Comparative Assessment of safety and effectiveness of Metformin Glimepiride and Metformin Vildagliptin in Type 2 Diabetes Mellitus

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***Abstract*- Diabetes, a prevalent chronic condition that require ongoing care to avoid complications. The mainstay of diabetic treatment, metformin is frequently enhanced in effectiveness by being taken with other drugs such as glimepiride or vildagliptin.Vildagliptin,a DPP4 inhibitor ,increase insulin secretion and controls blood glucose levels, whereas glimepiride, a sulphonylureas accelerates the release of insulin. The present study insight into compare the safety and effectiveness of Metformin glimepiride versus Metformin vildagliptin in the treatment of type 2 diabetic patients. The study was single centered, prospective randomized, comparative and observational study carried out for six months. Totally 50 patients were enrolled for this study who met inclusion criteria and are divided equally into 2 groups, Group A (Metformin glimepiride) and Group B(Metformin vildagliptin).To compare the safety and effectiveness of both groups by assessing patient glucose level, demographic details, dose,frequency,Adverse effect.The study shows that there was a significant reduction in the p values of FBS,RBS,HBAIC of both groups. Hence the study concluded that both groups work effectively in a same manner and Metformin vildagliptin resulted in better adverse event profile with lower risk of hypoglycemia.**

***Key words*- Type 2 diabetes, Metformin, Vildagliptin, Glimepiride, FBS, RBS, HbA1C, ADR's.**

INTRODUCTION

Diabetes is quite prevalent worldwide. It has devastating effects on individuals, societies and countries or territories and leads to over 4 million deaths per year. It affects all ages, communities, and continents. According to the International Diabetes Federation, approximately 463 million adults aged 20-79 of years were living with diabetes in 2019.This number is expected to increase rise to 700 million by 2045.[1]

Diabetes is predicted to be the seventh greatest cause of death by 2030, according to the World Health Organization (WHO)[2,3]. Diabetes may have a significant role in blindness, kidney disease, heart attacks, stroke, and lower limb amputations. Diabetes can be treated and its repercussions prevented or postponed through diet, physical exercise, medication, and regular screening for complications and therapy.[3]

To achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Achieving near-normal glycated hemoglobin significantly, decreases risk of macrovascular and microvascular complications. At present there are different treatments, both oral and injectable, available for the treatment of type 2 diabetes mellitus (T2DM). Treatment algorithms designed to reduce the development or progression of the complications of diabetes emphasizes the need for good glycemic control.[4]

Patients with type 2 diabetes, oral monotherapy may be initially effective for controlling blood glucose, but it is associated with a high secondary failure rate. (Primary failure is frequent only in patients with high baseline blood glucose at the time of beginning monotherapy, whereas secondary failure is to be expected in the course of the disease.) The different classes of oral agents used to treat type 2 diabetes have complementary mechanisms of action, and their use in combination often results in blood glucose reductions that are significantly greater than those that can be obtained with maximal doses of any single drug. A wide range of combinations (e.g. sulfonylurea plus metformin, a thiazolidinedione, or acarbose; metformin plus a thiazolidinedione or acarbose) have been used effectively to achieve glycemic control in patients in whom oral monotherapy has failed. The high secondary failure rates for oral monotherapy – and, moreover, the high primary failure rate in patients with very high blood glucose at diagnosis – coupled with the effectiveness of combination treatment, support the suggestion that multiple-drug regimens be considered for initial pharmacologic treatment in patients with symptomatic type 2 diabetes whose blood glucose is not controlled by diet alone.[5,6]

The choice of antidiabetic agents is based on efficacy along with drug safety. Metformin has been the most recommended monotherapy for the initial treatment of T2DM[5-7].However, majority of patients have advocated combined therapy in the long run to maintain glycemic control. The combined regimens are effective to minimize the dosage of antihyperglycemic agents and thereby their unwanted effects. A combination of glimepiride plus metformin is widely used in Indian clinical settings due to its cost effectiveness and efficacy in improving glycaemic control[8,9]. However, a combination of glimepiride and metformin is frequently associated with side effects such as weight gain and hypoglycemic events. Hence, physicians and researchers are in search of a combination having better efficacy and minimal side effects as compared to the present antidiabetic formulation available in the market.[10]

