ORIGINAL RESEARCH

Efficacy and safety of glimepiride-metformin versus glibenclamide-metformin combination in type II diabetics uncontrolled with metformin alone at a tertiary centre

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ABSTRACT

Background: An oral drug called metformin is frequently recommended for the treatment of type 2 diabetes mellitus. Its efficacy, safety record, and affordability make it the therapy of choice for most patients.**Materials & Methods:**120 uncontrolled type II diabetic patients of both genders were divided into two groups of 60 patients each. Patients in group I were given two pills of glimepiride (1 mg)/metformin (500 mg), while patients in group II were given one daily dose of glibenclamide (5 mg)/metformin (500 mg).**Results:** The mean fasting blood glucose (mg/dl) at baseline was 178.2 and 176.6, at 4 weeks was 166.4 and 156.0, and at 8 weeks was 152.6 and 138.8 in group I and group II respectively. Postprandial blood glucose (mg/dl) at baseline was 252.4 and 230.6, at 4 weeks was 206.2 and 208.4, and at 8 weeks was 180.4 and 198.2 in group I and group II respectively. Lipid profile (mg/dl) TC was 176.4 and 188.2, LDL- C was 96.6 and 95.8, HDL- C was 46.2 and 45.3 and TGs was 168.8 and 171.5 in group I and group II respectively. The difference was significant ($P< 0.05$). Adverse events were nausea seen in 2 in group I and 4 in group II, metallic taste in 4 in group I and 3 in group II, hypoglycemia in 3 in group I and 5 in group II, and abdominal pain seen in 1 in group I and 3 in group II.**Conclusion:** When compared to the glibenclamide and metformin combination group, glimepiride and metformin combination therapy has a superior effect on post-prandial blood glucose level reduction and a considerably lower incidence of hypoglycemia.

Keywords: glibenclamide, metformin, lipid

INTRODUCTION

An oral drug called metformin is frequently recommended for the treatment of type 2 diabetes mellitus. Its efficacy, safety record, and affordability make it the therapy of choice for most patients. Metformin is a useful treatment choice for those with uncontrolled type 2 diabetes mellitus.[1]It functions by slowing down the absorption of glucose in the intestines, decreasing the amount of glucose produced in the liver, and increasing insulin sensitivity in peripheral tissues. These activities enhance glycemic management by lowering blood glucose levels. To reduce gastrointestinal side effects like nausea, vomiting, and diarrhea, it's crucial to start metformin therapy at a low dose and raise it gradually over time for individuals with uncontrolled diabetes.[2]

Following up with a healthcare provider frequently and adhering to the recommended dosage is essential for tracking the patient's reaction to treatment and modifying the dosage as necessary. It is important to remember that not everyone should use metformin. Heart failure, liver illness, severe renal impairment, and a few other illnesses are among the contraindications.[3] Furthermore, some people might not respond well to metformin by itself, and in those cases, additional or other drugs might be required to obtain the best possible blood glucose control. People with uncontrolled type 2 diabetes must collaborate

closely with their medical team to create a personalized treatment plan that addresses medication management, lifestyle changes, andfrequent blood glucose testing.[4]

While glimepiride, a third-generation sulfonylurea drug, has some advantageous pharmacological effects over glibenclamide, a second-generation sulfonylurea, it is nevertheless the oral antidiabetic combination most commonly used in clinical practice today. Patients with type 2 diabetes who are unable to control their condition with oral antidiabetic medication alone have found that glimepiride plus metformin given as a single dosage is both safe and effective.[5,6]

AIMS AND OBJECTIVES

The present study was conducted to assess the efficacy and safety of glimepiride-metformin versus glibenclamide-metformin combination in type-2 diabetics uncontrolled with metformin alone.

MATERIALS & METHODS

The present randomized open label prospective comparative studycomprised120 uncontrolled type II diabetic patients of both genders attaining outpatients (OPD) at Department of Pharmacology in collaboration with Department of Medicine,Nalanda Medical College and Hospital, Patna, Bihar, India from a period of January 2020 to September 2021.All were informed regarding the study and their written consent was obtained those who met the specified criteria for inclusion and exclusion. The Institutional Ethics Committee gave the study its approval. Data such as name and age etc. was recorded.

Keeping power (1-beta error) at 80% and confidence interval (1-alpha error) at 95%, the minimum sample size required was 60 patients; therefore, we included 120 (the minimum required number of cases) patients in present study.

INCLUSION CRITERIA

- Patients to give written informed consent
- Type 2 diabetic patients uncontrolled with Metformin 500mg
- Patients of either sex aged between 35- 55 years
- HbA1c ≥ 7%
- Fasting blood sugar (FBS) >140mg/dl
- Available for follow up.

