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ORIGINAL ARTICLE

A COMPARATIVE STUDY REGARDING EFFICACY & SAFETY BETWEEN ADD-ON PIOGLITAZONE & METFORMIN IN TYPE II DIABETIC PATIENTS NOT CONTROLLED WITH GLIMEPIRIDE AND METFORMIN COMBINATION

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ABSTRACT: BACKGROUND & OBJECTIVES: Diabetes, heart disease, stroke and some types of cancer are the most common preventable chronic diseases observed in the modern society. Prevalence of type 2-diabetes is increasing in most of the countries, especially in developing countries such as India (67millions approx.) Metformin, glimepiride & pioglitazone are the most common ant diabetic drugs used. **SETTINGS, METHODS AND MATERIAL:** The study was undertaken in R.G. Kar Medical College and Hospital, Kolkata, India. The study population was obtained from the weekly diabetic clinic. Type-2 DM patients, with uncontrolled plasma glucose, determined by anyone of FBS >130mg/dl, PPBS >180mg/dl, and HbA1c >7% with a combination therapy of Metformin (1000mg) & Glimepiride (2mg) for at least 4wks and then treated with either additional Metformin (500mg) or Pioglitazone (15mg) as add-on therapy were included in the study. HbA1C levels were measured twice, first baseline level during inclusion and then after 12 weeks of follow up. Any adverse effects and/or drug intolerance, if present, were reported to the clinician by the subjects and were noted. Study population was 92. **RESULTS:** Group 1 (Getting additional Metformin 500mg) consisted of 45 subjects, Group 2 (Getting pioglitazone 15mg) with age and sex matched. Mean baseline FBG was slightly higher among the participants of group 1 (158.29mg/dl) than group 2 (154.43mg/dl) and also for PPBG. After 4 week follow up, the mean PPBG was slightly higher among the participants of group 1 than group 2. After 12 week follow up the results were reverse is the case of mean FBG & PPBG. Mean HbA1C at the initiation of study was 8% (group 1) and 7.86% (group 2). After 12 week follow up, the mean HbA1C among the participants of group 1 was 7.7mg/dl and that of the participants among group 2 was 7.63mg/dl, **CONCLUSIONS:** At the end of 12 week, statistically significant higher proportion of subjects of Pioglitazone group (71.1%) attained target blood glucose level (both FBS and PPBS) whereas 46.8% of subjects of Metformin group attained the same.
KEYWORDS: Glycemic control, HbA1c, Metformin, Glimepiride, pioglitazone.

INTRODUCTION & BACKGROUND: Diabetes, heart disease, stroke and some types of cancer are the most common preventable chronic diseases observed in the modern society. Chronic diseases accounts for 7 out of every 10 deaths in the US.[1] Type 2-diabetes (Non- insulin dependent diabetes, NIDDM) is the commonest form of diabetes constituting nearly 90% of the diabetic population of the world.[2]

Patients with diabetes have twice the risk of death compared to patients without diabetes at the same age.[3] Prevalence of type 2-diabetes is increasing in most of the countries, especially in developing countries such as India.[4] India is considered as the diabetic capital of the world as it contributes nearly 20% of the total diabetic population of the world.[5]

Good and persistent glycemic control is the prime objective of type 2-DM management. But achieving the goal is a challenging task for clinicians in spite of the fact that there is multiple

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treatment options available as add on therapy when monotherapy or combination therapy with oral hypoglycemics fails, choosing proper combination for add on therapy depends on experience and expertise as there is no fixed guidelines for add on therapy. Metformin, a biguanide, has been used in the treatment of type 2-diabetes since the 1960s. Well-designed studies have shown marked effects of metformin in decreasing the elevated hepatic glucose production that is associated with fasting hyperglycemia. The decrease in hepatic glucose production by metformin.[6] appears to be due primarily to a decrease in gluconeogenesis, although there is some contribution from a decrease in glycogenolysis. Administration of metformin has been shown to lower plasma levels of free fatty acids and to increase lipid oxidation.

Thiazolidinediones (Tzds) act to decrease insulin resistance by acting on ligands of peroxisome proliferator-activated receptor-gamma (PPAR-ϒ); found in muscle, fat, and liver [7]. PPAR-ϒ receptors modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation.

A choice is offered between sulfonylurea (SU), thiazolinediones, DPP-IV inhibitor or basal insulin is recommended after metformin as initial drug.

