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Comparative Efficacy and Safety of Glimepiride-Metformin and Glibenclamide-Metformin Combinations for Uncontrolled Type 2 Diabetes: A Randomized Controlled Trial

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ABSTRACT

Aim: To compare the effectiveness and safety of the glimepiride-metformin combination with the glibenclamide-metformin combination in patients with type-2 diabetes uncontrolled with metformin alone. **Material and methods:** This research was conducted at the department of pharmacology and followed a randomized, open-label, prospective, comparative design. 80 patients were chosen for the research based on the inclusion criteria mentioned above. The participants were randomly divided into two groups, group A and group B, with 40 participants in each group. Group A was administered a FDC of Glimepiride 1mg and Metformin 500mg orally, once day before meals, for a duration of 6 months. Group B was administered a once-daily oral dosage of FDC Glibenclamide 5mg and Metformin 500mg before meals for a duration of 6 months. **Results:** Group-A: The mean fasting blood sugar (FBS) levels were 244.87± 42.74, 192.28 ± 42.85, 155.23 ± 33.71, and 126.54 ± 21.68 mg/dl at baseline, 1st, 3rd, and 6th month, respectively. Group-B: The mean fasting blood sugar (FBS) levels were 259.15±48.58, 215.12 ± 47.94, 174.73 ±31.84, and 145.47 ± 20.98 mg/dl at baseline, 1st, 3rd, and 6th month, respectively. Group-A: The mean postprandial blood sugar (PPBS) levels were 309.02 ± 65.23, 246.36 ± 61.88, 192.09 ± 39.54, and 154.28 ± 29.82 mg/dl at baseline, 1st, 3rd, and 6th month, respectively. Group-B: The mean postprandial blood sugar (PPBS) levels were 330.31 ± 63.57, 278.43 ± 56.46, 231.28 ± 42.74, and 193.84 ± 33.98 mg/dl at baseline, 1st, 3rd, and 6th month, respectively. Group-A: The average body weight at baseline, 1st, 3rd, and 6th month was 73.01 ± 11.27 kg, 72.25 ± 10.26 kg, 71.18 ± 10.75 kg, and 70.98 ± 10.98 kg, respectively. Group-B: The mean body weight at baseline, 1st, 3rd, and 6th month was 76.66 ± 11.01 kg, 75.78 ± 11.89 kg, 74.96 ± 11.22 kg, and 73.75 ± 11.64 kg, respectively. **Conclusion:** In summary, this research has shown the benefits of adding Sulfonylurea to Metformin in Type 2 diabetes patients who have uncontrolled blood sugar levels despite taking Metformin alone. When Metformin 500mg is taken with Glimepiride 1mg, it is more effective than when paired with Glibenclamide 5mg. The occurrence of hypoglycemia is lower while using the combination of Glimepiride and Metformin compared to the combination of Glibenclamide and Metformin. The combination of Metformin with Glimepiride/Glibenclamide has the potential to induce weight loss in persons with type-2 diabetes.

Keywords: PPBS, Metformin, Glibenclamide, FBS

INTRODUCTION

Type 2 diabetes mellitus is a prevalent metabolic disorder that is rising in frequency globally. The pathogenesis of this illness is marked by impaired insulin secretion and heightened insulin resistance. The significance of maintaining blood glucose control was shown in the UK Prospective Diabetes Study (UKPDS). This study revealed that initiating rigorous blood glucose management immediately after the diagnosis of diabetes mellitus resulted in a decrease in both micro- and macrovascular problems, as well as death rates[1–3]. Several oral hypoglycemic medicines have been created and are presently being used. These treatments work by different methods, such as improving the pancreas' ability to produce insulin, decreasing insulin resistance in body tissues, or boosting the levels of glucagon-like peptide-1. Nevertheless, the use of a single glucose-lowering drug as a treatment method exhibits a progressive decline in its ability to regulate blood glucose levels as time goes on. This ultimately leads to the need of using several antidiabetic medicines in combination or resorting to insulin therapy[4]. Combination therapy involving the use of sulfonylurea and metformin, which enhance insulin secretion and improve insulin resistance, is a highly effective and complementary approach for addressing the two primary causes of type 2 diabetes. Clinical studies, including the UKPDS, have reported that this combination therapy is more effective than using either drug alone[5].