EXCLUSION CRITERIA

- Patients not give written informed consent
- Patients allergic/intolerant to sulfonylureas.
- Patients with systemic diseases- renal dysfunction, cardiac problems
- Patients on other diabetic medications, requiring hospitalization
- Consuming alcohol, pregnant and lactating women

Data such as name, age, gender, etc. was recorded. HemoglobinA1c ($HbA1_C$), triglycerides, high-density lipoprotein cholesterol, serum fasting, and postprandial glucose were examined. There were two groups of 60 patients each. Patients in group I were given two pills of glimepiride (1 mg)/metformin (500 mg), while patients in group II were given one daily doses of glibenclamide (5 mg)/metformin (500 mg). To meet the glycemic control objectives (fasting blood glucose ≤7.2 mmol/l, postprandial blood glucose 10.0 mmol/l, $HbA1_C$<7%, or $HbA1_C$≥1% reduction), the dosage was increased to a maximum of four pills.

STATISTICAL ANALYSIS

Data thus obtained were subjected to statistical analysis by using Microsoft 16 and Statistical Package for Social Sciences (SPSS) version 24.0. Mean difference between the two groups was done using unpaired t test. P value < 0.05 was considered significant.

RESULTS

The mean age (Mean ± SD) of the present studied was 45.79±3.80 years in Group I and 44.96±3.62 years in Group II. The mean baseline BMI (kg/m2) was 28.5 ± 4.3 in Group I and 28.1 ± 4.5 in Group II.

Table 1: Gender wise distribution of patients

Gender	Group I (n=60)	Group II (n=60)
Male	34	32
Female	26	28

Table I shows that there were 34 males and 26 females in group I and 32 males and 28 females in group II.

Table 2: Assessment of basic parameters

Parameters	Variables	Group I(n=60)	Group II(n=60)	P value
Fasting blood glucose (mg/dl)	Baseline	178.2± 65.67	176.6± 68.50	0.05
	4 weeks	166.4± 62.45	156.0 ± 58.96	
	8 weeks	152.6±35.81	138.8± 36.05	
Postprandial blood glucose (mg/dl)	Baseline	252.4 ± 86.72	230.6 ±84.98	0.03
	4 weeks	206.2 ± 90.05	208.4 ± 92.80	
	8 weeks	196.2 ± 30.92	198.2 ± 36.75	
Lipid profile	Total cholesterol	180.4 ± 20.85	188.2 ± 18.50	0.86

(mg/dl)	LDL- C	96.6 ± 15.26	95.8 ± 12.93	
	HDL- C	42.34 ± 3.65	38.3 ± 3.98	
	Triglycerides	168.8 ± 26.25	171.5 ±28.65	

Data expressed as Mean ± S.D. HDL-C: High- density lipoprotein- Cholesterol; LDL-C: low-density lipoprotein-. Cholesterol; TC: Total Cholesterol; TG: Triglycerides

Table 2, Figure I shows that the mean fasting blood glucose (mg/dl) at baseline was 178.2 and 176.6, at 4 weeks was 166.4 and 156.0, and at 8 weeks was 152.6 and 138.8 in group I and group II respectively. Postprandial blood glucose (mg/dl) at baseline was 252.4and 230.6, at 4 weeks was 206.2 and 208.4, and at 8 weeks was 180.4 and 198.2 in group I and group II respectively. Lipid profile (mg/dl) TC was 176.4 and 188.2, LDL- C was 96.6 and 95.8, HDL- C was 46.2 and 45.3 and TGs was 168.8 and 171.5 in group I and group II respectively. The difference was significant (P< 0.05).

Mean HbA1c in Group-A was 9.5% before start of the study and reduced to 7.03 % after treatments by 8 weeks, In Group-B before start of the study treatment was 9.3% and after it reduced to 8.10%. A higher proportion of hypoglycemic events were observed in the glibenclamide-metformin combination versus glimepiride-metformin combination in uncontrolled type-2 diabetics.