SUBJECTS AND METHODS: The study was undertaken in R.G. Kar Medical College and Hospital, Kolkata, India. The study population was obtained from the weekly diabetic clinic, which is being held in the OPD of the hospital by the department of Medicine. All those Type 2-diabetic patients attending the weekly diabetic clinic in the OPD of R G Kar Medical College and Hospital from 1st week of march 2014 to 4th week of August 2014. The research activity included protocol preparation, development of tool for data collection, obtaining clearance from Institutional Ethics Committee (IEC) and concerned authority of the hospital, data collection and compilation, analysis and write-up.

Those Type-2 DM patients, diagnosed by the clinician, who have uncontrolled plasma glucose, determined by anyone of FBS>130mg/dl, PPBS>180mg/dl, and HbA1c>7% with a combination therapy of Metformin (1000mg) & Glimepiride (2mg) for at least 4wks and then treated with either additional Metformin (500mg) or Pioglitazone (15mg) as add-on therapy were included in the study. Participants with chronic Kidney disease, heart Failure, progressive fatal disease, pregnancy, chronic liver disease, malignancy and who requires switch over to Insulin therapy due to presence of any other co-morbidities were excluded.

HbA1C levels were measured twice, first baseline level during inclusion and then after 12 weeks of follow up. Any adverse effects and/or drug intolerance, if present, were reported to the clinician by the subjects and were noted. If the clinician found that a particular drug was unsafe for any patient, drug discontinuation was recommended by him, which too was noted.

STUDY DESIGN, AIMS AND OBJECTIVES: It was a Prospective, open level, parallel group, observational study where therapeutic efficacy and safety of add-on therapy with Pioglitazone (15mg) and additional Metformin (500mg) was compared in patients having uncontrolled plasma glucose with Glimepiride (2mg) and Metformin (1000mg) daily dose.

AIMS:

1) To evaluate fasting & post-prandial blood glucose by glucose oxidase-peroxidase method at an interval of 4 weeks and 12 weeks & HbA1c by cationic exchange method at an interval of 3 months.
2) To find out any adverse effect clinically found by the clinician, or any such complaints by the patients.

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Patients of both gender and of age between and including 18-70yrs. were included in the study. Initially, all the patients who were assigned either of the intervention considered in the study by the treating physician were included in the study after application of inclusion and exclusion criterion. Verbal consent was obtained from the participants after explaining the purpose of the study. Subjects were placed into two groups, group 1 (Those prescribed with pioglitazone) and group 2 (Those whose metformin dose was escalated). Initial baseline data regarding FBS, PPBS and HbA1C were collected. All other relevant history was collected from the OPD ticket and by interviewing the patient using a semi-structured proforma. The patients were followed up for 12 weeks whenever they attended the clinic. Patients were checked for FBG, PPBG at the end of 1 month (4 week) following initiation of therapy. FBG PPBG of all the patients along with HbA1C was investigated again at the end of 12 weeks following initiation of therapy. Any patient who were shifted to insulin during this period, or for whom any modification of OHA combination were done or were lost to follow up were excluded from the study. The reason for change in therapy was noted asking the treating physician for collection of data regarding any serious adverse effect.

ANALYSIS OF DATA: Data entry and statistical analysis were done using SPSS version 20.0. Descriptive statistics (Frequency, percentage, mean and standard deviation) were used primarily to summarize and describe the data to make it more graspable. For analytical statistics, Chi-square was used where appropriate. For all the statistical tests of significance, p value of <0.05 was considered to reject the null hypothesis.

The mean blood sugar level of independent samples was compared with independent sample t test and for dependent samples alteration in the blood sugar level was analysed using paired t test.

RESULTS AND ANALYSIS: Majority (66.7%) of the study population were male, rest were female. Though proportion of male outnumbered female in all age groups, mean age of male and female participants were almost same (52.41 years Vs. 52.7 years) (Table 1). Study group 1 included 45 and rest 47 belonged to group 2. Majority of the subjects of both the group were male, rest were female (64.4% Vs. 68.1%) (Table 1). Majority of the study population of both the group belonged to the age group 40-49 years followed by 50–59 years. Chi square test showed there was no statistically significant difference in the age distribution of the participants among the two groups (p value: 0.94) (Table 2). Mean baseline FBG was slightly higher among the participants of group 1 (158.29mg/dl) than group 2 (154.43mg/dl) and also for PPBG. After 4 week follow up, mean FBS was slightly lower among the participants of group 1 (119.27mg/dl) than group 2 (121.72mg/dl), (Table 4). After 4 week follow up, the mean PPBG was slightly higher among the participants of group 1 (196.67mg/dl) than group 2 (184.32mg/dl) (Table 3). After 12 week follow up, mean FBG was slightly higher among the participants of group 2 (123.81mg/dl) than group 1 (118.56mg/dl). After 12 week follow up, mean PPBG was slightly higher among the participants of group 2 (183.64mg/dl) than group 1 (180.27mg/dl). Mean HbA1C at the initiation of study was 8% (group 1) and 7.86% (group 2). After 12 week follow up, the mean HbA1C among the participants of group 1 was 7.7mg/dl and that of the participants among group 2 was 7.63mg/dl (Table 3).