Metformin monotherapy is the recommended first-line treatment when non-pharmacological interventions, such as dietary changes and exercise, are unsuccessful in reaching desired blood sugar levels. Patients who do not attain their desired blood sugar levels with Metformin alone may be prescribed additional antidiabetic medications. The desired targets for managing diabetes are a fasting blood sugar (FBS) level between 80-130mg/dl and a glycosylated hemoglobin (HbA1c) level below 6.5%[6]. Monotherapy may decelerate but not halt the course of the illness. Effective management requires a treatment approach that targets both insulin resistance and beta cell malfunction.For individuals like these, it is often recommended to combine Metformin with a second-generation SU medication like as Glimepiride or Glibenclamide as the first treatment option[7]. Glimepiride and Glibenclamide exhibit variations in their mode and specificity of action, with Glimepiride sometimes classified as a 'third generation' sulfonylurea. Weight gain is a significant concern associated with sulfonylurea therapy. According to the UK Prospective Diabetes Study (UKPDS), the average increase in weight after using Glibenclamide for 10 years was 4.5 kg[8]. There is substantial data indicating that starting treatment with lower dosages of two drugs that have complimentary effects may enhance the overall effectiveness and reduce the occurrence of negative side effects. Thus, the combination of an agent that provides insulin with an agent that increases insulin sensitivity would enhance the effectiveness of existing antihyperglycemic drugs. The objective of the research is to evaluate and contrast the efficacy and safety characteristics of two combinations: Glimepiride 1mg + Metformin 500mg and Glibenclamide 5mg + Metformin 500mg, in individuals diagnosed with Type 2 Diabetes.

The result may impact the clinician's decision when choosing sulfonylureas as an additional treatment to Metformin for Type 2 Diabetics who have not achieved control with Metformin alone. The aim of this research was to evaluate the impact of combining Glimepiride 1mg+Metformin 500mg and Glibenclamide 5mg+Metformin 500mg on HbA1c levels in patients with Type 2 Diabetes. Additionally, the study aimed to examine the adverse effects of the Glimepiride+Metformin and Glibenclamide+Metformin combinations.

MATERIAL AND METHODS

This research was conducted at the department of pharmacology and followed a randomized, open-label, prospective, comparative design. The research comprised patients with uncontrolled Type 2 diabetes who were taking 1000mg of Metformin, were between the ages of 40-50, had a HbA1c level more than 7%, had a fasting blood sugar level of more than 140mg/dl, and agreed to provide written informed permission and be available for follow-up. Patients who have allergies or intolerances to sulfonylureas. The research excluded patients with renal failure, cardiac issues, alcohol use, pregnancy and lactation, patients on other diabetes drugs, those needing hospitalization, and those who withdrew their consent.

METHODOLOGY

80 patients were chosen for the research based on the inclusion criteria mentioned above. The participants were randomly divided into two groups, group A and group B, with 40 participants in each group.

Group A was administered a FDC of Glimepiride 1mg and Metformin 500mg orally, once day before meals, for a duration of 6 months.

Group B was administered a once-daily oral dosage of FDC Glibenclamide 5mg and Metformin 500mg before meals for a duration of 6 months.

Following parameters were recorded in a Case Record Form (CRF) maintained for each patient.

Fasting blood sugar (FBS)

Post prandial blood sugar (PPBS)

Body Weight (BW)

HbA1c: Baseline and after 6 months

The patient was informed about potential adverse effects and instructed to promptly report any such occurrences. Adverse effects of this medication may include hypoglycemic episodes, skin rashes, flushes, nausea, vomiting, constipation, diarrhea, headache, paresthesia, or any other side effects.

STATISTICAL ANALYSIS

The quantitative data was expressed using the mean and standard deviation. The mean within the group was compared using a paired t-test. The mean difference between the two groups was calculated using an unpaired t-test. A P value less than 0.05 is deemed statistically significant. The statistical analysis was conducted using IBM SPSS Version 23.0 for Windows.

RESULTS

Our research aimed to compare the effectiveness and safety of two different medication combinations in treating Type-2 diabetics who were not effectively managed with Metformin alone. The first combination consisted of Glimepiride 1mg and Metformin 500mg, while the second combination consisted of Glibenclamide 5mg and Metformin 500mg. A total of 80 patients were included in the study.

Table 1: Age and gender of the participants

Age	**Group-A=40**		**Group-B=40**	
	Number	**Percentage**	**Number**	**Percentage**
Age	44.69 ± 3.52		44.58 ± 3.05	
≤ 45 years	27	67.50	30	75
>45 years	13	32.50	10	25
Gender				
Male	28	70	24	60
Female	12	30	16	40

The average age in Group-A was 44.69±3.52, whereas in Group-B it was 44.58±3.05. The age of patients was similar in both groups. The gender distribution of patients was similar in both groups. Group-A consisted of 28 male participants and 12 female individuals, whereas Group-B included 24 male subjects and 16 female subjects.