Figure I:Assessment of basic parameters

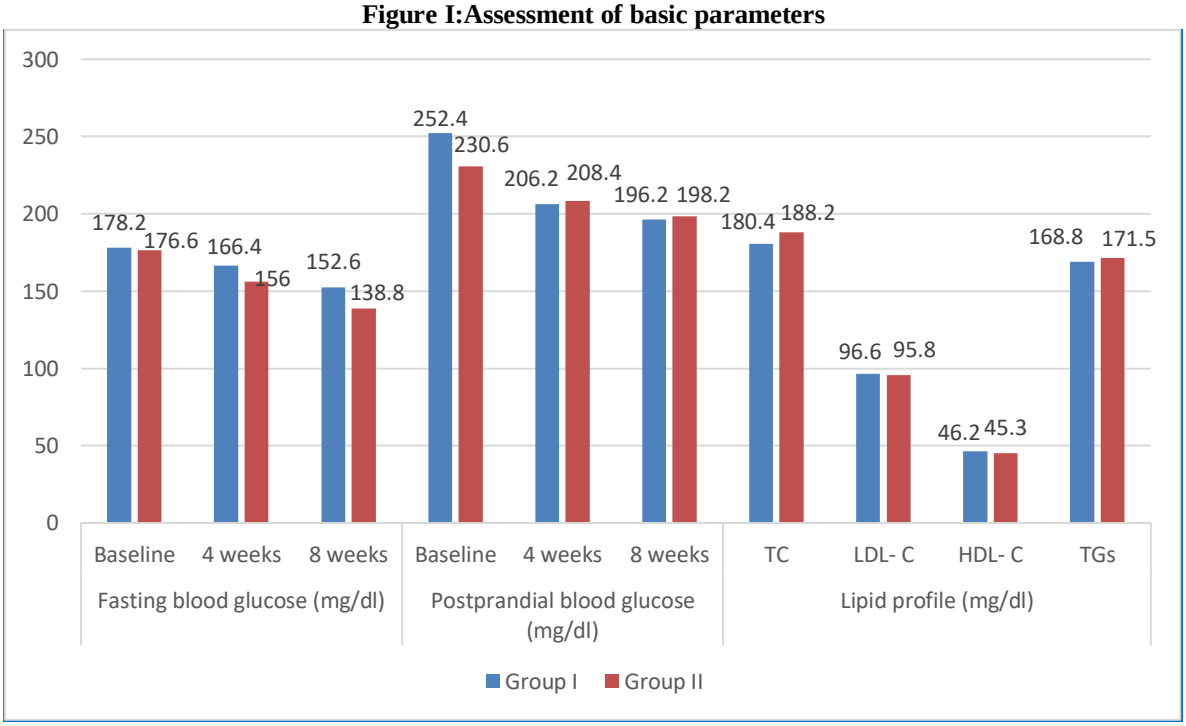


Table 3: After 8 weeks, patients reach their lipid control objectives

Serum lipid levels (mg/dl), Mean ±SD	Group I (n=60)	Group II (n=60)	P value
Total cholesterol	156 ± 28.90	158 ± 26.50	0.05
LDL- C	66.35 ± 22.25	75.83 ± 26.47	0.03
HDL- C	46.2 ± 3.05	42.3 ± 3.98	0.01
Triglycerides	132.0 ± 28.65	138 ± 30.50	0.01

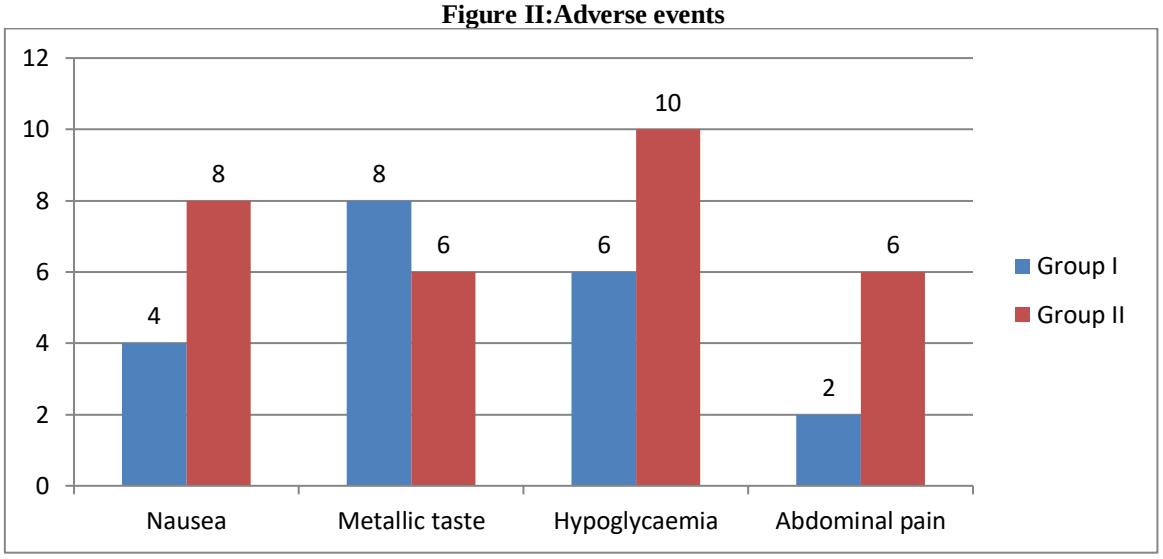
After taking two varied combination treatments for up to 8 weeks, lipid values decreased significantly while HDL-C values increased at the same time. In the present study, more significant results on lipid profiles were observed in the metformin plus glimepiride group as compared to the metformin plus glibenclamide group.

