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COMPARATIVE STUDY OF SITAGLIPTINAND PIOGLITAZONE AS ADD-ONTHERAPY OVER PLASMA GLUCOSE LEVEL IN TYPE 2 DIABETES MELLITUS PATIENTS : AN OBSERVATIONAL COHORT STUDY

Medicine

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ABSTRACT

BACKGROUND: Type 2 diabetes mellitus (DM) is a progressive chronic disorder and sustained control of plasma glucose is essential to prevent complications. Pioglitazoneofthiazolidinedionesand sitagliptin of Dipeptidyl peptidase-4 inhibitors (DPP4I) have recently been used as add-on therapy to control type 2 DM. The aim of this study was to compare the plasma glucose and glycocelatedHb% level of both the group who had poor glycemic control with Metformin and sulfonylurea. **MATERIAL AND METHODS:** In this observational cohort study, 100 patients with uncontrolled type 2 DM on 2000 mg/day of Metformin and 4 mg/day of Glimepiride were enrolled. The patients were randomly allocated into two groups with fifty each. One group received two divided doses of pioglitazone (30 mg/day) and the other received two divided doses of sitagliptin (100 mg/day) as the third medication. Plasma glucose fasting and 2 hours after drug and meal along with HbA1c were assessed before and after three months of treatment. **RESULTS:** Fasting plasma glucose level in the sitagliptin group was higher than the pioglitazone group; however, this difference was not statistically significant (130.30 ± 30.29 versus 124.58 ± 46.84, p=0.212). Significantdifferences were not observed in HbA1c (7.20±0.96 versus 7.43±0.99, p=0.563) and plasma glucose 2 hours after meal (194.56±66.22 versus 198.58±51.5, p=0.946) after treatment withsitagliptin and pioglitazone among the two groups. Mean weight in the sitagliptin group was lower compared to the pioglitazone group after treatment, however, this difference was not statistically significant (p=0.824). **CONCLUSION:** Both the molecule as third agent had similar efficacy in glycemic control. Sitagliptin is better choice to add-on therapy in obese overweight patients.

KEYWORDS

DPP4I (Dipeptidyl peptidase – 4 inhibitor); HbA1c (Glycocelatedhemoglobin%); Type 2 DM (Type 2 Diabetes Mellitus)

INTRODUCTION

Type 2 diabetes mellitus (DM) has different pathophysiology including decreased insulin secretion, insulinresistance, increased hepaticglucose production and decreased peripheral utilization in muscle along with environmental factor. Thiazolidinediones are PPAR-γ(Peroxisome Proliferator-Activated Receptor γ) receptoragonists and improve insulin resistance in adipose,muscle, and liver tissues and so Pioglitazone. Pioglitazone can causeside effects like bladder cancer, bone loss, bone fractures, weight gain, painful lower extremity edema and can precipitate congestive heart failure.

DPP-4 inhibitors, including sitagliptin, improve glucosemetabolism by stimulating GLP-1 receptors. GLP-1 receptorstimulates insulin secretion and inhibits glucagon secretion from pancreas and ultimately improvespostprandial blood sugar.

Insufficientstudies have been conducted to compare the use of sitagliptin and pioglitazone. On the other hand, the reported results onthe effects of these two drugs are contradictory.

Therefore, this study was designed to observe the effects ofsitagliptin and pioglitazone as add-on therapyin Type 2diabetic patients who have poor glycemic control followingmetformin and glimepiride therapy.

MATERIALAND METHODS

This observational cohort study was performed on 100 patients visited in outpatients department of Medicine in Darbhanga Medical College and Hospital fromMarch 2019 to February 2020. The age range of patients was 30to 65 and they were under treatmentwith full dose of metformin (2000mg/day) and full dose of sulfonylurea (glimepiride4 mg/day), and their sugar level were not controlled and also HbA1c were >7%.

Inclusion criteria were Type 2 diabetic who were taking full dose ofmetformin (2000 mg/day) and full dose of glimepiride (4 mg/day), the age range were 30-65 years, HbA1c≥7%,reluctant to take insulin and willingness to participate in the study. The work was started after getting the college ethics committee approval. There were no need to take approval from drug controller of India as the drugs used were in common use in patients of diabetes mellitus and another conditions.

Pregnant women, patients with heart failure, renal failure, history of bladdercancer andsevere glycemic complications including diabeticketoacidosis (DKA) were not included. Those who did not given written consent to participate the study were not included in the study.

Patients were then randomly allocated into two groups withequal numbers. One group received two divided doses ofpioglitazone 30 mg/day and the other received two divided doses of sitagliptin 100 mg/day as a third medication to control sugar of diabetes mellitus patients. Fasting bloodsugar and HbA1c levels were measured before the start of add-on therapy and again measured three month after the therapy.

Statistical Analysis

The statistical software SPSS version 22 had been used for the analysis. Categorical variables were expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi square test for independence of attributes/Fisher's exact test as appropriate continuous variables were expressed on descriptive statistics. An alpha level of 5% have been taken, i.e. if any p-value is less than 0.05 it had been considered as significant.

RESULTS

Table 1 shows the general characteristics and frequency ofcomorbidities out of 100 patients of the study 32 (32 %) and 28 (28 %) were female insitagliptin and pioglitazone groups respectively. The meanage of sitagliptin and pioglitazone groups were 50.40±8.69 and 51.75±9.28 respectively. The frequency of comorbiditiesanalysis including hypertension (HTN), hyperlipoproteinemia, toxic adenoma, and breastcancer showed no statistical differences between groups.