Vildagliptin is a dipeptidyl peptidase 4 (DPP 4) inhibitor, an oral antidiabetic agent, having moderate efficacy with a good overall safety profile including low risk of hypoglycemia, low risk of edema, lipid neutral effect, and weight neutrality.[10] When vildagliptin was used as add on treatment or initial combination therapy along with metformin, good glycemic

control was achieved due to their complementary mechanism of action.[11]Many randomized clinical trials have demonstrated the comparative effectiveness of glimepiride and vildagliptin as add on therapy to metformin But their results might not always reflect what actually could be expected in clinical practice. [12,13,14]Therefore, the present study aimed to compare the safety and efficacy of glimepiride and vildagliptin as add on therapy to metformin in patient diagnosed with T2DM.[15,16]

The present study compare safety and effectiveness of metformin glimepiride and metformin vildagliptin in type 2 Diabetic patients by assessing patient glucose level, demographic details, dose,frequency,,Adverse effect. These two combination drug are commonly given for DM patients in the hospital setting to control blood glucose level.By evaluating these drug combinations, we aim to provide valuable insight into their respective benefits, potential side effects and overall impact on glycemic control.

MATERIALS AND METHODS

The present Study was carried out at Tertiary care hospital, Bangalore,India..It was Single Centered prospective, randomized, comparative & observational study. The study period was six months. The study is being carried out in patients who are on metformin glimepiride and metformin vildagliptin. A sample of 50 prescriptions are being assessed and compared by dividing into two groups Group A(Metformin glimepiride) and Group B (Metformin vildagliptin) who met inclusion criteria.

Inclusion criteria:

1. All adult patients (over 18 years) on metformin glimepiride and metformin vildagliptin
2. Both male and female patients
3. Patients of type 2 DM with or without comorbidities

Exclusion Criteria:

1. Outpatient T2DM
2. Pregnant women's
3. Pediatric patients
4. Patient who are terminally ill

Method of study

Once the patient is prescribed with metformin glimepiride and metformin vildagliptin, the patient consent is taken followed by data collection. The data is collected in a semi-structured Performa which includes details such as:

- Patient demographic details
- Medical and medication history
- Indications for metformin glimepiride and metformin vildagliptin 20
- Agent prescribed and dosing
- Glycaemic status (HbA1C)
- Follow up details

After collection of the data, the details of the prescription including the prescribers details are collected. The lab reports also being recorded. The patient medical details are then recorded till discharge. Any discontinuation in the medication is also noted with the concerning evidence and reports.

Ethical consideration

Written informed consent will be taken from patients before recruitment. Patients will be made aware that their participation is voluntary and they can decide not to take part without any adverse influence on their treatment. Privacy and confidentiality of the research participants will be protected.

Data analysis

All the data observed were analyzed as per GraphPad software. The percentage, proportions were calculated and p-value (<0.05) was considered statistically significant. Results were represented as frequencies, percentages, mean,and medians. In some cases, inferential statistics like Analysis of variance (ANOVA) followed by student–tests, using SPSS software version 21.0 were also implemented.