Table 3:Adverse events

Adverse events	Group I (n=60)	Group II (n=60)	P value
Nausea	4	8	0.05
Metallic taste	8	6	0.89
Hypoglycaemia	6	10	0.04
Abdominal pain	2	6	0.02

Table 2, Figure II shows that adverse events were nausea seen in 4 in group I and 8 in group II, metallic taste in 8in group I and 6 in group II, hypoglycemia in 6in group I and 10 in group II, and abdominal pain seen in 2in group I and 6 in group II.

Figure II:Adverse events



DISCUSSION

Early in the course of type 2 diabetes, insulin resistance develops and can cause gradual beta cell loss as well as overt diabetes. While monotherapy can impede the disease's course, it cannot stop it.[7]

A combination therapy that targets both insulin resistance and beta cell dysfunction is necessary for successful management.[8] The use of antidiabetic drug combinations with complimentary modes of action, such as metformin and sulfonylurea, is supported by clinical trials.[8,9]

The present study was conducted to assess the efficacy and safety of glimepiride-metformin versus glibenclamide-metformin combination in type-2 diabetics uncontrolled with metformin alone.

We found that the mean fasting blood glucose (mg/dl) at baseline was 178.2 and 176.6, at 4 weeks was 166.4 and 156.0, and at 8 weeks was 152.6 and 138.8 in group I and group II respectively. Postprandial blood glucose (mg/dl) at baseline was 252.4 and 230.6, at 4 weeks was 206.2 and 208.4, and at 8 weeks was 180.4 and 198.2 in group I and group II respectively. Lipid profile (mg/dl) TC was 176.4 and 188.2, LDL- C was 96.6 and 95.8, HDL- C was 46.2 and 45.3 and TGs were 168.8 and 171.5 in group I and group II respectively. In patients with type 2 diabetes mellitus whose metformin and glibenclamidemonotherapy have not sufficiently controlled their condition.Mean HbA1c in Group-A was 9.5% before start of the study and reduced to 7.03 % after treatments by 8 weeks, In Group-B before start of the study treatment was 9.3% and after it reduced to 8.10%.After 8 weeks of treatment, a greater percentage of patients in the glimepiride and metformin groups, 26% as opposed to 13% in the metformin and glibenclamide reduction in HbA1c to achieved the target of an $HbA1_C$ of 7%.

Gawali et al.[10] compared the effects of combination therapy using metformin and glimepiride with metformin and glibenclamide combination on glycaemic control (HbA1c and plasma glucose) and lipid profiles {Total cholesterol (TC), Triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C)}. Changes in HbA1C from baseline to final assessment, i.e., at 12 weeks, and changes in fasting blood sugar (FBS) and postprandial blood sugar (PPBS) from baseline to 4 weeks, 8 weeks, and 12 weeks were the primary efficacy end goals. After 12 weeks, there was no statistically significant difference in the reduction of glycosylated hemoglobin (HbA1c) and fasting blood sugar (FBS) between the therapy groups. However, in the glimepiride and metformin groups, the drop in postprandial blood sugar (PPBS) was statistically more significant.

We found that adverse events were nausea seen in 4 in group I and 8 in group II, metallic taste in 8 in group I and 6 in group II, hypoglycemia in 6 in group I and 10 in group II, and abdominal pain seen in 2 in group I and 6 in group II.

A study by Gonzalez et al.[11] involved 152 patients with uncontrolled type 2 diabetes. HemoglobinA1c ($HbA1_C$), triglycerides, high-density lipoprotein cholesterol, and serum fasting, and postprandial glucose were examined. Following random assignment, each patient was given two pills, once daily, of either glimepiride (1 mg)/metformin (500 mg) or glibenclamide (5 mg)/metformin (500 mg). Every research group comprised 76 patients. There were no discernible variations in the groups' baseline clinical and laboratory features. The glimepiride/metformin group had a significantly decreased $HbA1_C$ concentration at the end of the study. After a year of treatment, a greater percentage

of patients in the glimepiride group (44.6% as opposed to 26.8%) achieved the target of an $HbA1_C$ of 7%. The glibenclamide group experienced a greater percentage of hypoglycemia episodes (28.9% vs. 17.1%).

In the present study, more significant results on lipid profiles were observed in the metformin plus glimepiride group as compared to the metformin plus glibenclamide group.

Switching to metformin monotherapy decreased TG a nd LDL-C levels by 7% and 5%, respectively, in a trial of individuals on sulfonylurea therapy and not attaining appropriate glycemic control.[12]

Limitations of the study: The limitation of the study is the small sample size and short duration of the study.

CONCLUSION

Authors found that when compared to the glibenclamide and metformin combination group, glimepiride and metformin combination therapy has a superior effect on post-prandial blood glucose level reduction and a considerably lower incidence of hypoglycemia.

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