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"A Comparative Study of Therapeutic Efficacy and Safety of Metformin + Vildagliptin Versus Metformin+ Glimepiride Combination in Type 2 Diabetes Mellitus Patients at Tertiary Care Center of Central India"

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Abstract:

Introduction: Diabetes is a complex, chronic illness requiring continuousmedical care with multifactorial risk reduction strategies beyond glycemic control. Diabetes mellitus is resulting in increased blood glucose levels due to deficiency of insulin secretion by the pancreas or ineffectiveness of secreted insulin, which can either be inherited or acquired.

Aim & Objectives: To evaluate the comparative efficacy and safety of metformin+vildagliptin versus Metformin + Glimepiride combination in type 2 diabetes mellitus patients.

Materials and Methods: This hospital-based, prospective, observational, open labeled, comparative study was conducted in the Department of Pharmacology and the Department of Medicine. Total 236 patients were enrolled in the study; Patients were divided into Group- 1 and Group- 2. Group- 1 Patients were treated with Metformin (500mg) + Glimepiride (1mg). Group -2 Patients were treated with Metformin (500mg) + Vildagliptin (50mg). Fasting plasma glucose (FPG),post-prandial plasma glucose (PPBS), Glycosylated hemoglobin (HbA1c) were assessed, investigations, (fasting, postprandial blood sugar and HbA1c profile) were carried out at the time of enrolment as baseline, 12 weeks and 24 weeks after therapy.Data were analyzed by using unpaired t-test to compare the study groups. Association among the study groups were assessedby using Chi-square and ANOVA test. p-value <0.05 was considered statistically significant.

Results: Total 236 patients were enrolled in the study; 36 were withdrawn, out of these patients most of them91 (45.5%) were belonged to 51-60 years of age group, manyof them 82 (41%) were businessmen, 40 (20%). The fall in FBS from baseline to end of study (After 24 weeks of therapy) in group -1 was 92mg/dl where as in group -2 it was 96mg/dl andthe fall of PPBS from baseline to end of study in group -1 was 123.6mg/dl where as in group-2 it was 149 mg/dl. The fall in HbA1c from baseline to end of study in group -1 was 0.75% where as in group -2 it was 0.72%.

Conclusion: Group -2 drugs showhigher efficacy in comparison to Group-1 drugsin management of type 2 diabetes mellitus.

Keywords: Diabetes Mellitus, FBS, PPBS, HBA1C, Efficacy, Safety

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1. INTRODUCTIION

Diabetes is a complex, chronic illness requiring continuousmedical care with multifactorial risk reduction strategies beyond glycemic control. Diabetes mellitus is resulting in increased blood glucose levels due to deficiency of insulin secretion by the pancreas or ineffectiveness of secreted insulin, which can either be inherited or acquired[1].Diabetes mellitus (DM) is one of the most common chronic disorders attaining epidemic proportion, worldwide, as per International Diabetes Federation (IDF) there were 366 million people with diabetes in 2011; India is one of the epicenters of the global diabetes epidemic and has the second-highest number of people with the disease in the world with 69.2 million individuals as of 2015[2].

Diabetes mellitus (DM) is definedaccording to WHO as "Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin." Glucose tolerance can be assessed using the fasting plasma glucose (FPG) or the hemoglobin A, (HbA1c). An FPG < 5.6 mmol/L (100 mg/dL), a plasma glucose <7.9 mmol/L (140 mg/dL) following an oral glucose challenge and an HbA1c, <5.7% are considered to define normal glucose tolerance.The broadly used combination of Metformin and a sulphonyl urea (SU) fails to maintain glycemic control over time or often results in sub-optimal outcomes[3].

The addition of a third antihyperglycemic agent is required. When choosing options for the third agent, physicians should consider improvement of glycemic control without additional risks such as hypoglycemia and weight gain[4].

Recently, several new classes of oral hypoglycemic agents have been introduced. Vildagliptin is an oral and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor which prevents the rapid degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and increases the levels of the intact, active form of endogenous GLP-1. It improves glycemic control in type 2 diabetic patients either as a monotherapy or administered in combination with Metformin, sulfonylurea, thiazolidinediones or insulin[5].

Therefore, keeping all above fact in consideration, we planned to compare therapeutic efficacy and safety of Glimepiride (1mg) + Metformin (500mg) V/S Metformin (500mg) + Vildagliptin (50mg) therapy in newly diagnosed treatment type 2 diabetic patients with moderate hyperglycemia in 24 weeks.