After 4 weeks of follow up, 60% of patient population among group 1 was found to be controlled, whereas in group 2, 42.5% of the patient population had glycemic control. At the end of 12 week, 71.1% subjects of group 1 found to have attained desired blood glucose level whereas 46.8% of

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subjects of group 2 attained the same. This difference was statistically significant with chi square test (P value: 0.018) (Table 4 & 5).

There was no statistically significant difference in the mean value of HBA1c between group 1 and group 2 in both occasions (Baseline & after 12th weeks follow-up). At the end of 12 weeks, no statistically significant difference was noted among the two intervention groups regarding HBA1c lowering effect (Table 6 & 7). Abdominal discomfort and nausea were two most common adverse effects (Table 8) in both the intervention group. One patient out of 50 in Pioglitazone group and 2 patients in the Metformin group were shifted to insulin due to increased renal failure markers.

DISCUSSIONS: Present study was a hospital- based prospective comparative study conducted among Type 2 DM patients who had uncontrolled blood sugar level despite treatment with Metformin (1000mg) and Glimepiride (2mg). The patients were divided into two groups and add on therapy either extra Metformin (500mg) or add on Pioglitazone (15mg) was assigned to them respectively and short term glycaemic control were evaluated. Both the groups were comparable regarding age-sex distribution, BMI, alcohol and tobacco intake, physical exercise, family history of T2DM, duration of disease, duration of ant diabetic treatment, presence of hypertension and Dyslipidaemia.

Mean baseline FBS was slightly higher among the participants of Pioglitazone group (158.29mg/dl) than Metformin group (154.43mg/dl) and mean PPBS was slightly higher among the participants of Pioglitazone group (269.60mg/dl) than Metformin group (262.78mg/dl).

The difference between pre and post-interventional mean FBS and PPBS after 4 weeks (from baseline) when compared with that of 12th week (from 4th week) does not show any statistically significant difference. But both the groups shows significant improvement in glycaemic control at the end of 4th week when compared to baseline

At the end of 12 week, statistically significant higher proportion of subjects of Pioglitazone group (71.1%) attained target blood glucose level (both FBS and PPBS) whereas 46.8% of subjects of Metformin group attained the same. But majority of the patients who could not achieve glycaemic control in the metformin group and were designated as uncontrolled, had their FBS and PPBS much closer to the target i.e. just above the targeted levels (>140mg/dl for FBS and >180mg/dl for PPBS). Thus, though there is a significant different in between the proportions of subjects with controlled status (71.1% in group 1 Vs. 46.8% in group 2) at the end of 12 weeks, the comparison between the mean changes in FBS and PPBS in both the groups does not showed any significant difference. Univariate logistic regression revealed, Pioglitazone group had attained better desired glycaemic control with compare to Metformin group and the difference was found statistically significant. Presence of coexisting Hypertension and Dyslipidaemia found to have statistically significant adverse effect on glycaemic control.

After adjusting for all the significant covariates, multivariate logistic regression showed addition of Pioglitazone as third OHA have 3.56 times more chance of desired glycaemic control at the end of 12 week with compare to the doubling the dose of Metformin with the baseline therapy of Glimepiride & Metformin. Mostly minor side effects like nausea, abdominal discomfort were reported though 1 patient of Pioglitazone group and 2 patients of Metformin group were shifted over to insulin therapy due to increased urea/creatinine.

Few randomised controlled clinical studies have assessed the effects of combination therapy over periods greater than 1 year. Two recent head-to-head studies evaluating the long-term efficacy, safety and tolerability of pioglitazone when added to failing metformin or a sulphonylurea in patients

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with type 2 diabetes are reported here.[8,9]. The first of these randomised, double-blind, parallel-group studies compared pioglitazone as add-on therapy to Metformin with the widely used combination of sulphonylurea and metformin. Gliclazide was chosen as it is one of the most commonly prescribed sulphonylurea. In the second study, pioglitazone add-on therapy was compared with the addition of metformin to existing sulphonylurea therapy.

An analysis conducted at 1 year suggested that, although no significant differences in change from baseline of glycaemic parameters were observed between treatments, the pattern of glycaemia over time was different and longer-term effects might reveal differences [8]. Furthermore, the 1-year analyses revealed additional benefits with Pioglitazone add-on therapy over gliclazide or metformin add-on therapies in terms of improvements in insulin sensitivity and specific abnormalities of diabetic dyslipidaemia.