RESULT

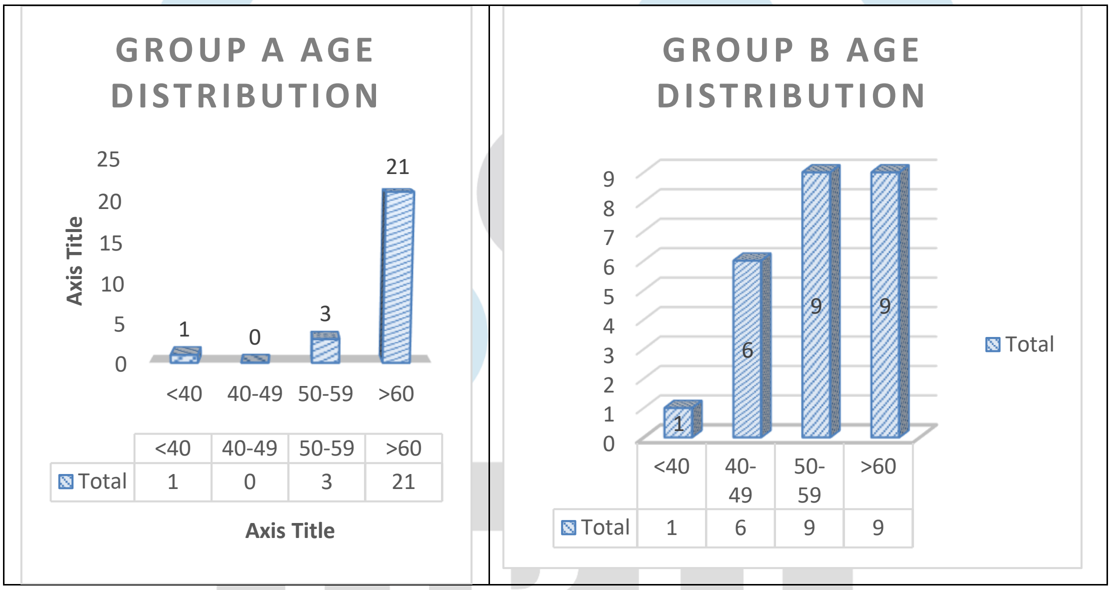
To compare the safety and effectiveness by assessing patient glucose level, demographic details, dose,frequency,Adverse effect in both the groups i.e., group A(Metformin glimepiride) and group B(Metformin vildagliptin) of randomized patients are mentioned below.

In Age wise distribution of patients is summarized in Table 1 and Figure 1. In Group A, the mean average age was 64.12 and in Group B, the mean average age was 55.84.patients of age more than 60 years are more prone to diabetes than other groups and lesser in 40 years of age group.

TABLE-1 AGE WISE DISTRIBUTION OF CASES

AGE GROUP	GROUP A N=25(%)	GROUP B N=25(%)	TOTAL N=50(%)
<40	1(4)	1(4)	2
40-49	0(0)	6(24)	6
50-59	3(12)	9(36)	12
>60	21(84)	9(36)	30
Average	64.12	55.84	

FIGURE-1 AGE WISE DISTRIBUTION OF CASES

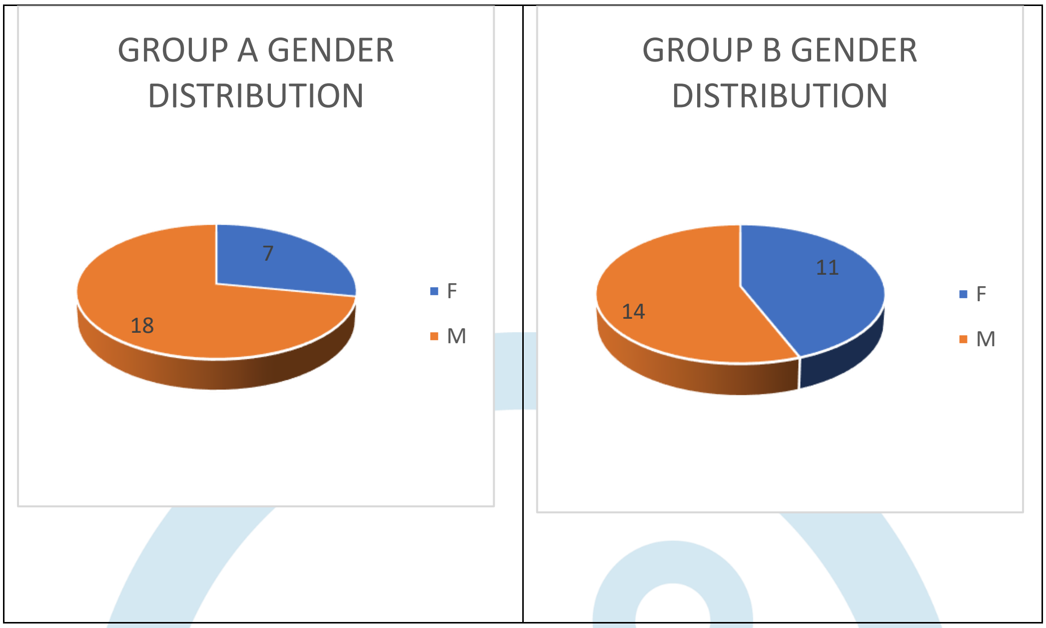


Among 50 patients, out of 25 patients belonging to Group A, 7 were male, 18 were female. Out of 25 patients belonging to Group B,11 were male, 14 were female. It has been shown in Table 2 and figure 2. Female patients are more prone to diabetes compare to the Male patients.