2. MATERIAL AND METHODS

The present prospective, open labeled, comparative study was conducted at the Department of Pharmacology and the Department of Medicine (OPD), S.S. Medical College and associated Hospital, Rewa(M.P.) No. of patients with newly diagnosed diabetes mellitus were enrolled into the study, these patients were divided into two groups, Group 1and Group 2. The duration of study was 12 months (from 1st July 2018 to 30th June 2019).

Group 1– Patients were treated with Metformin (500mg) + Glimepiride (1mg).

Group 2 – Patients were treated with Metformin (500mg) + Vildagliptin (50mg).

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The patients were selected on the basis of following inclusion and exclusion criteria**.**Type-2 Diabetes Mellitus patients Uncontrolled with life intervention with or without OHG, Patients Age > 30 years of either gender, Fasting plasma glucose (FPG) >126 mg/dl,post-prandial plasma glucose (PPBS) > 200 mg/dl, Glycosylated hemoglobin (HbA1c) > 6.5%. Patients willing to give written informed consent and ready to come regularly for follow up were included in the study. Patients with type - 1 Diabetes Mellitus, patients of type-2 DM age < 30 years, Pregnant and lactating women and patients of type-2 DM with complications like retinopathy, nephropathy, diabetic foot, severe liver and/or kidney disease, patients taking any other medications for any other diseases and those who are not willing to give written informed consent were excluded from the study.

Patients satisfying inclusion criteria were divided into two equal groups. The patients were assessedand investigations,(fasting and postprandial blood sugar)were carried out at the time of enrolment as baseline and then every 4 weeks of interval up to 24 weeks via glucometer. HbA1c profile were carried out at time of enrolment and at the end of study (24 weeks).

STATISTICAL ANALYSIS

Quantitative data is presented in form of Mean and Standard deviation. Qualitative data is presented in form of frequency and percentage. Comparison among the study groups is done by using unpaired t test.

3. RESULTS

Total 236 patients were enrolled in the study; they were divided into two groups, 117 patients in group 1 and 119 patients in group 2 respectively. Patients were similar in terms of age, baseline demographic characteristics and other variables. During the 12 months of study, total 36 patients discontinued treatment and lost during follow up and 200 patients continued their follow-up, up to end of study (24 weeks).Of these discontinue patients, 13 were from group 1 and 23 patients were from group 2 hence Group 1 consist of 104 patients and Group 2 consist of 96 patients up to end of study (24weeks). Observations of the study are as follows.

Table 1: Demographic distribution of patients

AGE GROUP (YEARS)	**Group-1**	**Percent**	**Group-2**	**Percent**	**Grand Total**	**Percent**
31-39	35	33.65 %	23	23.95 %	58	29%
40-49	24	23.07 %	27	28.12 %	51	25.5 %
50-60	45	43.26 %	46	47.91 %	91	45.5 %
SEX						
Male	68	65.38 %	55	57.29 %	123	61.5 %
Female	36	34.62 %	41	42.71 %	77	38.5 %
OCCUPATION						
Businessman	42	40.38 %	40	41.66 %	82	41 %
Govt	17	16.35 %	23	23.96 %	40	20 %
House wife	15	14.452 %	16	16.67 %	31	15.5 %
Others	30	28.4%	17	17.70%	47	23.5%
RELIGION						

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Hindu	74	71.15 %	76	79.17 %	150	75 %
Muslim	21	20.19 %	8	8.33 %	29	14.5%
Sikh	6	5.77 %	5	5.21 %	11	5.5 %
Others	3	2.88 %	7	7.29 %	10	5 %
RESIDENT						
Rural	31	29.81 %	26	27.08 %	57	28.5 %
Urban	73	70.19 %	70	72.92 %	143	71.5 %
SOCIOECONOMIC STATUS						
Lower	76	73.08 %	74	77.08 %	150	75 %
Middle	14	13.46 %	13	13.54 %	27	13.5 %
Upper middle	9	8.65 %	6	6.25 %	15	7.5 %
Upper	5	4.81 %	3	3.13 %	8	4 %

In this study, most of the patients91 (45.5%) belonged to 51-60 years of age group, while 123 (61.5%) patients were males and rest 77 (38.5%) were females. Occupation wise data shows that 82 (41%) patients were businessmen,40 (20%) government employees and 31 (15.5%) were housewives and 47 (23.5%) patients werebelonged to other occupations.
Community wise data shows that150 (75%) were belongs to Hindu religion followed by 29 (14.5%) Muslims, 11 (5.5%)Sikh religion and10 (5%) patients were belongs to other religions. Demographic data shows that 143 (71.5%) were belongs to urban area and57 (28.5%) belongs to Rural area.Socioeconomic data shows that 150 (75%) were belong to lower class followed by 27 (13.5%) Middle class, 15 (7.5%) upper-middle class and 8 (4%) were belonged to upper class.(Table-1)