Table 2: Mean HbA1c profile at 0, 1st, 3rd and 6th

Assessment	**Group-A =40**	**Group-B=40**
Baseline	10.03 ± 1.31	9.87 ± 1.95
At 6th Month	7.83 ± 1.11	8.74 ± 1.52
Mean FBS profile at 0, 1st, 3rd and 6th month		
Baseline	244.87± 42.74	259.15±48.58
At 1st Month	192.28 ± 42.85	215.12 ± 47.94
At 3rd Month	155.23 ± 33.71	174.73 ±31.84
At 6th Month	126.54 ± 21.68	145.47 ± 20.98
Mean PPBS profile at 0, 1st, 3rd and 6th month		
Baseline	309.02 ± 65.23	330.31 ± 63.57
At 1st Month	246.36 ± 61.88	278.43 ± 56.46
At 3rd Month	192.09 ± 39.54	231.28 ± 42.74
At 6th Month	154.28 ± 29.82	193.84 ± 33.98
Mean Body weight at 0, 1st, 3rd and 6th month in kilogram (kg)		
Baseline	73.01 ± 11.27	76.66 ± 11.01
At 1st Month	72.25 ± 10.26	75.78 ±11.89
At 3rd Month	71.18 ± 10.75	74.96 ± 11.22
At 6th Month	70.98 ± 10.98	73.75 ± 11.64

The mean HbA1c level in Group-A decreased from 9.34% to 7.97% after 6 months of therapy. In Group-B, the HbA1c level decreased from 9.76% to 8.87% following treatment.

Group-A: The mean fasting blood sugar (FBS) levels were 244.87± 42.74, 192.28 ± 42.85, 155.23 ± 33.71, and 126.54 ± 21.68 mg/dl at baseline, 1st, 3rd, and 6th month, respectively. Group-B: The mean fasting blood sugar (FBS) levels were 259.15±48.58, 215.12 ± 47.94, 174.73 ±31.84, and 145.47 ± 20.98 mg/dl at baseline, 1st, 3rd, and 6th month, respectively.

Group-A: The mean postprandial blood sugar (PPBS) levels were 309.02 ± 65.23, 246.36 ± 61.88, 192.09 ± 39.54, and 154.28 ± 29.82 mg/dl at baseline, 1st, 3rd, and 6th month, respectively.

Group-B: The mean postprandial blood sugar (PPBS) levels were 330.31 ± 63.57, 278.43 ± 56.46, 231.28 ± 42.74, and 193.84 ± 33.98 mg/dl at baseline, 1st, 3rd, and 6th month, respectively.

Group-A: The average body weight at baseline, 1st, 3rd, and 6th month was 73.01 ± 11.27 kg, 72.25 ± 10.26 kg, 71.18 ± 10.75 kg, and 70.98 ± 10.98 kg, respectively.

Group-B: The mean body weight at baseline, 1st, 3rd, and 6th month was 76.66 ± 11.01 kg, 75.78 ± 11.89 kg, 74.96 ± 11.22 kg, and 73.75 ± 11.64 kg, respectively.

Table 3: Group-A: Intragroup comparison of parameters

Group-A			
Parameters	**Basal Vs 1st Month**	**Basal Vs 3rdMonth**	**Basal vs 6thMonth**
HbA1C	--	--	18.28, P<0.001**
FBS	13.86, P<0.001	19.89, P<0.001	22.85, P<0.001**
PPBS	7.32, P<0.001	13.27, P<0.001	17.62, P<0.001**
Body Weight	9.02, P<0.001	11.25, P<0.001	10.22, P<0.001**

**Highly significant (p<0.001)

Illustrates the comparison of initial values within a group with values at the 1st, 3rd, and 6th month follow-up, demonstrating statistical significance.

Table 4: Group-B Intragroup comparison of parameters

Group-B			
Parameters	**Basal Vs 1st Month**	**Basal Vs 3rd Month**	**Basal vs 6th Month**
HbA1C			17.92, P<0.001**
FBS	17.22, P<0.001	25.01, P<0.001	20.04, P<0.001**
PPBS	14.05, P<0.001	17.20, P<0.001	17.39, P<0.001**
Body Weight	11.68, P<0.001	13.45, P<0.001	9.05, P<0.001**

**Highly significant (p<0.001)

Illustrates the comparison of initial values within a group with the values at the 1st, 3rd, and 6th month follow-up, demonstrating statistical significance within the group (p<0.001).

