to metformin. Many studies indicated similar efficacy profile for glimepiride and vildagliptin.

More adverse effect profile was observed with glimepiride in comparison with vildagliptin. This could be due to meal stimulated release of insulin by the vildagliptin.

Mathews DR, Dejagers, Ahern B showed that vildagliptin added to metformin is not inferior to glimepiride in reducing HbA$_{1C}$ levels. Mean (S.E.) change in HbA$_{1C}$ was comparable between vildagliptin and glimepiride treatment-0.1% and -0.1% respectively. Fewer patients experienced hypoglycemia with vildagliptin (2.3% Vs 18.2% with glimepiride) with a 14 fold difference in the

number of hypoglycemic events (59 Vs 838). Vildagliptin had a beneficial effect on body weight[19].

Ferrannini E, Fonseca V, Zinman B compared the efficacy and safety of vildagliptin Vs glimepiride as add on therapy to metformin demonstrated a mean (SE) change from baseline HbA$_{1C}$ (7.3% in both groups) to week 52, end point was -0.44% with vildagliptin and -0.53 with glimepiride. Fasting plasma glucose (FPG) reductions were comparable between groups mean (SE) -1.01 mmol/lit and -1.14 mmol/lit respectively[20].

Vildagliptin significantly reduced body weight relative to glimepiride and resulted in a 10 fold lower incidence of hypoglycemia than glimepiride (1.7 Vs 16.2% presenting at least one hypoglycemic event; 39 Vs 554 hypoglycemic events P<0.01). No severe hypoglycemia occurred with vildagliptin compared with 10 episodes with glimepiride (P<0.01) and no patient in the vildagliptin group discontinued because of hypoglycemia compared with 11 patients in the glimepiride group[20].

Whereas in this study the percentage change of FBS from starting of therapy was -35.09% in glimepiride group, -43.75% in vildagliptin group. Change of PPBS from starting of therapy was -29.49% in glimepiride group, -34.17% in vildagliptin group at the end of three months of therapy.

Change of HbA$_{1C}$ from starting of therapy was 0.47% in glimepiride group, -0.45% in vildagliptin. The results obtained from both regimens were statistically not significant except with FBS where 'p' value is significant (p<0.05) and were well tolerated. Incidence of hypoglycemia is 16 times more in glimeperide group (94%) and 6% in vildagliptin group. Weight gain was reported by glimepiride group (13%) weight was neutral in vildagliptin group. Adverse effects were absent in 30% of subjects in glimepiride group, 90% of subjects in vildagliptin group.

Bosi E, Datta F, Jia Y, Goodman M showed that vildagliptin plus metformin therapy provides superior glycemic control that is -1.8% from baseline at the end of 24 weeks and low risk of hypoglycemia and weight gain. Despite superior HbA$_{1C}$ lowering, the vildagliptin plus metformin combination demonstrated a favourable G.I. tolerability prolife compared with metformin monotherapy. In the present study vildagliptin and metformin therapy provides a glycemic control of -0.45% from base line at the end of three months and low risk of hypoglycemia. No reports of GIT intolerability and weight gain by vildagliptin and metformin group[21].

The study (VECTOR) is the first and only prospective comparative study measuring the relative incidence of hypoglycemia in Muslim people with Type-2 diabetes fasting during Ramadan. Vector study shows vildagliptin with metformin is an effective treatment option with low risk of the unpleasant and sometimes devastating consequences of hypoglycemia. In this study also

reporting of hypoglycemia is less in vildagliptin group (1) compared to the glimepiride group (16)[22].

Those treated with vildagliptin and metformin also experienced significantly lower HbA$_{1C}$ measurement, post Ramdan (7.7% to 7.2%) versus those treated with an SU(sulfonylureas) and metformin(7.2% to 7.3%)(p=0.0262). Body weight remain unchanged in both groups. In the present study there is no significant difference in reduction of HbA$_{1C}$ between both the groups, weight was neutral in vildagliptin group[22].

Bo Ahren, James E. Foley determined that vildagliptin therapy but not glimepiride improves postprandial α cells function by reducing prandial glucagon AUC (baseline 66.6 ± 2.3 pmol.h^{-1}.l^{-1}) decreased by (3.4 ± 1.6 pmol.h^{-1}.l^{-1}) by vildagliptin and increased by (3.8 ± 1.7 pmol.h^{-1}.l^{-1}) by glimepiride. The between group difference was (7.3 ± 2.1 pmol.h^{-1}.l^{-1}). (p<0.001)[23].