Table 2: Commonly Observed Adverse Effects

Adverse events	Group-1	%	Group-2	%	Total Number of Patients	Percent
Headache	5	4.81%	7	7.29%	12	6%
Hypoglycemia	3	2.88%	2	2.08%	5	2.50%
Nausea	3	2.88%	4	4.17%	7	3.50%
Dizziness	0	0	2	2.08%	2	1%
Diarrhoea/Flatulence	1	0.96%	1	1.04%	2	1%
Arthralgia	0	0	0	0	0	0
Dyspepsia	0	0	0	0	0	0
Metallic Taste	7	6.73%	3	3.13%	10	5%
Weight Gain	4	3.85%	1	1.04%	5	2.50%
Edema	0	0	0	0	0	0
Sweating	3	2.88%	1	1.04%	4	2%
Jaundice	0	0	0	0	0	0%
Total	26	25.20%	21	21.88%	47	24.50%

Out of 26 patients in group-1, 7 (6.73%) patients experienced metallic taste while5(4.81%) patients felt headache. In 4 (3.85%)patients, weight gain was observed and 3 (2.88%)patients experiencednausea,hypoglycemia and sweating. Only 1 (0.96%) patient showed symptoms of diarrhoea/flatulence, and dizziness.

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Out of 47 patients in group-2, 7 (7.29%) patients experienced headache whereas4 (4.17%) patients experienced nausea. 3 (3.13%) patients experienced metallic taste while hypoglycemia, and dizziness was observed in 2 (2.08%) patients. Mild adverse effects such as diarrhoea/ flatulence, weight gain and sweating were observed in 1 (1.04%) patient only. In both the groups, no major adverse effects were observed.(Table -2).

Table :3Comparative Efficacy of Metformin 500 mg + Glimepiride 1 (mg) vs. Metformin 500 (mg) + Vildagliptin 50 (mg) combination in fasting blood sugar, postprandial blood sugar and HbA1c at different time interval (baseline, 12, and 24 weeks)

		Group 1	Group 2	p and t values
FBS	baseline	204.06±39.67	215.23±30.06	p=0.066, t=2.743
	12 WK	169.06±39.62	162.23±30.06	p=10.17,t=1.364
	24 WK	112.96±34.57	119.23±30.06	p=0.179,t=1.348
PPBS	base line	293.7±41.22	308.35±35.07	p=0.008,t=2.696
	12 WK	245.10±74.23	244.35±35.07	p=0.268,t=1.112
	24 WK	170.11±42.03	159.35±35.07	p=0.052,t=1.957
HbA1c	base line	9.71±0.84	9.82±0.77	p=0.336,t=0.9623
	12 WK	9.43±0.81	9.55±0.80	p=0.293,t=1.053
	24 WK	8.96±0.75	9.1±0.80	p=0.203,t=1.277

The fall in FBS from baseline in group -1 was 35mg/dl (baseline to12 weeks) where as in group -2 it was 53mg/dl. After 24 weeks of therapy fall in FBS in group -1 was 92mg/dl where as in group -2 it was 96mg/dl.

The fall in PPBS from baseline in group -1 was 48mg/dl (baseline to12 weeks) where as in group -2 it was 64mg/dl. After 24 weeks of therapy fall in PPBS in group -1 was 123.6mg/dl where as in group -2 it was 149 mg/dl.

The fall in HbA1c from baseline in group -1 was 0.28% (baseline to12 weeks) where as in group -2 it was 0.11%.After 24 weeks of therapy fall in FBS in group -1 was 0.75% where as in group -2 it was 0.72%. (Table-3)

4. DISCUSSION

In the present study total 236 patients were enrolled, of these, 36 patients withdrawn during the study.

among 200 patients most ofthe (45.5%)patientswere belonged to age group 51-60 years of age group, and minimum (24%) patients were belonged 31-40 years. This was similar to **Tamboli et al[6] study** in which was maximum (47.8 %) patients belonged to 50–60 years.

Of these (61.5%) were males and (38.5%)were females.This was similarto **Afzal et al[7]**study in which maleswere showed higher prevalence of Diabetes than females. However, several other studies showed dissimilar result like **Tamboli et al[8]**in which females (51.7%) had high prevalence than males (46.8%).

