a COMPARISON OF PIOGLITAZONE WITH METFORMIN IN MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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Abstract

Objectives: To compare hypoglycemic effect of Pioglitazone and Metformin in type 2 Diabetes Mellitus.
Study Design: Quasi experimental study
Place and Duration of study: Department of Medicine, Military Hospital Rawalpindi Cantt from 11-01-2007 to 12-08-2007.
Material and Methods: Sixty patients of type 2 diabetes mellitus from outdoor department were selected. On arrival at OPD each patient was examined thoroughly. Therapeutic option was allocated to the patients simply by using a table of random numbers and dividing them in two equal groups. Informed written consent was obtained. Each patient was followed on monthly subsequent visits (six in total) and his HbA1c, fasting and random blood glucose were recorded carefully.
All the data thus obtained was processed and analyzed using SPSS version 10.0. Mean and SD were calculated for age, BMI, fasting blood glucose, random blood glucose and HbA1c levels.
Results: Mean drop of all three parameters were compared among two groups. At the end of six months, it was revealed that fasting and random (2 hours postprandial) blood glucose dropped more in Pioglitazone group; P=0.000 and 0.02 respectively. While almost comparable effect was observed in HbA1c (P=0.2).
Conclusion: Pioglitazone has significantly better hypoglycemic effect than Metformin in type 2 diabetes mellitus at the end of six months therapy.

Keywords : Type 2 Diabetes Mellitus, Pioglitazone, Metformin

Article

INTRODUCTION

Uncontrolled diabetes can lead to dreadful complications that cause physical, emotional and economical burden on the individual as well as on the society1. The only effective way to avoid complications of diabetes is a good glycemic control, which in type 2 diabetes, can be achieved by oral hypoglycemic drugs. In the last few years new drugs have emerged targeting at better pharmacokinetic and low side effect profile. Among them have been various insulin sensitizers and Pioglitazone is one of them.

In United Kingdom Prospective Diabetes Study, type 2 diabetes is characterized by an inexorable progression of glucose control deterioration3. Both ß-cell dysfunction and insulin resistance are core defects in the progression of type 2 diabetes and the associated metabolic syndrome2.

Metformin lowers plasma glucose concentrations while simultaneously decreasing plasma insulin and may act by decreasing hepatic glucose production, increasing splanchnic and hepatic glucose utilization, and having a secondary effect on insulin resistance3. The metabolic effects of Metformin may be due to its ability to phosphorylate and activate AMP-activated protein kinase4. In obese patients with creatinine 1.5mg/dl, Metformin should be considered as initial therapy5.

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Pioglitazone, a thiazolidinedione, is a peroxisome proliferator-activated receptor agonist that affects

regulators of carbohydrate and lipid metabolism6. Pioglitazone reduces insulin resistance by enhancing the action of insulin, thereby promoting glucose utilization in peripheral tissues, suppressing gluconeogenesis, and reducing lipolysis7.

Pioglitazone is a relatively new drug. It can safely be used as a monotherapy for glycemic control in patients of type 2 diabetes mellitus. Pioglitazone has been demonstrated to provide clinically equivalent control of HbA1c in comparison with Metformin, traditionally the agent of choice for treatment of obese patients with type 2 diabetes8. Significantly greater reductions in fasting blood glucose have been observed with Pioglitazone compared with Metformin9. Use of this drug is quite limited despite its good tolerability and efficacy. Whereas, traditionally, Metformin is used more in type 2 diabetics conventionally10. No comparative trial could be seen among the two dugs in our country. Wherever pioglitazone is used, it is being prescribed without having complete knowledge about profile of the drug because very little work has been done on its efficacy particularly in our population as local material is hardly seen on its efficacy. In the present study, this drug was studied and its effects were compared with one of the traditional drug used for type 2 cases of diabetes mellitus i.e. Metformin. It has really helped to guide our treatment strategy so that we no longer are using this drug blindly.

MATERIALS AND METHODS

The study was conducted in department of medicine, military hospital, Rawalpindi for the period of six months from 11-01-2007 to 12-08-2007. Sixty patients of Type 2 Diabetes Mellitus coming to the OPD of the hospital were selected and divided into 2 groups with 30 patients in each group by using table of random numbers.

Diagnosed patients of type 2 Diabetes Mellitus reporting to medical outdoor department of Military Hospital Rawalpindi between 35-65 years of age of both genders were included in the study. Lactating, pregnant females or those who have required chronic use (>6 months) of insulin for glycemic control had a history of ketoacidosis, or required the administration of insulin were excluded.

