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Research Article

Comparative study of efficacy and safety of sitagliptin versus glimepiride in patients of type-2 diabetes mellitus inadequately controlled with metformin alone

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ABSTRACT

Background: Di-peptidyl peptidase-4 inhibitors when used as monotherapy or in combination with other drugs such as metfomin, thiazolidinedione or sulphonylurea are effective and well tolerated in diabetes management. The aim was to evaluate the safety and efficacy of sitagliptin compared to glimepiride as a dual therapy for the treatment of type-2 diabetes patients inadequately controlled with metformin.

Methods: It was an observational, open, comparative and multiple follow up study, included 70 patients visiting department of medicine and department of pharmacology at Gandhi Medical College and associated Hamidia Hospital, Bhopal, Madhya Pradesh, India for the period of 1 year. Patients of type 2 diabetes who were on metormin at least for last 3 months and were with inadequate glycemic control (HbA1C levels >7% and <10%) were included. All the patients were divided into two groups: Group G (35 patients; received glimepiride 2 mg per day) and Group S (35 patients received sitagliptin 100 mg per day). Treatment was provided for the period of 18 weeks and patients were called for 3 follow ups at the end of 4, 12 and 18 weeks. All the patients were investigated for glycated hemoglobin (HbA1c), fasting blood glucose (FBG) and post prandial glucose (PPG) along with adverse drug reaction if any.

Results: Female predominance was observed with mean age of study population being 48.07±10.07 years. Mean duration of diabetes and weight at baseline in Group G was 4.56±1.24 years and 48.23±2.15 kgs respectively and in Group S was 4.34±1.12 years and 49.61±3.21 kgs respectively. Mean dose of Metformin was 1819 mg/day. Mean glycated hemoglobin (HbA1c), fasting plasma glucose (FBG) and post prandial glucose (PPG) at baseline and 18th week in Group G was 8.31±0.12 % and 7.42±0.22%, 186.34±58.09 mg/dl and 109.9±17.69 mg/dl, 261.9±67.92 mg/dl and 159.21±15.96 mg/dl respectively whereas in Group S was 8.56±0.11% and 7.75±0.31%, 194±48.24 mg/dl and 112.3±15.58, 287.27±62.04 mg/dl and 162.6±.16.42 mg/dl respectively. In Group G weight of the patients increased from 64.59±7.9 kgs at baseline to 66.06±8.02 kg at 18 weeks of treatment whereas in Group S body weight of patients decreased from 62.06±7.02 kgs to 60.57±6.66 kgs at 18 weeks of sitagliptin treatment. The incidence of hypoglycemia (0%), nausea (6.06%) and vomiting (3.03%) in sitagliptin group was low as compared to glimepiride group (hypoglycemia (3.12%), nausea (12.5%) and vomiting (6.25%)).

Conclusions: Addition of sitagliptin in patients who are inadequately controlled with metformin monotherapy provide similar efficacy but better safety as compared to glimepiride.

Keywords: Sitagliptin, Glimepiride, Combination therapy, Hypoglycemia

INTRODUCTION

For the prevention of diabetes related complications, improvement in glycaemic control is of the prime importance. Thus far, different oral anti-hyperglycemic agents are available to achieve euglycemia. Reports have shown that about 60% of the diabetes patients do not achieve their therapeutic targets when on monotherapy making dual therapy a necessity to achieve glycaemic control.[1]

During trial of mono or dual therapy for optimal efficacy, tolerability and safety of the patients is of prime importance. A drug combination which is efficacious and is with less adverse effects should be chosen for the treatment of T2DM.[2]

Oral drug classes such as metformin, sulphonylurea, thiazolidinedione, alpha glucosidase inhibitors and DPP IV inhibitors are available which significantly lower the HbA1c level and are routinely used in the management of diabetes. Sulphonylureas are associated with weight gain and hypoglycaemia, thiazolidinedione causes fluid retention and metformin in many patients leads to gastrointestinal irritation.[3] The drugs of class dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are equally efficacious as compared to other anti-diabetic agents and also has very limited adverse effects.[4] Sulphonylurea are associated with weight gain and hypoglycaemia, thiazolidinedione causes fluid retention and metformin in many patients leads to gastrointestinal irritation.[4]

Sitagliptin which is a DPP-4 inhibitors is orally active and routinely prescribed as monotherapy or as an add on therapy. Safety and efficacy of sitagliptin is well established for the treatment of T2DM.[5]

The present trial was performed to determine the efficacy and safety of sitagliptin as compared to previously established glimepiride in patients who were uncontrolled on metformin monotherapy.

