|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2020: 79.44
Original Research Article
Volume 4, Issue 2; February: 2020; Page No. 385-391

A Comparative Study of Safety and Efficacy of Sitagliptin and Glimepiride in Patients with type 2 Diabetes Mellitus

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Article Info: Received 13 October 2020; Accepted 29 December2020

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Conflict of interest: No conflict of interest.

Abstract

BACKGROUND: Over the past three decades, diabetes mellitus (DM) prevalence has risen significantly worldwide. The management of DM necessitates a significant expenditure of healthcare resources, which places a financial strain on society and patients. When taken as monotherapy or in conjunction with other medications like metformin, thiazolidinedione, or sulphonylurea, di-peptidyl peptidase-4 inhibitors are efficient and well tolerated in the control of diabetes. Although the overall frequency of adverse events (AEs) was not statistically different, a post-marketing monitoring analysis of glimepiride, the most widely used SU, revealed a considerably greater incidence of hypoglycemia in older patients than in nonelderly patients. It is crucial to reduce the risk of hypoglycemia episodes because they are linked to major medical issues such impaired consciousness, cardiovascular illness, and fractures from falls or unsafe diabetes treatment. Furthermore, due to its absence of negative effects on ischemia preconditioning, glimepiride is regarded as safe in patients with cardiovascular disease and also has powerful antioxidative, anti-inflammatory, and angiogenic capabilities.

AIM: a comparison of the effectiveness and safety of glimepiride with sitagliptin in people with type 2 diabetes.

MATERIAL AND METHOD: This study is conducted in a tertiary care hospital, from March2017 to September 2019. As an add-on therapy for 14 weeks, eligible patients were randomized to receive sitagliptin 100 mg and glimepiride 2 mg once daily. Demographic variables were recorded on preformed proforma. Control on diet and regular exercise were advised to all the subjects/patients during study period. All patients had their HbA1C, FBS, weight, Alanine aminotransferase (ALT), serum urea, and serum creatinine measures taken at week 0 and then again at the end of the trial at week 14. Attainment of the target HbA1C upper normal limit at study's conclusion was the main objective. Each patient was split into two groups: Group G (25 patients receiving 2 mg/day of glimepiride) and Group S. (25 patients received sitagliptin 100 mg per day). Patients were called for three follow-up appointments at the end of 4, 12, and 14 weeks of treatment, which lasted for 18 weeks.

RESULTS: 50 patients in all, 25 in each group, were enrolled in the trial. 13 males and 12 females made up group A, while 13 males and 12 females made up group B. When compared to the glimepiride group, group A using sitagliptin showed a significant decrease in HbA1C and BMI. The most common side effects in both groups were hypoglycemia, diarrhea, and vomiting. Both groups experienced the same frequency of incidence, with no statistically significant difference.

CONCLUSION: The results of the current trial provide evidence that sitagliptin is equally effective as glimepiride in improving glycemic control as an add-on medication to metformin and is well tolerated with no significant adverse effects. After 18 weeks of treatment, sitagliptin addition to the current

metformin monotherapy significantly lowered HbA1c, FBG, and PPG values and was comparable to glimepiride in efficacy. None of the patients using sitagliptin had hypoglycemia, though.
KEYWORDS: Diabetes Mellitus, Sitagliptin, Glimepiride, HbA1C, BMI, Combination therapy, sulphonylureas.

Introduction

Diabetes mellitus (DM) is among the most common chronic diseases in the world, affecting an estimated 422 million adults in 2014.[1] Sedentary life style, obesity, high BMI, decreased physical activity and increasing longevity result in exponential rise in incidence and prevalence of type 2 DM. This high prevalence rate is one of the major factors for economic burden to society as well as patients. Type 2 DM is a major risk factor for developing both micro-vascular and macro-vascular complications.[2] The focus of available therapies is on lowering hyperglycemia and raising insulin sensitivity. These treatments are highly alluring and require focus because they primarily aim to treat the primary faults and prevent complications caused by type 2 diabetes. However, glycemic control deteriorates over time despite the abundance of effective treatments.[3]

Combination therapy, which targets both insulin resistance and beta cell dysfunction, is crucial for the efficient management of type 2 diabetes mellitus.[4] The first-line oral treatment for T2DM is universally recognized to be metformin. The selection of a second line medication when metformin alone is insufficient has remained difficult. Sulfonylureas remain the most popular second-line supplement to metformin despite the abundance of new drugs, particularly in Indian clinical settings.[5,6] Modern sulfonylureas, such as glimepiride and modified release gliclazide, are preferred to traditional sulfonylureas like glibenclamide because they are supported by a vast body of research, experience, and outcome data.[7]

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.[8] The drugs of class dipeptidyl peptidase-4 inhibitors are equally efficacious as compared to other anti-diabetic agents and also has very limited adverse effects.[9]