Patients on sulphonylureas and having unstable or severe angina, coronary insufficiency, congestive heart failure or severe hypertension, hepatic or renal impairment, history of drug or alcohol abuse were also excluded.

Data Collection Procedure

Patients were enrolled from the Medical out patient department with poor glycemic control on diet alone and were diagnosed cases of type 2 Diabetes Mellitus with at least 2 abnormal readings of fasting blood glucose(>126mg/dl). Random and fasting blood glucose were measured in addition to HbA1c levels.

Confounding variables were controlled by excluding pregnant or lactating patients (on the basis of history), patients taking any medication for diabetes mellitus (on history and past record), patients on treatment of ischemic heart disease, hepatic or renal disease.

Informed written consent was obtained after explaining the risks and benefits of respective medication given to the patient (particularly gastrointestinal side effects from Metformin and hepatotoxicity in case of Pioglitazone). All the treatment protocols and all related ethical issues were also thoroughly met and the patients were explained that both treatment modalities are internationally recommended for the treatment of diabetes mellitus.

Patient's population was divided in two groups with 30 patients in each group. Group 1 was given tablet Pioglitazone in a dose 45 milligrams per oral daily and group 2 tablet Metformin 3 grams per oral daily. Care was taken that any patient having contraindication to one treatment modality (e.g. hepatotoxicity in Pioglitazone) was subjected to the other mode of treatment but it was totally unbiased to assign the mode of treatment initially by using table of random numbers. These subjects were advised to follow a diet containing about 50% carbohydrate, low saturated fat, and moderately high fiber, with reduced total energy content if obese.

Fasting blood glucose was measured after at least 8 to 10 hours of fasting i.e., early in the morning (before breakfast). Patient history and clinical examination along with open conversation including dietary advice and compliance was carried out. Patients were then allowed to take a normal breakfast (as per their routine) and then random blood glucose was checked 2 hours after breakfast.

Blood samples were drawn from peripheral vein and immediately sent to laboratory for accurate glucose estimation. HbA1c level was also measured with these blood samples. The patient's baseline HbA1c, fasting and random (2 hours postprandial) blood glucose were recorded and maintained in the patient proforma. On each subsequent monthly visit he was again assessed carefully while fasting and random blood glucose were again recorded, but HbA1c was recorded at 3 months interval only. The difference between the initial blood glucose was recorded subsequently. The mean HbA1c, fasting and random blood glucose was also calculated for each group at every visit and compared with the baseline values. The percentage reduction in these parameters induced by the two drugs in both the study groups was ultimately compared with each other and thus the conclusion regarding better hypoglycemic effect of one drug was made.

Data Analysis Procedure

Data was analyzed using statistical software SPSS version 10.0. Categorical data for male and female was given in percentages. Descriptive statistics were used to calculate mean and SD for age, BMI (weight in kilograms/height in meters square), fasting blood glucose, random blood glucose and HbA1c levels. Mean and SD for fasting blood glucose, random blood glucose and HbA1c was calculated for each visit. Independent sample T test was applied to compare means of fasting blood glucose, random blood glucose and HbA1c values of both groups at baseline and at each subsequent visit. Drop in fasting blood glucose, random blood glucose and HbA1c was calculated between baseline and last follow up visit i.e. after six months of treatment. Their mean values were calculated and were also compared by using the same statistical test to assess whether there was any significant difference in hypoglycemic effect among the two groups. A p value of < 0.05 was considered significant.

RESULTS

Sixty adult patients with type 2 Diabetes Mellitus were selected fulfilling inclusion criteria. They were divided into two groups for therapeutic purposes, 30 patients in each. Group 1 was given tablet Pioglitazone and group 2 received tablet Metformin. All the patients were followed up for 6 months. Descriptive statistics (for age) of both groups are shown in table 1

(P=0.6). In group 1 there were 60 % males and 40% females. In group 2 there were 73.3 % males and 26.7 % female (p=0.2). Body Mass Index (BMI) was also calculated in 2 groups using standard formula of weight (in kilograms) per height2 (in meters). It showed mean BMI (kilograms per meter square) of 22.6 in group 1 and 23.2 in group 2 (P=0.11). There was no significant difference in terms of age, sex and BMI among the two groups.