METHODS

An observational, open, comparative and multiple follow up study was done including 70 patients in the department of medicine and department of pharmacology at Gandhi Medical College and associated Hamidia Hospital, Bhopal, Madhya Pradesh, India for a period of 1 year, between December, 2014 to December, 2015.

This study was initiated after submitting the protocol and obtaining the approval of institutional review board (IRB). The study was conducted in accordance with ethical principles originating from the declaration of helsinki and good clinical practices, and in compliance with regulatory requirements. No medical or surgical intervention was done in the study subjects. The drugs given to the study subjects were already well established and were in common use for treatment of diabetes mellitus. Case collection was done during first 6 months of the study. Last 6 months were the follow up period, analysis and integration of the collected data and interpretation of results.

Patients with age between 18 to 70 years of either sex with type 2 DM, who were using only metformin as antidiabetic agent at least for last 3 months and were with inadequate glycemic control (HbA1C levels >7% and <10%) were included in the present study.

Patients with type-1 diabetes mellitus, who had previously been treated with sitagliptin or had previously been in a study using a DPP-4 inhibitor, alcoholic patients, pregnant and lactating females, females of childbearing age group planning pregnancy in recent future, HIV positive patients, current participation in a weight loss program or is receiving weight loss medication, patient who had undergone a surgical procedure within the prior 4 weeks, history of hypersensitivity to any of the investigational agents and other drugs of their class, patients with other systemic illness like congestive cardiac failure, severe respiratory diseases, renal insufficiency, hepatic insufficiency and other terminal illnesses were excluded from the present study.

Tablet glimipiride 1 mg and sitagliptin 100 mg was used as the treatment option. Study cohort was randomly divided into two groups: group G (32 patients; received glimepiride 2 mg per day) and group S (33 patients; received sitagliptin 100 mg per day). If glycemic control was not reached then patient was excluded from the study and given further treatment for benefit of the patient. Dose of metformin was kept constant throughout study which was 500 mg twice a day and no other hypoglycemic agent was added. If subject was on some other medications for associated illnesses, then doses of such drugs were kept constant during whole study period.

Treatment was provided for the period of 18 weeks and patients were called for 3 follow ups at the end of 4, 12 and 18 weeks. The blood samples were taken at each visit to test HbA1c level, fating blood sugar (FBG) and post prandial glucose (PPG) level in the department of medicine and department of pharmacology at Gandhi Medical College. At the time of follow up patient were evaluated for efficacy, safety and tolerability.

Statistical analysis was done using IBM SPSS ver.20 software. The collected data was analysed statistically using paired t-test and student t-test. A p-value of less than 0.05 was considered to be statistically significant

RESULTS

Majority of the patients in both groups, belongs to 41-50 years (30 (42.9%)) followed by 51-60 years (15 (21.1%)). Mean age of study population was 48.07±10.07 years.

Mean age of patients in Group G and Group S was 45.17±9.37 and 50.97±10.04 years respectively (p >0.05).

There were 29 (41.4%) males (14 (40%) in Group G and 15 (42.9%) in Group S) and 41 (58.6%) female (21 (60%) in Group G and 20 (57.1%) in Group S) (p >0.05). The primary endpoints in both the groups are shown in Table 1 and adverse effects reported by the patients are shown in Table 2.

Table 1: Showing comparison of primary end points between both the groups at follow ups.

Parameter	Follow up (weeks)	Group G (n=35)	Group S (n=35)	P value
HbA1c* (%)	0	8.31±0.12	8.56±0.11	NS
	18	7.42±0.22	7.75±0.31	NS
FBG* (mg/dl)	0	186.34±58.09	194±48.24	NS
	4	147.06±39.88	161.72±41.9	NS
	12	131.3±24.64	129.48±26.16	NS
	18	109.9±17.69	112.3±15.58	NS
PPG* (mg/dl)	0	261.9±67.92	287.27±62.04	NS
	4	213.5±55.03	234.51±49.01	NS
	12	179.34±25.04	184.75±38.26	NS
	18	159.21±15.96	162.6±.16.42	NS
Weight* (kgs)	0	64.59±7.9	62.06±7.02	NS
	18	66.06±8.02	60.57±6.66	NS

Data is expressed as Mean± SD, *p value<0.05; between 0 and 18th week follow up in Group G, p value<0.05; between 0 and 18th week follow up in Group S. HbA1c; glycated hemoglobin, FPG; fasting plasma glucose, PPG; post prandial glucose, NS; not significant. P value < 0.05 is considered as significant

Table 2: Comparison of adverse drug reactions reported in both the groups.