Table 5: Intergroup comparison of mean difference in values of various parameters between Basal and 6th month

Baseline Vs 6th Month						
Parameter	**Group-A (N=40)**		**Group-B (N=40)**		**Unpaired t test**	
	Mean difference	**Std. Deviation**	**Mean difference**	**Std. Deviation**	**t Value**	**P Value**
HbA1C	2.20	0.61	1.13	0.42	5.61	P<0.001**
FBS	118.33	38.03	113.68	40.96	0.34	P<0.23, NS
PPBS	154.74	63.65	136.47	59.93	1.27	P<0.17, NS
Body Wt	2.03	2.87	2.91	2.24	2.73	P<0.006*

**Highly significant (p<0.001)

*Very significant (p<0.05)

In Group-A, 7 patients (17.50%) had hypoglycemic incidents, whereas in Group-B, 10 patients (25%) had similar occurrences throughout the treatment period. The chi-square test yielded a p-value of less than 0.37, indicating that the results were not statistically significant. However, there may still be clinical significance.

Group-B had a higher incidence of weight increase, with 3 individuals affected, as opposed to just 1 patient in Group-A.

Group-A exhibited a noteworthy decrease in HbA1c in comparison to Group-B. The other metrics, such as FBS (fasting blood sugar) and PPBS (postprandial blood sugar), were similar and did not exhibit any significant differences between the groups.

The effectiveness parameters in our trial were measured by improvements in HbA1c, FBS, and PPBS. The average HbA1c level in Group-A was 10.03 ± 1.31% before therapy. After six months of treatment, it decreased to 7.83 ± 1.11%, resulting in a mean difference of 2.20 ± 0.61%. The initial value of Group-B before treatment was 9.87 ± 1.95, which decreased to 8.74 ± 1.52% by the 6th month. The mean difference between these two values was 1.13 ± 0.42, indicating a very significant drop in Group-A (p<0.001).The mean fasting blood sugar (FBS) in Group-A was 244.87±42.74 mg/dl before therapy. After 6 months of treatment, it decreased to 126.54±21.68 mg/dl, resulting in a mean difference of 118.33±38.03 mg/dl. The initial mean value of Group-B before therapy was 259.15±48.58 mg/dl. After 6 months of treatment, it decreased to 145.47 ± 20.98 mg/dl, resulting in a mean difference of 113.68±40.96 mg/dl. This indicates a similar decline in both groups, which is not statistically significant.

The mean postprandial blood sugar (PPBS) level in Group-A was 309.02 ± 65.23 mg/dl before therapy. After 6 months of treatment, it decreased to 154.28 ±

29.82 mg/dl, resulting in a mean difference of 154.74 ± 63.65 mg/dl. The initial mean value of Group-B before therapy was 330.31 ± 63.57 mg/dl. After 6 months of treatment, it decreased to 193.84 ± 33.98 mg/dl, resulting in a mean difference of 136.47±59.93 mg/dl. This reduction was similar in both groups and was not statistically significant.

The data above indicate that Group-A has a higher level of effectiveness compared to Group-B. Weight gain and hypoglycemic episodes were used as safety measures to assess adverse effects. The initial mean body weight in Group-A was 73.01 ± 11.27 kg. After treatment by the 6th month, the mean body weight fell to 70.98 ± 10.98 kg, resulting in a mean difference of 2.03 ± 2.87 kg. The initial weight of Group-B participants was 75.13±10.87 kg, which decreased to 73.18±11.07 kg during the third month of therapy. The mean difference in weight was 2.24±2.73 kg, indicating a substantial reduction in Group-B.

Group-A had 7 patients who had hypoglycemic incidents, whereas Group-B had 10 patients who experienced such occurrences throughout the therapy period. While the results were clinically significant, they did not reach statistical significance on the chi-square test. Additionally, there was an observed rise in weight gain in three patients in Group-B, as opposed to just one patient in Group-A.

DISCUSSION

The current recommendations for managing patients with Type 2 Diabetes Mellitus are established using glycaemic criteria that are derived from epidemiologic data. HbA1c is highly associated with microvascular problems such as nephropathy, retinopathy, and neuropathy. HbA1c offers a protracted indication, akin to a mean value, of the elevated levels of blood sugar over a span of around 90 days. The primary goal of therapy for most persons with Type 2 Diabetes should be to attain a HbA1c level of ≤6.5% in order to avoid both microvascular and macrovascular problems. Research has shown that individuals diagnosed with Type 2 Diabetes who lower their HbA1c level by 1% may decrease the occurrence of microvascular problems by 25%[9].Treatment for the majority of Type-2 Diabetic patients often starts with lifestyle improvements, including as food adjustments and increased physical activity. Metformin is prescribed as the first treatment for patients shortly after they are diagnosed, unless there are specific reasons not to do so. If the desired HbA1c level is not reached within a 6-month period, we will explore combining Metformin with one of the following therapy options: a SU, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin. The selection is determined by the patient's and drug's features, with the primary objective of enhancing glycaemic control while reducing adverse effects. Sulfonylureas are the preferred option when combining with Metformin[10].