In groups 1 and 2, the mean baseline fasting blood glucose value was found to be 186.7±5.83 and 185.7±7.76 (p=0.575) respectively. Maximum values being 204 mg/dl in group 1 and 204 mg/dl in group 2 while minimum values being 175 mg/dl in group 1 and 174 mg/dl in group 2. Mean fasting blood glucose on initial and subsequent monthly visits in both the groups is given in table 2.

Comparison of mean fasting blood glucose among the two groups (over six months) is shown in figure 1.

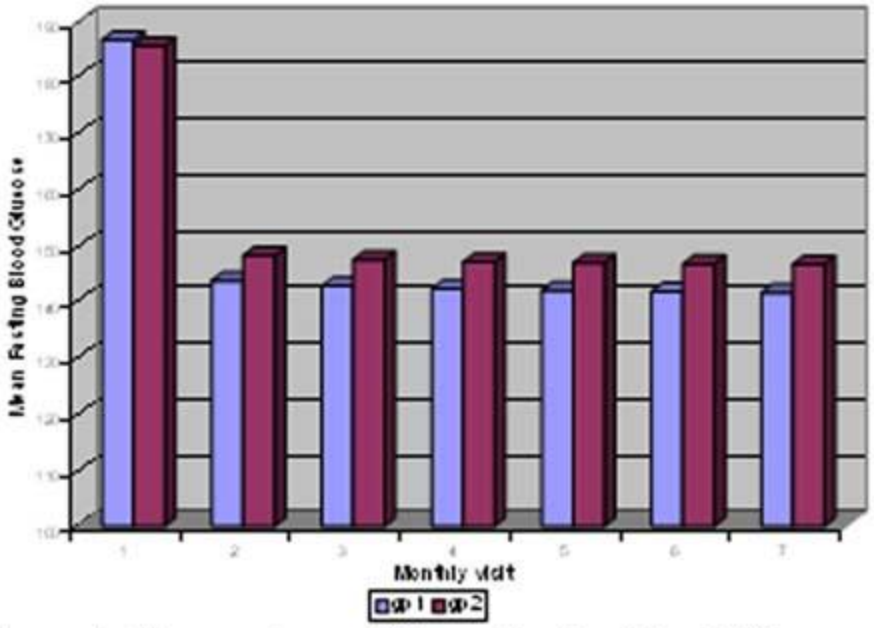

Figure-1: Comparison of Mean Fasting Blood Glucose Over Six Months

In groups 1 and 2, the mean baseline random blood glucose value was found to be 241.8±5.73 and 241.7±6.82 respectively (p=0.96). Maximum values being 250 mg/dl in group 1 and 252 mg/dl in group 2 while minimum values being 230 mg/dl in group 1 and 234 mg/dl in group 2. Mean random blood glucose on initial and subsequent monthly visits in both the groups is given in table 3

Table-3: Mean Random Blood Glucose of Both Groups (Over Six Months) n=60

Mean random blood glucose	Treatment group	Number	Mean	Std deviation	p value
Baseline	Pioglitazone	30	241.80	5.71	0.966
	Metformin	30	241.73	6.25	
At 1 month	Pioglitazone	30	210.40	8.04	0.174
	Metformin	30	213.40	8.3	
At 2 months	Pioglitazone	30	208.46	9.13	0.092
	Metformin	30	212.36	8.48	
At 3 months	Pioglitazone	30	207.06	11.02	0.086
	Metformin	30	211.60	8.94	
At 4 months	Pioglitazone	30	209.13	8.50	0.116
	Metformin	30	212.70	8.80	
At 5 months	Pioglitazone	30	205.90	7.93	0.005
	Metformin	30	278.96	8.83	
At 6 months	Pioglitazone	30	205.80	9.36	0.066
	Metformin	30	210.40	9.61	

and their comparison over six months is shown in figure 2.