Most of the patients with type 2 DM require more than one antidiabetic agents in combination with or without insulin as monotherapy might leads failure in maintaining of glycemic control and may leads to many complications.[10] The various anti-diabetic medications currently on the market reduce blood glucose levels in various ways. However, the unique pharmacokinetic and pharmacodynamic characteristics of each one place restrictions on their use and dosage titration.[4] Sitagliptin is an oral, once-daily, powerful and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor that has been given the green light by the US Food and Drug Administration for use in combination with diet and exercise to help adults with type 2 DM improve their glycemic control.[11] Sitagliptin increases fasting and postprandial levels of intact incretins, glucagon-like peptide-1, and glucose-dependent insulinotropic polypeptide via inhibiting DPP-4 activity.[12] Regulation of glucose level is maintained by incretins as they play an important role in elevating the insulin release in response to meal and decreasing glucagon secretion is also done by GLP-1. Both of these effects are glucosedependent.[13] When metformin or a thiazolidinedione therapy alone does not adequately manage blood sugar, it can be administered alone or in conjunction with those medications. The typical adult dose is 0.1g given once daily. Patients with moderate-to-severe renal impairment should take 25–50 mg once daily.[11]

Sitagliptin, a DPP-4 inhibitor, is frequently recommended as either a monotherapy or adjunctive treatment.[14] In patients who were uncontrolled on metformin monotherapy, the current trial was conducted to compare the effectiveness and safety of sitagliptin to previously recognized glimepiride. This study was carried out to examine the safety and efficacy of sitagliptin as compared to glimepiride in patients whose metformin-alone control was insufficient because

there are no substantial data about the safety and efficacy of this medication in our community.

MATERIAL AND METHODS

A tertiary care hospital served as the site of this study. Eligible patients were randomized using a randomization software to receive sitagliptin 100mg and glimepiride 2mg once daily as add-on medication for 14 weeks after receiving consent from the institutional ethics committee. Age, gender, smoking history, and hypertension were among the demographic factors of the study population that were entered on a pre-made proforma. Regular exercise and strict diet control were advised to all the subjects during the study period. 50 patients from the departments of medicine and pharmacology were included in an observational, open, comparative, and multiple follow-up study. All patients had their HbA1C, FBS, weight (Kg), Alanine aminotransferase (ALT), serum urea, and serum creatinine levels measured at week 0 and again at the end of the trial at week 14. Attainment of the target HbA1C upper limit normal (ULN) at study's conclusion was the main objective.

Inclusion criteria:

- ✓ Patients with type 2 DM with poor glycemic control on metformin monotherapy
- ✓ FBS and PPBS values more than 100 mg/dl and 140 mg/dl respectively
- ✓ Patients with HbA1C levels of >7% 4. Patients of both sexes are included.

Exclusion criteria:

- ✓ Study subjects with any history of allergy or hypersensitivity to the study drugs
- ✓ Patients with type I DM, pregnancy,
- ✓ Patients with liver and renal system dysfunction,
- ✓ Uncontrolled diabetes, indicated by a HbA1C >9% or a fasting blood sugar (FBS) > 300 mg/dl,
- ✓ Unstable angina and uncontrolled hypertension.

In the current study, patients with type 2 DM between the ages of 18 and 70, of either sex, who had been using solely metformin as an anti-diabetic drug for at least the previous three months and had insufficient glycemic control were included. The medication of choice was a tablet containing 1 mg of glimepiride and 100 mg of sitagliptin.

Two groups were randomly selected from the study cohort: group G (25 patients receiving 2 mg/day of glimepiride) and group S. (25 patients; received sitagliptin 100 mg per day). If glycemic control couldn't be achieved, the patient was taken out of the research and received additional care for their benefit. Metformin dosage of 500 mg twice day was maintained throughout the research; no additional hypoglycemic medication was introduced. The doses of any additional medications the person was taking for comorbid conditions were maintained throughout the duration of the trial.

Data Collection:

After submitting the protocol and receiving institutional review board approval, this study was started (IRB). The study was carried out in conformity with ethical standards established by the Helsinki Declaration, appropriate clinical practices, and 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. Over the course of the study's first six months, cases were collected. The follow-up period, data integration and analysis, and result interpretation took place throughout the previous six months. Patients were called for three follow-up appointments at the end of 4, 12, and 14 weeks of treatment, which lasted for 18 weeks.

Blood Sample Collection:

Each time a patient visited, blood samples were drawn to measure the patient's HbA1c, fasting blood sugar (FBG), and post-meal glucose (PPG) levels at the pharmacology and medical departments at Gandhi Medical College. Patients were assessed for effectiveness, safety, and tolerability at the time of the follow-up visit.

Statistical analyses: In order to analyze the data, SPSS 17 for Windows was used. With PS software, the sample size was determined using an 80% power. Chi-square (x2) for categorical variables and student 't' test for continuous variables, where necessary, were used to compare the two groups.

RESULT: -

The trial enrolled 50 patients in total, with 30 in each group. The mean age in the sitagliptin group (A) was 40 years, compared to 43 years in the glimepiride group (B). Regarding age distribution, there was no significant difference between the groups.

