THREE MONTHS COMPARATIVE STUDY OF EFFICACY AND SAFETY OF METFORMIN PLUS GLIBENCLAMIDE VERSUS ROSIGLITAZONE PLUS GLIBENCLAMIDE IN THE TREATMENT OF DIABETES MELLITUS

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Abstract: *The objective of our study was to make a three months comparative assessment of the efficacy of metformin plus glibenclamide versus rosiglitazone plus glibenclamide in the control of glycemic status of patients suffering from type 2 diabetes with moderate hyperglycemia and to make a comparative assessment of safety profile of these drugs by monitoring their adverse drug reaction profile. In this single centre, single blind parallel group study patients were randomized to receive either metformin 500 mg twice daily and glibenclamide 5mg (gr1, n=30) or rosiglitazone 2 mg twice daily glibenclamide 5 mg once daily (gr2, n=30). All patients were thoroughly examined clinically and all biochemical parameters were recorded at screening and at termination of the study. HbAIC was reduced by 2.01% in group 1 and 1.99% in group 2. Fasting plasma glucose was reduced by 57.96 mg/dl and 52.04 mg / dl in the respective groups. PPGwas also glucose was reduced by 93.50 mg/dl and 105.10 mg/dl respectively. A mean weight gain of 1.87 kg was observed in the rosiglitazone plus glibenclamide group compared to a reduction of 2.60 kg in the metformin plus glibenclamide group over 12 weeks. Metformin addition to glibenclamide significantly reduced trighlycerides (-4.98% vs – 1.31%) and increased HDL cholesterol (6.37% vs 4.19%) compared with rosiglitazone and glibenclamide. The significant reduction of total cholesterol (-5.36% vs – 30.02) and LDL cholesterol (-6.05% vs – 3.02) was also noted in the respective groups, both combinations were well tolerated. The double drug therapy demonstrated early and sustained reduction in fasting and post – prandial glucose levels; as also in glycosylated haemoglobin levels. Compared with rosiglitazone plus glibenclamide, addition of metformin to glibenclamide resulted in a better reductionb of LDL, total Cholesterol and significantly greater improvement in triglycerides level and HDL cholesterol level. Both combinations were .significantly effective.*

INTRODUCTION

Type 2 Diabetes is often characterized by hyperglycemia as a result of increased insulin resistance, in addition to deficit in insulin secretion, pancreatic B-cell dysfunction[1,2] and is manifested in adipose tissue, skeletal muscle and the liver. Excess visceral adiposity, dyslipidemia and hypertension often accompany insulin resistance. This defect increase lipolysis in adipose tissue, elevates free fatty acid and leads to raised triglycerides levels. The inability to suppress hepatic glucose production is a major contributor to the fasting Hyperglycemia[3]. Post prandial hyperglycemia can precede fasting hyperglycemina. Hyperglycemia itself exacerbates insulin resistance and impairs insulin secretion. Thus interacting defects in multiple organs of pancreas, muscle, adipose tissue and liver generate the pathogenic milieu which results in diabetes. Various oral glucose lowering agents are now available that target the different pathophysiologic factors contributing to diabetes but once, initial monotherapy starts to loose its effect, long term management with combination therapy with two groups of oral antidiabetics having different mechanisms of action is often necessary[4]. Metformin improves glucose tolerance by lowering both fasting and post prandial plasma glucose. It decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization[5]. Metformin also reduced the cardiovascular compolications of diabetes.

Studies have shown that thiazolidinediones, when used as monotherapy[6,7] or in combination with either nsulfonylureas[8] or with Metformin[9] improve glycemic control. Rosiglitazone, a TZD, is a peroxisome proliferators activated receptor (PPAR) – y agonists, that enhances the action of insulin mainly by suppressing gluconeogeneis in the liver and increasing glucose utilization in peripherals tissues, in particular, in skeletal muscle[10,11]. Rosiglitazone reduces FPG, PPG, HbAIC, insulin and C-peptide and prevents the on set of hyperglycemia. Clinical studies suggests that rosiglitazone has the potential to sustain a improve B-cell function in type 2 diabetes. Glibenclamide works by inhibiting ATP sensitive potassium channels in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening of voltage dependent calcium channels, thus triggering an increase in intracellular calcium into the beta cell which stimulates insulin release[10,11]. The study was conducte4d to compare efficacy and safety of Rosiglitazone added to Glibenclamide with the commonly used combination of Metformin and glibenclamide over 12 weeks in the control of glycemic status of patients suffering from type 2 diabetes with moderate hyperglycemia.