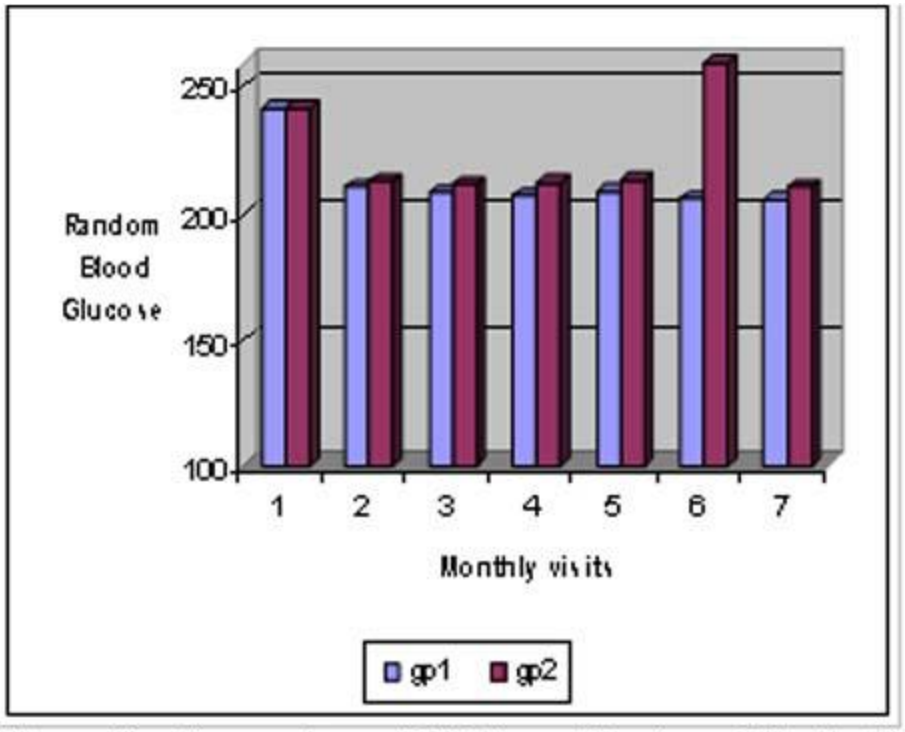

Figure-2: Comparison Of Mean Random Blood Glucose Over Six Months

HbA1c was checked three times, first was the baseline reading, then at 3 months interval and last on final visit i.e. 6 months visit. In group 1 and 2, the mean baseline HbA1c value was found to be 8.6±0.39 and 8.51±0.41 respectively. Maximum values being 9.4% in group 1 and 9.6% in group 2 while minimum values being 7.7% in group 1 and 7.9% in group 2. Mean HbA1c on subsequent visits in both the groups is given in table 4

Table-4: Mean Hbalc of Both Groups (Over Six Months) N=60

Glycosylated Hb	Treatment group	Number	Mean	Standard deviation	p value
Baseline	Pioglitazone	30	8.670	0.395	0.140
	Metformin	30	8.513	0.415	
At 3 months	Pioglitazone	30	7.357	0.496	0.272
	Metformin	30	7.223	0.434	
At 6 months	Pioglitazone	30	7.173	0.426	0.207
	Metformin	30	7.033	0.425	

and comparison among both groups over six months is shown in figure 3.

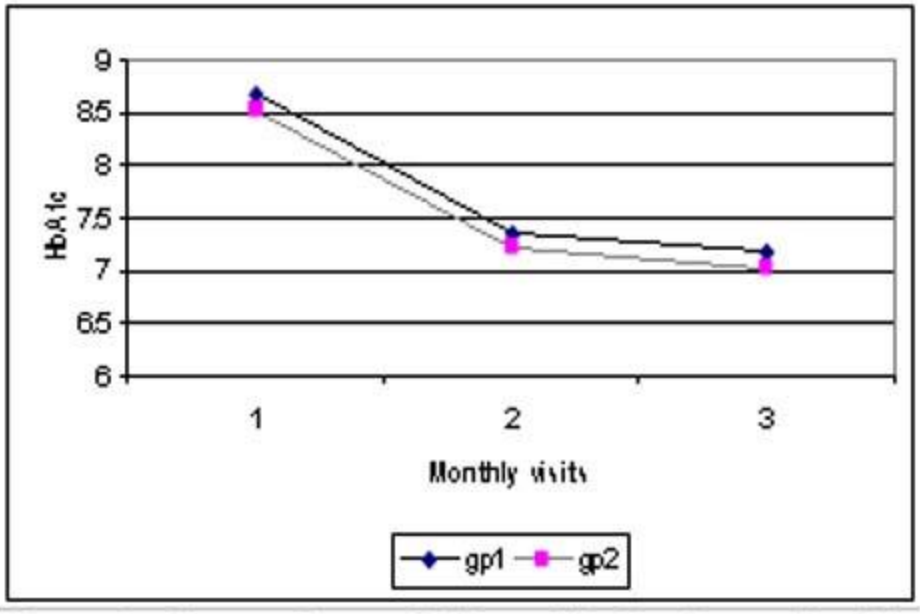

Figure-3: Comparison of Mean Hbalc Over Six Months Visits

Oach other, this decrease in group 1 was statistically significant than group 2 (p=0.02). Likewise, mean drop in HbA1c from baseline was found to be 1.49±8.8 in group 1 and 1.48±8.0 in group 2. There was no significant difference in HbA1c drop among the two treatment groups (p=0.4).

