ORIGINAL ARTICLE

EFFECT OF PIOGLITAZONE AS ADDITIONAL THERAPY ON GLYCAEMIC CONTROL

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ABSTRACT

Background: Many studies have shown benefits of tight glycaemic control in Diabetes Mellitus. This study was conducted to know the effect of pioglitazone as additional therapy on glycaemic control in Type 2 Diabetes Mellitus.

Material & Methods: It was a prospective, double blind, placebo controlled study, conducted at Rauf Medical Center, D.I.Khan, from March 11, 2005 to January 10, 2008. Patients with Type 2 Diabetes Mellitus who were taking oral anti-diabetics other than glitazone, with poor glycaemic control were included. Pioglitazone was added to their treatment and followed for three months with fasting blood glucose every month and HbA_{1C} at three months. Student t test was applied to compare the results.

Results: Forty-four patients were initially included and randomly assigned to receive pioglitazone (n=30) or placebo (n=14) for three months. Seven patients dropped out. In the remaining 36 patients, the mean fasting blood glucose on presentation was 216.71±48.81mg/dl and HbA_{1C} 10.05±1.81% in experimental as compared to placebo group 197.75±52.92mg/dl and 10.20±1.42% respectively. After three months, mean fasting blood glucose was 168.71±58.66mg/dl and HbA1c 9.10±0.43% in pioglitazone group and 211±39.47 mg/dl and 9.42±1.83% respectively in placebo group. The drop in fasting blood glucose was statistically not significant ($p>0.05$) but that in HbA_{1C} was significant ($p<0.01$).

Conclusion: Addition of pioglitazone to oral anti-diabetic therapy in Type 2 Diabetes Mellitus improves the glycaemic control.

Key words: Diabetes Mellitus, Oral anti-diabetic, Pioglitazone, Glycaemic control.

INTRODUCTION

Diabetes mellitus (DM) is a multi-factorial metabolic disorder. The main defects include insulin resistance and insulin deficiency.[1,2] Type 2 Diabetes Mellitus affects about 5% of the population in developed countries and over 150 million people worldwide. It is believed that this number will double in the next 25 years.[3]

Several studies have shown the benefits of tight glycaemic control in Type 2 DM.[4-6] In these studies, microvascular complications were significantly reduced by aggressive glycaemic control. Consequently, various professional organizations have proposed increasingly stringent metabolic targets in the management of DM.[7,8]

There is innumerable evidence of efficacy of sulphonylureas, biguanides and α-glucosidase inhibitors in the treatment of Type 2 Diabetes Mellitus, but few regarding the efficacy of glitazones, especially as additional therapy to other oral anti-diabetic medications. Although some studies have shown better glycaemic control than metformin or gliclazide, in patients treated with pioglitazone, used as monotherapy or in combination,[9] but it needs further evaluation. Glitazones are activators of the nuclear transcription factor peroxisome proliferator-activated receptor-γ and modulate the activity of a host of genes that regulate carbohydrate and lipid metabolism.[10] Some reports also suggest that glitazones may preserve β-cell function.[11] Few small studies suggest benefit on markers of beta cell function.[12,13] Published trials have confirmed that the HbA_{1C}-lowering effect of the glitazones is equivalent[14] and typically in the same range as that of sulphonylureas or metformin.[15-17]

Data from UKPDS suggested that about 50% loss of beta cell function was already present in newly diagnosed Type 2 Diabetes Mellitus patients.[18] As the disease progresses, further functional decline in beta cell output is apparent. As a result, only 50% of patients were adequately controlled on monotherapy three years after diagnosis, and by nine years, this figure had fallen to 25%.

Thus, combination therapy involving agents with complementary mechanisms of action is logical to achieve good glycaemic control.[19] Published trials confirm the additive beneficial effects on glycaemic control of agents from different therapeutic classes.[20-27] Typically, HbA_{1C} reduction resembles the effect of added individual agent but few studies suggest even synergistic effect. Precisely how various regimens function together metabolically remains incompletely understood. The ideal drug choice for a specific individual is a complex decision that needs to be made by the treating physician, taking into account the risks and benefits of each agent and the requirements of each patient.[19]

This trial was conducted to know the effect of pioglitazone as additional therapy on glycaemic control in patients with Type 2 DM patients having poor glycaemic control, who were already taking a sulphonylurea, biguanide, α-glucosidase inhibitor or any of their combination.