MATERIALS AND METHODS

This was a prospective e, randomized, single blind, parallel group study conducted on 60 patients of type II diabetes. All patients gave written, informed consent to participate in the study which was conducted with the approval from Institutional ethical committee and in accordance with the good clinical practice guidelines of Govt. of India. The study was also carried out in accordance with the principles in the Declaration of Helsinki for Biomedical Research[12] on human subjects. The *screening for the eligibility* of the patients with type 2 diabetes were performed based on 3 major criteria.

1) Male and female patients in the age group of 25-65 years. (provided they would adopt contraceptive methods during study period)
2) Fasting plasma glucose level (FPG) ≥7.2 mmol/L

or

3) Two hour post prandial plasma glucose level (PPG) 10 mmo /l.

Exclusive criteria included patients with type I diabetes or ketoacidosis, type 2 diabetes with severe hyperglycemia (FPG 15 mmol/L or above,) transient ischemic attacks or stroke in the previous six months, pancreatitis, a history of myocardial infarction, symptomatic heart failure, polyposis, malignant disease in the previous

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12 years, known hypersensitivity to the trial drugs, history of chronic alcohol intake, impaired renal function, acute or chronic liver disease and impaired liver function elevated, AST/ALT level; pregnant or breast feeding woman, were also excluded.

The **trial patients** received the test drugs for a total period of 3 months comprising of three monthly follow up visits. Eligible patients were randomized in two groups to receive combination therapy of either metformin and glibenclamide or rosiglitazine and glibenclamide. Patients of grop 1 recieved metformi 500 mg twice daily and glibenclamide 5 mg once daily. The patients were followed up every month for 3 months. At each visit, thorough clinical examination was conducted and FPG, PPG levels were estimated. Routine blood biochemistry was done at baseline and at study and visit. Adverse events, as elicited from the history, clinical examination and review of the trial diary being maintained by the patients were recorded to assess the safety parameters.

Statistical analysis was performed using statistical version 6 software. Mean differences between groups were calculated with 95% CI and A two sited students's 'test' test (a=0.05) was performed. Data were presented as mean SD; p value < 0.05 was considered statistically significant.

RESULTS

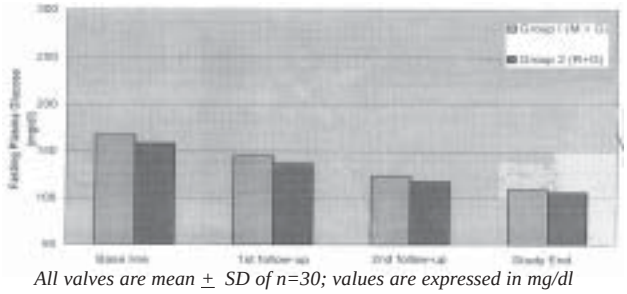
In total 60 patients received study treatment in two groups (n=30 with met5formin plus glibenclamide; n=30 with rosiglitazone plus glibenclamide). Both the groups were evenly matched with respect to baseline demographic, disease duration and disease severity profile. The baseline glycemic indices i.e. fasting, post prandial plasma glucose and glycosylated haemoglobin levels were not significantly different (P.o.05) in the two groups. A mean weight gain of 1.87 kg (mean increase in BMI 0.77 kg/m2) was observed in the rosiglitazone plus glibenclamide group 1 metformin plus glibenclamide) and group 2 rosiglitazone plus glibenclamide) were inadequately controlled as evident by the mean baseline glycoslyated haemoglobin levels of 8.19 + 0.89% and 8.08 0.65% respectively. After medication of three months, the mean glycosylated haemoglobin levels of group 1 and group 2 reduced to 6.18% and 6.09% respectively. The mean FPG level of group 1 reduced to 109.07 + 16.51 mg / dl from 167.03 + 25.79 mg / dl and that of group 2, reduced to 106.13 + 23.52 mg dl from 158.17 + 22.79 mg/dl when compared study end levels with baseline values. The mean PPG level reduced from 254.57 + 42.10 mg / dl to 161.07 + 36.50 mm / dl and from 260.13 + 28.99 mm / dl to 155.03 + 35.88 mg /dl for group 1 and Group 2 respectively when compared study end level with baseline level (table-I fig. 1,2,3, changes in total cholesterol, HDL cholesterol, triglicerides, LDL cholesterol and VLDL cholesterol from baseline to 12 weeks are shown in Table 2 (Fig. 4-5). No serious adverse events were encountered during the entire course of the present study. In the rosiglitazone plus glibeclamide group, only one patient complained of vertigo but the clinical signs and plasma glucose level showed no substantial derangement. In the metformin plus glibenclamide group several patients had initial nausea and diarrhea episode , hwoever they were non – serious and disappeared with therapy continuation. Although rosiglitazone is reported to cause hepatotoxicity. We did not detect any significant hepatotoxicity with rosiglitazone plus glibeclamide group therapy. There was no significant change in AST, ALT and ALK levels in both groups. They were found to be with in normal ranges at study end.