DISCUSSION

Poor glycemic control in cases of type 2 diabetes mellitus with resultant complications like dyslipidemias, retinopathy, neuropathy, nephropathy, coronary artery, peripheral and cerebrovacular diseases makes the proper treatment more demanding and accurate.

In a multicenter randomized trial11 it was shown that Pioglitazone had comparatively better reduction in fasting blood glucose than Metformin. (P = 0.016). Results of this large multicenter trial are comparable to the present study. Drop in fasting blood glucose was significant in pioglitazone group but drop in HbA1c was similar. While random blood glucose was not measured in this international study.

Another study trial (n=114) conducted by Yamanouchi T et al12 in the department of internal medicine, University of Teikyo, Tokyo, Japan, compared the metabolic effects of pioglitazone, metformin, and glimepiride (monotherapy and combined) in the treatment of Japanese patients with newly diagnosed Type 2 diabetes. It demonstrated that patients taking pioglitazone had relatively lower fasting plasma glucose than patients taking the other two drugs but there were no significant difference among the three groups in HbA1c levels at the end of the study. Results of this study match our results for both HbA1c and fasting blood glucose control.

However, slightly different results were seen in a study conducted by Ceriello A et al13, carried at department of pathology and medicine, university of Udine P. le S. Maria della Misericordia, Udine, Italy. It showed that there were no differences in the changes in HbA1c and fasting blood glucose between the pioglitazone and metformin groups but postload glycemia was reduced more by pioglitazone than by metformin. However, Pioglitazone had a significant reduction from baseline for fasting insulin as compared to metformin. This study showed similar results for postload (after meal) glycemia and HbA1c as per our study but differs in terms of fasting blood glucose control. (Insulin index was beyond our scope)

Another study was carried out by Imre Pavo et al14, conducted at Bajcsy-Zsilinszky Hospital, Budapest Hungary. In this study effect of Pioglitazone was compared with Metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes mellitus. It showed that both treatment groups (pioglitazone and metformin) had statistically

significant reductions from baseline in HbA1c ($p<0.0001$ for both treatments), and there was no statistically significant difference between the two groups in HbA1C change from baseline. So, HbA1c results matched our study. In this study, both treatment groups had significant decrease from baseline in fasting blood glucose ($P < 0.0001$ for both treatments), and there was no statistically significant difference between the treatment groups in fasting glucose change from baseline. This fasting blood glucose result is not in concordance with our study which has showed greater reduction in pioglitazone group on subsequent visits. However, at the endpoint of the study, a significant decrease in fasting serum insulin was shown in the pioglitazone treatment group ($P < 0.0001$), but this parameter could not be studied in our setup.

Only one local study15 was found which was carried out at King Edwards medical college Lahore, published in Annals of King Edwards medical college in March 2005. But this was different from our project. In that study, they added rosiglitazone, another thiazolidinedione, to treatment in type 2 diabetics who were poorly controlled with metformin alone. However, addition of this thiazolidinedione in ongoing metformin showed better response.

Although postprandial levels could be a source of bias due to possibility of poor adherence to dietary advice (especially that particular breakfast). This factor was tried to be minimized by having counseling with patients on monthly sessions. Therefore, result of mean drop in random (postprandial) blood glucose was significantly better in pioglitazone group. Results were not significant in terms of HbA1c among the two groups. This could be because patients were followed for six months only. Therefore, a longer duration study is required to explore this effect further.

Most of the international studies have similar findings regarding hypoglycemic effect of pioglitazone which were also seen in our results. Local material is very limited and no comparison of these two drugs could be found. This study becomes important in this respect also. However, further research is recommended in this field to fulfill deficiencies.

CONCLUSION

Type 2 diabetes is quite common and reaching almost epidemic level. There are many drugs available for the treatment that differ in efficacy, cost, availability and side effects. We compared Pioglitazone with Metformin and found that Pioglitazone has better hypoglycemic effect than Metformin in terms of efficacy. And this fact has been validated by international studies as well.

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