Emanuele Bosi, Riccardo paolo camisasca evaluated the efficacy and safety of vildagliptin when added to metformin is well tolerated and produces clinically meaningful, dose related decreases in A1C and FPG. Adverse events were reported by 65% of patients receiving vildagliptin 100mg daily. In this study only 10% of people receiving vildagliptin 50mg bid reported adverse events[24].

Anja Schweizer, Sylvie Dejager assessing general safety and tolerability of vildagliptin from a large pooled database of Phase II and Phase III trails shows vildagliptin was well tolerated in trials up to > 2 years in duration.

The incidence of adverse effects was -69% in patients receiving vildagliptin. In the present study incidence of adverse effects was -90% in vildagliptin group[25].

The most common adverse reactions occurring in 5% of patients or more who received DPP-4 inhibitors were upper respiratory tract infection, nasopharyngitis, and headache, while in the resent study headache is seen in two atients receiving vildaglitin treatment and nasoharingitis is not seen[26].

Brown NJ, Byiers reported vildagliptin use may be associated with increased risk of angioedema in patients taking ACE inhibitor and DPP-4 inhibitor. There is no case of angioedema reported in my observation with ACE inhibitors[27].

Bosi E, Ahren B, Foley JE vildagliptin added to stable dose of metformin elicits a dose related decrease in both HbA$_{1C}$ and fasting plasma glucose (FPG).

The additional efficacy seen with 50 mg twice daily (Λ HbA$_{1C}$(-1.1%(-12.0mmol/mol)) relative to 50mg once daily (Λ HbA$_{1C}$ -0.7% (-7.7mmol/mol) is attributable to an overnight effect of evening dose at vildagliptin, with prolonged DPP-4 inhibition and elevated fasting levels of the intact and insulinotropic form of glucagon like peptide (GLP-1). To achieve prolonged DPP-4 inhibition we also administered vildagliptin 50 mg twice daily[28].

He YL, Paladni, Saiba H reported that the fixed dose combination tablet of vildagliptin / metformin is bioequivalent to administration of the individual drugs as a free combination at dose levels of 50/850 and 50/1000 mg is well tolerated. Consequently, the fixed dose combination tablets are considered therapeutically equivalent and exchangeable to the free combination in clinical practice. In the present study free combination drugs of 50/500mg bid of vildagliptin / metformin are used [29].

CONCLUSION

Non insulin dependent diabetes mellitus is a progressive disease that is prevalent in the elderly as well as among the youth. Diabetes has become the major cause of peripheral neuropathy, afflicting 20% to 30% of type 2 diabetics for which there is currently no treatment other than strict control of blood glucose levels. The new approach for treatment of diabetes mellitus achieved by DPP-IV inhibition has the potential to reduce and may even normalize both fasting and postprandial glucose concentrations without adverse effects such as weight gain. This approach also raise the hope that such a therapy may be able to delay or even halt the progression of the disease by providing a means of safety in treating subjects with impaired glucose tolerance. Finally this approach may turn out to be inherently safer than existent insulin secretagogue therapy because of its glucose dependency. Thus DPP-IV inhibitors have not been associated with any incidence of severe hypoglycemia even when given in combination with existing oral antidiabetic agents.

In this study, both metformin + glimepiride and metformin + vildagliptin achieved optimal glycemic control almost equally at the end of 3 months of therapy. But in terms of adverse effect profile, hypoglycemia was observed in 53% of glimepiride group and 3% in vildagliptin treated group. Weight gain was reported only in glimepiride group. Headache was reported 6% in vildagliptin group. Hence, Vildagliptin+metformin offers advantage and represents an important new treatment option for optimal glycemic control without weight gain and risk of hypoglycemia. Vildagliptin is effective, better tolerated than glimepiride for the treatment of diabetes mellitus. When combined with metformin as it showed improved efficacy over time (may be due to GLP-1 induced increase in beta cell numbers and mass) without weight gain and hypoglycemia which are the common side effects with the other antidiabetic drugs. Due to glucose dependent insulinotropic action of GLP-1 hypoglycemia is less with vildagliptin. Inhibition of gastric emptying might account for the satiety after GLP-1 administration.

In future long term safety studies are required on these drugs especially on vildagliptin particularly in preventing the development and halting the progression of the disease, which has not been possible till now with any other antidiabetic agents.

Limitations of the Study

1) As the sample size is small the inference of the study has limited value.

2) Cost of vildagliptin is the main limiting factor to enroll more number of patients in a government set up.

3) Though dose ranges are high for studied drugs i.e., 50-100 mg for vildagliptin, 1-4 mg for glimepiride, we studied the effects with fixed dose of i.e., 50 mg bid for vildagliptin, 1 mg bid for glimepiride.

4) Blood glucose measurements done at the end of every month may not necessarily represent blood sugar levels throughout the month.

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