No rescue medicines were used on any patient to control glycemic status as the study drug achieved the required glycemic control over the study period. Of other concurrent ailments present, only one patients in rosiglitazone plus glibeclamide group, had associated hypothyrodism and hypertriglyceridemia which was well controlled with levothyroxine and statin supplementation. Twelve (12) patients belonging to group Metformin plus Glibenclamide and thirteen patients of rosiglitazone plus glibeclamide group were hypertensive and were on Enalapril with doses ranging from 5-10 mg daily. Their blood pressure levels were adequately controlled through out the study period.

Table -1: *Serial Changes In Efficacy Parameters*

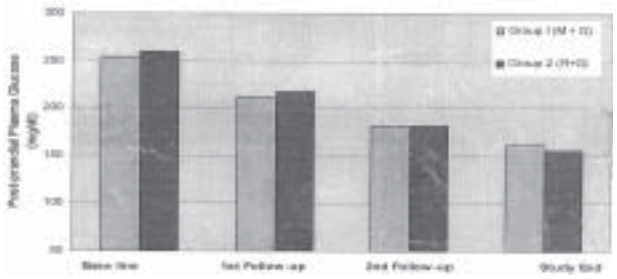
Item	Group	Baseline	1st Follow up	2nd Follow up	Study End
FPG (mg / dl)	Group 1 (M+G)	167.03 ±25.79	144.67 ± 20.57	122.93 ± 16.75	109.07 ± 16.51
	Group 2(R+G)	158.17± 22.79	136.70 ± 22.14	117.60 ± 20.03	106.13 ± 23.52
FPG (mg / dl)	Group 2(R+G)	254.57± 42.10	212.67 ± 40.91	181.80 ± 38.52	161.07 ± 36.50
	Group 2(R+G)	260.13± 28.99	218.33 ± 30.29	181.70 ± 32.23	155.03 ± 35.88
HbAIC	Group 1 (M+G)	8.19± 0.89			618. ± 0.71
	Group 2(R+G)	8.08 ±0.65			6.09 ± 0.72

All values are Mean ± SD; N=30 in each group FPG = fasting plasma glucose PPG = postprandial plasma glucose HbAIC = Glycosylated hemoglobin. Denotes p < 0.001 in comparison with baseline values in respective groups (paired test).



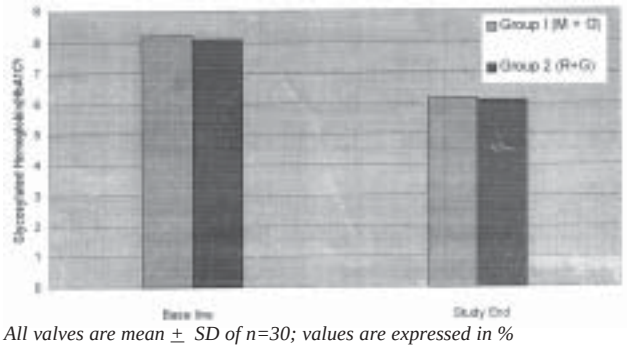
All valves are mean ± SD of n=30; values are expressed in mg/dl

Figure 1: *Serial Changes in fasting plasma glucose levels in both groups.*



All valves are mean ± SD of n=30; values are expressed in mg/dl

Figure 2: *Serial Changes in Post-prandial plasma glucose levels in both groups.*



All valves are mean ± SD of n=30; values are expressed in %

Figure 3: *Serial Changes in Glycosylated Hemoglobin levels in both groups.*

Table 2 *Effects On Lipid Profile*

Parameters	Group	Baseline	Study End
Total Cholesterol (mg/dl)	Group 1	174.80 ± 11.84	165.43 ±10.53
	Group 2	170.17± 10.86	165.03± 8.45
Serum LDL (mg/dl)	Group 1	86.67 ±10.35	81.43± 8.14
	Group 2	83.73± 6.99	81.20 ±5.62
Serum HDL (mg/dl)	Group 1	41.30 ±1.97	43.93 ±2.33
	Group 2	40.57 ±1.94	42.27 ±2.02
Serum Triglyceride (mg/dl)	Group 1	130.50 ±7.15	124.00± 8.61
	Group 2	127.60 ±9.26	125.93 ±16.89
Serum VLDL (mg/dl)	Group 1	23.60 ±2.82	21.23± 2.11
	Group 2	23.57±4.00	22.43± 4.53

All values are mean ± SD of n = 30 for both groups
Group 1: Metformin + Glibenclamide; Group 2: Rosiglitazone + Glibenclamide; HDL = High – Density Lipoprotein; LDL=Low Density Lipoprotein; VLDL =Very low – Density Lipoprotein