Table 2 represents the variations in measured parameters before and after intervention between the groups. Asignificant reduction in FBS (178.48±41.42 versus131.27±39.18, p<0.0001 and 189.64±49.24 versus123.47±36.73, p<0.0001, respectively);plasma glucose 2 hours after meal (272.6±66.01versus 193.56±63.02, p<0.0001 and 304.75±87.58 versus198.58±51.5, p<0.0001, respectively) and HbA1c (8.55±1.31versus 7.18±0.86, p<0.0001 and 8.42±1.0 versus 7.23±1.03,p<0.0001, respectively) were observed in sitagliptinand pioglitazone groups. This significant decreased sugar and HbA1c level

were not significant when the groups were compared.

Table 1 : General characteristics and frequency of comorbidities in studied groups

General characteristics	Sitagliptin	Pioglitazone	p-value
Sex, Female (No., %)	18 (18%)	22 (22%)	-
Age (year)	50.40±8.69	51.75±9.28	-
Weight (kg)	72.50±5.4	70.40±6.2	
Height (m)	163±0.1	1.64±0.09	-
BMI	27.29±0.99	26.17±0.82	
HTN (%)	30(66.7%)	29(64.4%)	0.824
HLP (%)	23(52.3%)	28(62.2%)	0.343
Hypothyroidism (%)	4(8.9%)	2(4.4%)	0.398
Toxic adenoma (%)	0	1(2.2%)	0.315
Breast cancer (%)	2(4.4%)	0	0.153

Data are presented as mean±standard division (SD), number or percent. $p<0.05$ was considered as statistically significant. HTN: hypertension; HLP: hyperlipoproteinemia; IHD: ischemic heart disease; AF: atrial fibrillation

Table 2 : Values before and after the intervention

Parameter	Sitagliptin		p-value	Pioglitazone		p-value	p*
	Before	After		Before	After		
Weight (kg)	72.50±5.4	73.24±5.8	0.877	71.7±6.2	73.3±6.6	0.616	0.902
BMI (kg/m2)	27.29±0.99	27.31±1.02	0.896	26.17±0.82	27.20±0.9	0.544	0.816
FBS (mg/dl)	178.48±41.42	131.27±39.18	<0.0001	189.64±9.24	123.47±36.73	<0.0001	0.234
2h after drug & meal (mg/dl)	272.6±66.01	193.56±63.02	<0.0001	304.75±87.58	198.58±5.15	<0.0001	0.992
HbA1c (%)	8.55±1.31	7.18±0.86	<0.0001	8.42±1.0	7.23±1.03	<0.0001	0.572

DISCUSSION

Type 2 diabetes mellitus requires management in order toprevent complications. Various drugs have beenintroduced for diabetes management. In recent years it has been proved by different studies that multidrug therapy is more beneficial.Thiazolidinediones (suchas pioglitazone) and DPP-4 inhibitors (such as sitagliptin) arethe therapeutic agents now commonly used. In this study, theeffects of the addition of sitagliptin and pioglitazone to thetreatment of those patients whose glycemic status was notcontrolled by metformin and sulfonylurea were investigated.

The results of the present study showed no significantdifferences between the two groups regarding the frequency of comorbidities, weight, and BMI, as well asglycemic state including FBS, 2hours after drug and meal, and HbA1c.

After treatment, both drugs significantly reduced plasma glucose fasting , 2 hours after drug & mealand HbA1c among the groups.

However, no significant differences were observed betweenthe two groups regarding the FBS, 2 hour after drug and meal, and HbA1c levels indicating the equal value of glycemic control in thestudied population. Theside effects of patients taking pioglitazone showed a higher weight gain but notsignificant when compared to the sitagliptin group.

Additionally, BMI also showed no significant differencesbetween groups after intervention.

The efficacy of sitagliptin was also in line with the results of previous studies. Aschner et al. in a study reported thatsitagliptin as a monotherapy in type 2 diabetic patientssignificantly reduced FBS, 2hpp, and HbA1c levels comparedto the placebo group. This study also showed no significantdifference in the weight of patients taking sitagliptincompared to pre-treatment status.

The efficacy of pioglitazone in the present study was in linewith the results of previous studies. Goldberg et al. in adouble-blind clinical trial showed that pioglitazonesignificantly decreased the FBS and HbA1c levels andimproved the lipid profile of patients.

Goldstein et al. in aplacebo-controlled double-blind clinical trial also showed asignificant decrease in HbA1c levels in patients receivingsitagliptin compared to placebo. Chawla et al. evaluatedthe effect of sitagliptin or pioglitazone in patients withuncontrolled type 2 diabetes mellitus and reported no significant differences in FBS levels between two groups.

However, BMI and weight were significantly decreased in thesitagliptin group. Additionally, pioglitazone administrationresulted in a significant weight gain.

Regarding the action mechanism of two drugs, pioglitazoneis a medication belonging to the thiazolidinedione classincreasing glucose uptake in skeletal muscle and adiposetissue and reduces hepatic glucose production. In contrast,sitagliptin is a DPP-4 inhibitor leading to glucose metabolismimprovement through GLP-1 receptor stimulation. GLP-1receptor stimulation causes insulin secretion and inhibitsglucagon secretion in the pancreas and ultimately improvespostprandial blood sugar. Although the two drugs controlblood sugar with different mechanisms, as shown in thisstudy and most of the studies mentioned above, the two drugshave similar efficacy.

The present study had some limitations. According to manyprevious studies on drug side effects, the most emphases wereon weight changes in this study and the other side effects werenot evaluated in both groups. Additionally, the placebo group and the different doses of the drug were not evaluated becauseof the limitation in the number of admitted patients.

CONCLUSION

The results of the present study showed that both pioglitazoneand sitagliptin have a similar effect on glycemic control in type 2 diabetes mellitus. The side effect profile like weight gain was not taken in consideration due to small sample size and short duration of follow up. Further scope of the study, evaluation of sugar level after giving four oral hypoglycemic drugs in low dose or as needed so.

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