MATERIAL AND METHODS

It was a prospective, double blind, placebo controlled study, conducted at Rauf Medical Center, D.I.Khan, Pakistan, from March 11, 2005 to January 10, 2008. Adult patients of any age, suffering from Type 2 Diabetes Mellitus patients, who attended the general medical clinic, having poor glycaemic control with fasting blood sugar (FBS) >150 mg/dl and/or Haemoglobin A_{1C} (HbA_{1C}) >9.0%, willing to participate, were included in the trail. Pioglitazone *(Zolid)* was given as 30mg tablet in a single daily dose. Placebo was given as a tablet of lactose with the same colour and shape. FBS was estimated by glucose oxidase method using spectronic-20 colorimeter in the local laboratory. HbA_{1C} was estimated at Shifa International Laboratories Islamabad. Patients were randomly assigned to receive pioglitazone or placebo for three months.

FBS was measured before starting pioglitazone /placebo and every month, for three subsequent months. HbA_{1C} was measured at the start and the end of the three months therapy.

Student's t test was applied to compare the results of FBS and HbA_{1C} and p values calculated using the null hypothesis by SPSS version 13.

RESULTS

Forty-four patients were initially included. All these patients were taking one or more anti-diabetic drugs other than a glitazone, with poor glycaemic control i.e. FBS >150 mg/dl or HbA_{1C} >8%. They were randomly assigned to receive pioglitazone (n=30) or placebo (n=14) for three months. One patient dropped out from the placebo group due to the complaint of deafness in the right ear. Seven patients didn't return for follow up, 2 from pioglitazone group and 5 from placebo group. Out of the remaining 36 patients, 20 were males and 16 females. The age range was 38-75 years (Mean 51.95) and BMI 23.79-34.25 Kg/m^2 (Mean 27.81).

The mean FBS on presentation was 216.71±48.81 mg/dl and HbA_{1C} 10.05±1.81% in experimental as compared to placebo group with FBS 197.75±52.92 mg/dl and HbA_{1C} 10.20±1.42% (p>0.5 for both). After three months pioglitazone add on therapy, the mean FBS was 168.71±58.66 mg/dl and HbA1c 9.10+0.43% in pioglitazone group as compared to FBS of 211±39.47 mg/dl and HbA1c 9.42±1.83% in placebo group.

The drop in FBS was statistically not significant (p>0.05) while that in HbA_{IC} was significant (p<0.01). (Table-1,2)

Table-1: Comparison of fasting blood sugar before and after treatment.

	Pioglitazone Group Mean±SD	Placebo Group Mean±SD
Before Treatment	216.71±48.81	197.75±52.92
After Treatment	168.71+58.66	211+39.47

Table-2: Comparison of HbA1C before and after treatment.

	Pioglitazone Group Mean±SD	Placebo Group Mean±SD	p value
Before Treatment	10.05±1.81	10.20±1.42	>0.5
After Treatment	9.10±0.43	9.42+1.83	<0.01

No unwanted effects of pioglitazone were observed during the study period.

DISCUSSION

The results of our trial favor the results of the previous trail by Miazaki et al which showed that pioglitazone therapy in Type II DM decreases fasting and postprandial plasma glucose levels by improving hepatic and peripheral tissue (muscle) sensitivity to insulin.[28]

A recently conducted trial by European Association for the study of Diabetes Athens 2005 has shown for the first time in a prospective study that pioglitazone reduces the composite all cause mortality, non-fatal myocardial infarction and stroke. It also decreases the need for conversion to insulin therapy. This study compared pioglitazone with placebo in addition to the existing therapy and it also showed reduction in HbA_{1C}.[29]

In our study the fall in fasting blood glucose was obvious but not statistically significant while that in HbA_{1C} was significant. As FBS may vary and HbA_{1C} is the better indicator of long term glycemic control, so it shows better glycemic control in the group with additional pyoglitazone.

This was a small study in which an important issue i.e. combination therapy of pioglitazone with other oral anti-diabetic agents in the management of Type 2 DM was investigated. Further studies are required to strengthen these results.

CONCLUSION

Addition of pioglitazone to oral anti-diabetic therapy in type 2 Diabetes Mellitus improves the glycaemic control.

Pioglitazone is a safe drug to be used in combination with other oral anti-diabetic drugs.

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