DISCUSSION

This study provides evidence supporting the use of combination therapy metformin plus glibenclamide or rosiglitazone plus glibeclamide) in patients with type 2 diabetes mellitus with moderate hyperglycemia. The double drug therapy method used in this study demonstrated early and sustained reduction in fasting and post prandial glucose levels, followed by similar reductions in glycosylated haemoglobin levels. Rosiglitazone enhances insulin sensitivity in adipose tissue, liver and skeletal muscle and thus lowers blood glucose[13,14]. This study also tried to assess the responders and their relationship with the other clinical characteristics such as body weight and BMI. The mean weight gai of 1.87 kg observed in rosiglitazone plus glibenclamide group may be observed in rosiglitazone plus glibenclamide group may be attributed to increased adipocyte differentiation[15], fluid retention or increased appetite[16] which suggrests that Rosiglitazone treatment leads to increased energy storage in the subcutaneous adipocytes. Weight gain in type 2 diabetes is generally associated with worsening of insulin resistance and deteriorating in glycemic control. However, in this case, despite of weight gain of 1.87 kg over 12 weeks, there was an improvement in glycemic control In the metformin plus glibenclamide group, there was a mean reduction of 2.01 % in HbAIC after 12 weeks of treatment, similar to the reduction of 1.99% observed in the rosiglitazone plus glibenclamide group. The patients of both groups achieved an HbAIC < 7.0% after 12 weeksd of treatment. The glycemic status of patients of both controlled in oth the groups (GR.1 – paired difference 2.01 + 0.55, Gr. 2 1.99 0.47, p<0.01, in comparison with baseline, paired 't' test). Mean fasting plasma glucose were reduced by 57.96 mg / dl and 52.04 mg / dl in the respective groups over study period. Similarly mean PPG was also reduced by 93.50 mg / dl and 105.10 mg / dl in the respective groups over study period. The mean reduction of FPG, PPG and HbAIC of both the groups were highly significant (p< 0.01). With metfgormin plus glibenclamide, the mean HDL Cholesterol was increased by 2.63 mg / dl and by 1.70 mg / dl in the rosiglitazone plus glibeclamide group. In the metformin plus glibenclamide group, mean tryglicerides were reduces by 6.50 mg / dl and by 1.67 mg / dl in the rosiglitazone plus glibeclamide group. The significant reduction of mean total cholestrerol (- 5.36% vs -3.02%) and mean LDL Cholesterol (-6.05% vs – 3.02) was also noted in respective groups. Mean VLDL levels of patients of both the groups were reduced (-10.04% vs. – 4.84%) at the study end. Improvements in HDL cholesterolo, triglycerides, total cholesterol, LDL cholesterol and VLDL cholesterol with Metformin plus glibenclamide group were much better comnpared to rosiglitazone plus glibeclamide group. The total cholesterol to HDL cholesterol ratio (3.77 vs 3.90 of group 1 and group 2 study end respectively) gives an indication of the overall changes in the lipid profile and has been found to be a useful indicator of cardiovascular risk.

Both Metformin and rosiglitazone (when used with glibenclamide as combination therapy) were highly efficacious oral anti diabetic agents. The three months duration of the study was intended to provide sufficient exposure to demonstrate the maximal therapeutic effect, as assessed by reduction in glycosylated haemoglobin levels, FPG and PPG levels. Various previous studies have shown that Thiazolidinediones used in combination with sulphonylurea or Metyformin improved glycemic control. Analysis of the result of this study also shows that Thiazolidinedione (Rosioglitazone) is effective and well tolerated when used with sulphonylurea (glibenclamide). The other combination therapy of Metformin and Glibenclamide is equally effective in treatment. Use of intensive and demanding combination therapy for type 2 diabetes over a three months period if feasible and in the present study, it resulted in significant attainment of efficacy. The study also achieved control of FPG,PPG and HbAIC levels. No patients of the study group withdrew because of the therapy. Body weight was stable over three months intervention period.

CONCLUSION

This study was made to determine the best combination of drugs (either Metformin plus Glibenclamide or Rosiglitazone plus glibenclamide) for achieving target glycemic control in Type 2 diabetic patients. However, at the end it has been found that both combination of drugs are significantly effective but there is no significant advantage of one group of drugs over other in controlling efficacy and safety parameters of type 2 diabetes mellitus patients. These agents can, therefore, be prescribed (as combination therapy of metformin and glibenclamid or rosiglitazone and nglibvenclamide) as effective oral anti diabetic agents for control of mild to moderate degree of hyperglycemia in subjects of type 2 diabetes mellitus.

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