Age	**Sex**	
	Male (% within age group)	**Female (% within age group)**
<30 years	2(66.7%)	1(33.3%)
30- 39 years	10(62.5%)	6(37.5%)
40 - 49 years	15(60.0%)	10(40%)
50 - 59 years	17(81.0%)	4(19.0%)
60 - 69 years	11(73.3%)	4(26.7%)
>= 70 years	6(50.0%)	6(50.0%)
Total	**61(66.3%)**	**31(33.7%)**
Mean(SD): Range:	**52.41(12.5) 28 - 77**	**52.7(14.6) 29 – 80**

Table 1: Age and Sex distribution of the study population: (n=92)

Age	**Type of Intervention**	
	Group 1	**Group 2**
<30 years	2(4.45%)	1(2.13%)
30- 39 years	9(20%)	7(14.89%)
40 - 49 years	12(26.67%)	13(27.66%)
50 - 59 years	10(22.23%)	11(23.4%)
60 - 69 years	6(13.33%)	9(19.149%)
>= 70 years	6(13.33%)	6(12.76%)
Total	45(100)	47(100)

Table 2: Distribution of study population according to Age and type of intervention: (n=92)

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Study Variables	Group 1		Group 2	
	Mean(SD)	Range	Mean(SD)	Range
FBS (Baseline)	158.29(29.58)	96 - 245	154.43(22.34)	93 - 199
FBS at 4th week of Follow up	119.27(14.24)	90-172	121.72(12.18)	93-154
FBS at 12th week of Follow up	118.56(17.45)	87 - 158	123.81(12.98)	97 - 165
PPBS (Baseline)	269.60(50.88)	190 - 380	262.78(43.09)	176 - 345
PPBS at 4th week of Follow up	196.67(33.62)	160-306	184.32(12.18)	156-209
PPBS at 12th week of Follow up	180.27(20.74)	142 - 240	183.64(15.98)	155 - 231
HbA1C (Baseline)	8.0(0.55)	7.69 – 9.0	7.86(0.69)	6.2 – 9.0
HbA1C at 12th week of Follow up	7.70(0.58)	6.5 - 8.9	7.63(0.68)	6.0 – 8.8

Table 3: Distribution of study population according to gender and type of intervention: (n=92)

Intervention group	Outcome		Total
	Controlled	Uncontrolled	
Group 1	27(60.0%)	18(40.0%)	45(100.0%)
Group 2	20(42.5%)	27(57.2%)	47(100.0%)
Pearson Chi-Square: 2.67; df: 1; P Value: 0.04			

Table 4: Distribution of study population according to glycaemic control at the end of 4th week following intervention: (n=92)

Intervention Group	Outcome		Total
	Controlled	Uncontrolled	
Group 1	32(71.1%)	13(28.9%)	45(100.0%)
Group 2	22(46.8%)	25(53.2%)	47(100.0%)
Pearson Chi-Square: 5.60; df: 1; P Value: 0.018			

Table 5. Distribution of study population according to glycaemic control at the end of 12th week following intervention: (n=92)

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Variables	Group	Mean	Std. Deviation	Mean Difference	P Value
Baseline HBA1C (%)	Group 1	8.009	0.55	0.14	0.283
	Group 2	7.868	0.69		
12th week Follow up HBA1C (%)	Group 1	7.71	0.58	0.08	0.190
	Group 2	7.63	0.68		

Table 6: Independent Sample t Tests for HBA1C: (n=92)

		Mean	Std. Deviation	Mean Difference	P Value
Group 1	Baseline HBA1C (%)	8.01	0.55	0.30	**<0.05**
	12thFollow up HBA1C (%)	7.71	0.58		
Group 2	Baseline HBA1C (%)	7.86	0.69	0.23	**<0.05**
	12th week Follow up HBA1C (%)	7.63	0.68		
	4th week Follow up PPBS(mg/dl)	84.32	12.18		

Table 7: Paired Sample t Tests between Baseline and 12th week Follow- up HBA1C

Adverse Effects	Pioglitazone add-on therapy group(n=45)	Metformin add-on therapy group(n=47)	Total
Nausea	7(15.5%)	4(8.5%)	11(11.9%)
Abdominal Discomfort	5(11.1%)	7(14.9%)	12(13.0%)
Hypoglycemic Episodes	1(2.2%)	0	1(1.1%)
Significant Weight Gain	4(8.9%)	1(2.1%)	5(5.4%)
Discontinuation of therapy due to serious adverse effect:			
Increased urea / creatinine	1(2%)	2(3.84%)	3(2.94%)

Table 8: Adverse effects during the course of intervention among the study population: (n=92)

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