In present study, most of the patients were businessmen (41%) This was similar to **Sharma et al[9]**in which businessmen and government employees

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(54.22%).However,**Narayanamurthy et al[10]** shows dissimilar results in which Private employees (36.5%).

In our study 75% patients belong to the Hinduism religion. This was similar to **Gautam et al[11]**study in which most of (90.6%) were Hindu however **Kotresh et al[12]** showed that there is no influence of religion in type 2 diabetes mellitus.

In our study 71.5% patients were resided to urban area and 28.5% resided to rural areas**.** This was similar to severalstudies like **Asha et al[13]andAynalemet al[14]**studies in which prevalence of Diabetes Mellitus among the urban population is usually higher than rural householders.

In present study, incidence of ADR group-1 patients(Metformin + Glimepiride) shows that, maximum patientsexperienced metallic taste 6.73% followed by headache4.81%, weight gain3.85%, nausea, hypoglycemia, and sweating2.88% and minimum0.96% patients were present with diarrhoea/flatulence, and dizziness.This was dissimilar to **Gautam et al[11]** study in which maximum patients were present with hypoglycemia (6.81%) followed by headache4.54%, nausea 2.27% and minimum adverse effects were dizziness, diarrhoea/flatulence, Arthralgia and Dyspepsia.

Group 2 patients (Metformin + Vildagliptin),maximum ADR were headache (7.29%) followed by nausea 4.17%, metallic taste 3.13% hypoglycemia and dizziness 2.08%,diarrhoea/flatulence, weight gain and sweating1.04%. This was similar to**Gautam et al[11]** study (in whichmaximum 2 (5%) headache and Arthralgia and minimum 1 (2.50%) dizziness, diarrhoea/flatulence, hypoglycemia and Dyspepsia.

Among both groups weight gain was more with group 1 (metformin + glimepiride) compared to group 2 (metformin + vildagliptin), this was similar to various studies like **Mokta et al[2]**, **Shimpi et al[15]**, **Charpentier et al[16]**, **Wang et al[17].**

The efficacy of the study showed non-significant decrease of blood sugar from base line to 12 weeks of therapy, fall in FBS, in group 1 was observed (169.06 mg/dl) from baseline 204.06 mg/dl while group-2 results were 162.23 mg/dl from baseline value (215.23 mg/dl). This was statistically not significant (p=1.017) and after 24 weeks of therapy showed similar results which was also statistically not significant (p=0.179) between the groups.

In group -2 patients fall of FBS was also non-significant(as group-1) from baseline to 12 weeks and from base line to 24 weeks.

Present study findings were similar to studies of **Ferrannoni et al[18], Jeon and Oh et al[19],Gautam et al[11].**However**, Shimpi et al[15]**and**Mokta et al[2]**study showed dissimilar results to our study.

After 12 weeks of therapy, fall in PPBS, in group 1 was observed 245.10 gm/dl from baseline 293.7 mg/dlwhile group 2 was 244.35 mg/dl from baseline 308.35. This wasstatistically not significant (p=0.286). After 24 weeks of therapy showed similar results which was also statistically not significant (p=0.052) between the groups.

In present study Comparison ofHbA1c results were presented as follows. After 12 weeks of therapy, fall in HbA1c, in group 1 was 9.43% from baseline 9.70% and in group 2 was 9.55 % from baseline 9.82 %. This was statistically not significant (p=0.293).After 24 weeks of therapy showed similar results which was also statistically not significant (p=0.052) between the groups.

Findings of PPBS and HbA1c were similar tothe studies done by **Guatam et al[11]**study**,Ferrannoni et al[18], Jeon and Oh[19].** However, **Shimpi et al[15]** and **Mokta et al[2]**studies showed dissimilar results to our study**.**

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5. CONCLUSION

In this study, Metformin + Glimepiride (Group -1) and Metformin + Vildagliptin (Group-2) both combinations achieved optimal glycemic control almost equally at the end of 24 weeks of therapy. However, in terms of adverse effects profile, hypoglycemia and weight gain was observed more inGroup -1 as compared to Group -2. Hence, Group -2 drugsoffer advantage over Group -1 drugsand represents as an important treatment option for optimal glycemic control, without weight gain and risk of hypoglycemia. Group -2 drugs arealso slightly more effective and better tolerated than Group -1 drugs for the treatment of diabetes mellitus.

Conflicts of Interest: **None**

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