Adverse drug reaction	Group G (n=35)	Group S (n=35)
Headache	2 (6.25)	3 (9.09)
Abdominal pain	2 (6.25)	2 (6.06)
Nausea	4(12.5)	2 (6.06)
Vomiting	2 (6.25)	1 (3.03)
Hypoglycemia	1 (3.12)	0 (0)

Data is expressed as no of patients (%)

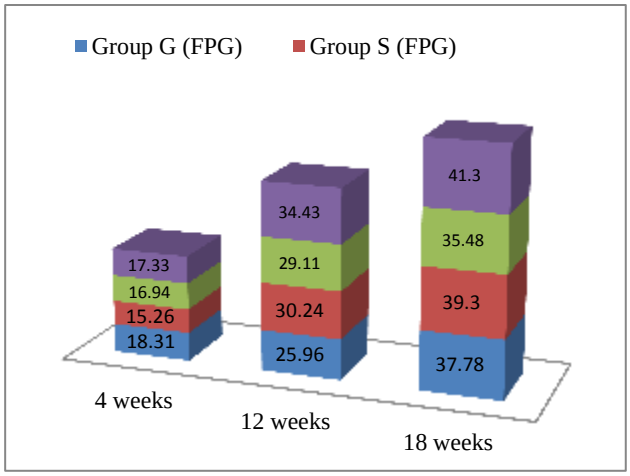

Figure 1: Mean percentage reduction in FBG and PPG over baseline.

DISCUSSION

Mean duration of diabetes and weight at baseline in Group G was 4.56±1.24 years and 48.23±2.15 kgs respectively and in Group S was 4.34±1.12 years and 49.61±3.21 kgs respectively. Mean dose of metformin was 1819 mg/day.

American diabetes association (ADA) and National Institute for Health and Clinical Excellence (NICE) has recommended DPP-4 inhibitors as the second and third line treatment option as an alternative to well established therapy.[6,7] It is well known that glimepiride has the disadvantage of causing hypoglycaemia and weight gain though efficacious.[8] Sitagliptin is reported to reduce the HbA1c by 0.6-0.8% whereas glimepiride by 1.4%.[3,9]

Srivastava et al, in their study of 50 patients who were uncontrolled on metformin monotherapy reported a significant reduction in HbA1c, FBG and 2HPPG values with sitagliptin addition, when compared to baseline values (p <0.05).[10] They also reported a decrease in bodyweight (-0.102kg) in sitagliptin group compared to glimepiride group (0.493 kg) where weight gain was observed.[10]

Anjoom et al in a similar study involving 60 T2DM patientsreported a significant difference in HbA1c, between glimepiride (8.79±0.11 and 7.32±0.11% (p < 0.001)) and sitagliptin (8.98±0.13 and 7.09±0.13% (p < 0.001)) group at 24 weeks follow up compared to

baseline values which is almost similar to the present study observations.[11]

In present study after 18 weeks follow up there was a significant improvement in both FBG and PPG values in glimepiride and sitagliptin groups which is accordance with the study done by Goldstein et al.[5] Anjoom et al, also reported significant improvement in both the values of FBG and PPG after 24 weeks of follow up in both the groups ($p < 0.001$).[11]

Intergroup comparison between both the groups revealed no significant difference in terms of glycaemic control which is in accordance with the Srivastava et al, Anjoom et al, Goldstein et al and Reasner et al, Hou et al performed a metaanalysis to compared sitagliptin with glimepiride and reported no significant difference between these two agents.[5,10-13]

Another study done by Hayati et al with 95 T2DM patients, who were previously taking metformin and glimepiride and adding sitagliptin as a third agent significantly reduced HbA1c by 0.41% ($P<0.007$) as compared to dual therapy alone, about 18.27% achieved their HbA1c targets.[14]

Present study data also revealed that sitagliptin was well tolerated as compared to glimepiride as none of the patients felt hypoglycemia in sitagliptin group. Other adverse drug reactions such as nausea, and vomiting were also less observed in sitagliptin group. Almost similar results were documented by Kumar et al. Arechavaleta et al also reported a lower rate of hypoglycemia in sitagliptin group (7%) as compared to glimepiride group (22%).[15,16]

In sitagliptin group there was a decrease in weight (1.49 kg) as compared to glimepiride group which is similar to the reports by Kumar et al, Arechavaleta et al who reported a weight loss of 0.8 kg.[15,16]

CONCLUSIONS

Addition of sitagliptin to current monotherapy with metformin provided significant lowering in HbA1c, FBG and PPG values after 18 weeks of treatment and was non inferior to glimepiride. However, none of the patient taking sitagliptin felt any episodes of hypoglycemia. Sitagliptin also provided weight loss as compared to glimepiride.

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Ethical approval: The study was approved by the institutional ethics committee

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