Table 1: Comparing the primary end points for the two groups

	Sitagliptin Group		Glimeperide Group	
	Baseline	**Week 14**	**Baseline**	**Week 14**
HbA1C (%)	6.01±0.43	5.37±0.18	6.85±0.51	6.01±0.15
FBS	160±5.4	110±4.2	155±4.33	106±2.1
BMI	22±1.1	20.1±0.98	22.0±1.2	24.02±0.92

HbA1C, fasting blood sugar, and BMI baseline readings were kept; a second reading was done during the 14th week of follow-up. The student t test was used to compare and assess both readings. In the HbA1C and BMI follow-up, there was a statistically significant difference between Groups A and B. When comparing group A receiving sitagliptin to group B taking glimeperide, we discovered a significant decrease in HbA1C and BMI.

Table 2: Side effects in both the groups mostly included hypoglycemia, diarrhea and vomiting.

	Sitagliptin Group	Glimeperide Group
Hypoglycemia	2	1
Diarrhea	1	1
Vomiting	1	2
others	1	1

The most common side effects in both groups were hypoglycemia, diarrhea, and vomiting. Both groups experienced the same frequency of incidence, with no statistically significant difference. These side effects were minor, necessitated no prescription interruptions, and did not cause any dropouts.

DISCUSSION

A significant risk factor for multiple consequences, from microvascular damage to organ failure, is having diabetes mellitus.[2] The major goal of treating DM is to keep blood glucose levels within the normal range. A marker for that metric, HbA1C, which represents glucose control during the previous two to three months. HbA1C between 6 and 7 percent is considered to be acceptable and demonstrates satisfactory DM control.[4] According to American Diabetes Association recommendations, metformin and lifestyle modifications should be thought of as first-line treatments for people with type 2 DM. Step-2 therapy, which may involve the use of sulfonylureas, thiazolidines, insulin, or other medications, may be required if glycemic control is not successfully accomplished and DM is still not under control during step-1/first line therapy.[15] DPP-4 inhibitors have been suggested as an alternative to well-established therapy by the American Diabetes Association (ADA) and National Institute for Health and Clinical Excellence (NICE).[16.17] Though effective, glimepiride is well recognized to have the side effects of hypoglycemia and weight gain.[15] Sitagliptin reportedly lowers HbA1c by 0.6-0.8%, compared to glimepiride's claimed reduction of 1.4%.[3,9]

In their research of 50 patients who were uncontrolled on metformin alone, **Srivastava et al.**[18] found that the addition of sitagliptin significantly decreased baseline values of HbA1c, FBG, and 2HPPG. 10 Additionally, they revealed that the sitagliptin group had a lower body weight (-0.102 kg) than the glimepiride group (0.493 kg), where weight gain was seen.

Anjoom et al.[19] observed a significant difference in HbA1c between the glimepiride and sitagliptin

groups at 24 weeks of follow-up compared to baseline values, which is almost identical to the present study data. This trial had 60 T2DM patients.

According to **Arechavaleta et al.**[20], 65% of patients met the goal HbA1C level of 7%. Similar results were found in research by **Charbonnel et al.**[21], where 47% of sitagliptin-using patients met their goal HbA1C. FBS was decreased in both groups, although there was no statistically significant difference between them.

In the **Goldstein et al.**[22] research, sitagliptin reduced FBS by 63.9mg/dl. According to **Nauck et al.**[23], the sitagliptin group experienced a considerable weight loss compared to the glimepiride group. There were no significant negative effects detected in our trial. 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.2007**[22]

According to **Srivastava et al.**, an intergroup comparison between the two groups showed no discernible change in glycaemic management.[18] **Anjoom et al.**[19], **Goldstein et al.**[22] and **Reasner et al.**[24], **Hou et al.**[25] performed a meta-analysis to compared sitagliptin with glimepiride and reported no significant difference between these two agents. In a different study by **Hayati et al.**[26] with 95 T2DM patients, sitagliptin was added as a third drug and significantly lowered HbA1c by 0.41% as compared to dual treatment alone. About 18.27% of the patients reached their HbA1c objectives.

The results of the current trial also showed that sitagliptin was more tolerated than glimepiride since none of the patients in the sitagliptin group experienced hypoglycemia. In the sitagliptin group, other negative medication responses such nausea and vomiting were also less common. According to **Kumar et al**[27], the results were essentially same. As compared to the glimepiride group, the sitagliptin group experienced a decreased risk of hypoglycemia, according to **Arechavaleta et al**[28].

CONCLUSION:

According to the results of the current study, sitagliptin, when used in conjunction with metformin, is just as effective at enhancing glycemic control as glimepiride while being well-tolerated and free of harmful side effects. After 18 weeks of treatment, sitagliptin was not inferior to glimepiride when added to the present metformin monotherapy. It significantly lowered HbA1c, FBG, and PPG levels. None of the sitagliptin-treated patients experienced any instances of hypoglycemia, though. Comparatively speaking to glimepiride, sitagliptin also promoted weight loss.

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