This research was a comparison of two second generation SUs, Glimepiride 1mg and Glibenclamide 5mg, when used in conjunction with Metformin 500mg. The purpose was to evaluate their effectiveness and safety profiles.Glucose levels are reduced, and HbA1c readings are lowered to a similar extent as other second-generation SUs[10]. The main criterion used to assess effectiveness was the decrease in HbA1c levels at the conclusion of the third month. In addition, a comparison was conducted between the average fasting blood sugar (FBS) and postprandial blood sugar (PPBS) values of the groups at the 1st, 3rd, and 6th follow-ups. The purpose of this study was to assess if there is a distinct effect on these parameters caused by the two medicines. An attempt was made to establish a link between these levels and the HbA1c readings generated by the medicines at the conclusion of the trial. Both Glimepiride and Glibenclamide demonstrated statistically significant improvements in HbA1c, FBS, and PPBS levels in this trial. This demonstrates the efficacy of both medicines as adjunctive treatment to Metformin in Type-2 diabetics who have inadequate glycemic control with Metformin alone. Glimepiride shown superior improvement in all three measures when compared across different groups. However, a statistically significant improvement was seen in HbA1c levels, indicating that Glimepiride is more effective than Glibenclamide when used in addition to Metformin. Comparable findings were achieved by comparative trials that assessed the impact of Glimepiride against Glibenclamide as a single form of treatment[11]. Research conducted by Fadia.According to Y. Al-Hamdani et al., Glimepiride was shown to be more effective in improving high blood sugar levels compared to Glibenclamide, even when both drugs were given at the same dosage[12].

There was a notable difference in the variations in the postprandial blood sugar (PPBS) readings between the two medications, with Glimepiride demonstrating superior control. Regarding FBS, there was no discernible difference between the two medications. This may be due to the fact that Glimepiride has the ability to significantly enhance the initial release of insulin, resulting in a reduction in the increase of postprandial blood sugar levels. Research has shown that postprandial blood sugar (PPBS) is a more accurate indicator of glycated hemoglobin (HbA1c) levels compared to fasting blood sugar (FBS)[13]. Therefore, the higher effectiveness seen with Glimepiride may be attributed to a more significant decrease in postprandial blood sugar (PPBS) levels compared to fasting blood sugar (FBS) levels. Regarding weight change, both medicines demonstrated a decrease in average weight throughout the research period, with Glimepiride-Metformin resulting in a more significant drop. Two patients saw weight increase while using Glimepiride, whereas five patients experienced weight gain while taking Glibenclamide. Considering both of these data,

Glimepiride has the benefit of causing a more significant decrease in weight and a lower occurrence of weight gain. Nevertheless, there was no statistically significant disparity between the two groups in terms of weight increase. However, a statistically significant decrease in mean weight was seen. Our research has shown an unexpected conclusion that SUs actually lead to weight decrease, which contradicts the well-established knowledge that SUs often promote weight increase. The result may be attributed to the concurrent use of Metformin and the enhanced regulation of blood sugar levels. In a study conducted by Ingle Pravinkumar V et al., it was found that the combination of Metformin and Glimepiride was more effective in improving glycaemic control compared to the combination of Metformin and Glibenclamide in patients with Type 2 Diabetes Mellitus. Additionally, the combination of Metformin and Glimepiride had weight neutralizing/reducing effects in these patients.

CONCLUSION

In summary, this research has shown the benefits of adding Sulfonylurea to Metformin in Type 2 diabetes patients who have uncontrolled blood sugar levels despite taking Metformin alone. When Metformin 500mg is taken with Glimepiride 1mg, it is more effective than when paired with Glibenclamide 5mg. The occurrence of hypoglycemia is lower while using the combination of Glimepiride and Metformin compared to the combination of Glibenclamide and Metformin.The combination of Metformin with Glimepiride/Glibenclamide has the potential to induce weight loss in persons with type-2 diabetes.Therefore, Glimepiride 1mg may be a more favorable option than Glibenclamide 5mg for co-administration with Metformin 500mg in Type-2 Diabetic patients who have inadequate glycemic control with Metformin alone.

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