TABLE-2 GENDER WISE DISTRIBUTION OF CASES

GENDER	GROUP A N=25(%)	GROUP B N=25(%)	TOTAL
MALE	7(28)	11(44)	18
FEMALE	18(72)	14(56)	32

FIGURE-2 GENDER WISE DISTRIBUTION OF CASES

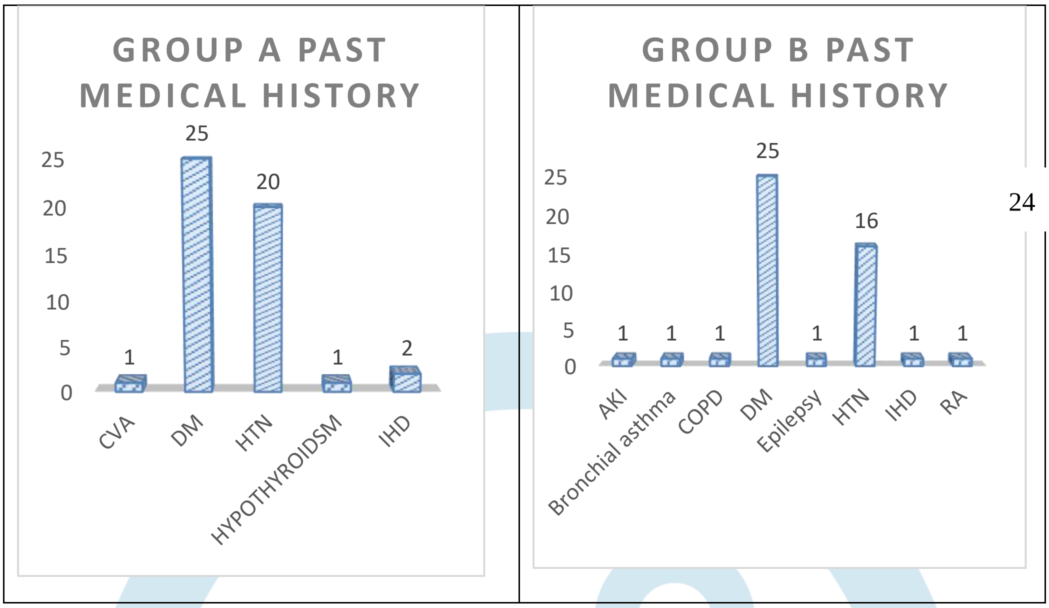


In Table 3 and Figure 3 shows the past medical history wise distribution of cases. In Group A out of 25 patients, 20(80%) patients were found to have past medical history of HTN, 1(4%) had past medical history of CVA,1(4%) had past medical history of Hypothyroidism whereas 2(8%) had past medical history of IHD. In Group B out of 25 patients,25(100%) had past medical history of DM,1(4%) had past medical history of AKI,1(4%) had past medical history of Bronchial Asthma,1(4%) had past medical history of COPD,1(4%) had past medical history of epilepsy,16(64%) had past medical history of HTN,1(4%) had past medical history of IHD whereas 1(4%) had past medical history of RA.

TABLE-3 PAST MEDICAL HISTORY WISE DISTRIBUTION OF CASES

PAST MEDICAL HISTORY	GROUP A N=25 (%)	GROUP B N=25 (%)
AKI	0(0)	1(4)
Bronchial asthma	0(0)	1(4)
COPD	0(0)	1(4)
CVA	1(4)	0(0)
EPILEPSY	0(0)	1(4)
HTN	20(80)	16(64)
HYPOTHYROIDSM	1(4)	0(0)
IHD	2(8)	1(4)
RA	0(0)	1(4)

FIGURE-3 PAST MEDICAL HISTORY WISE DISTRIBUTION OF CASES

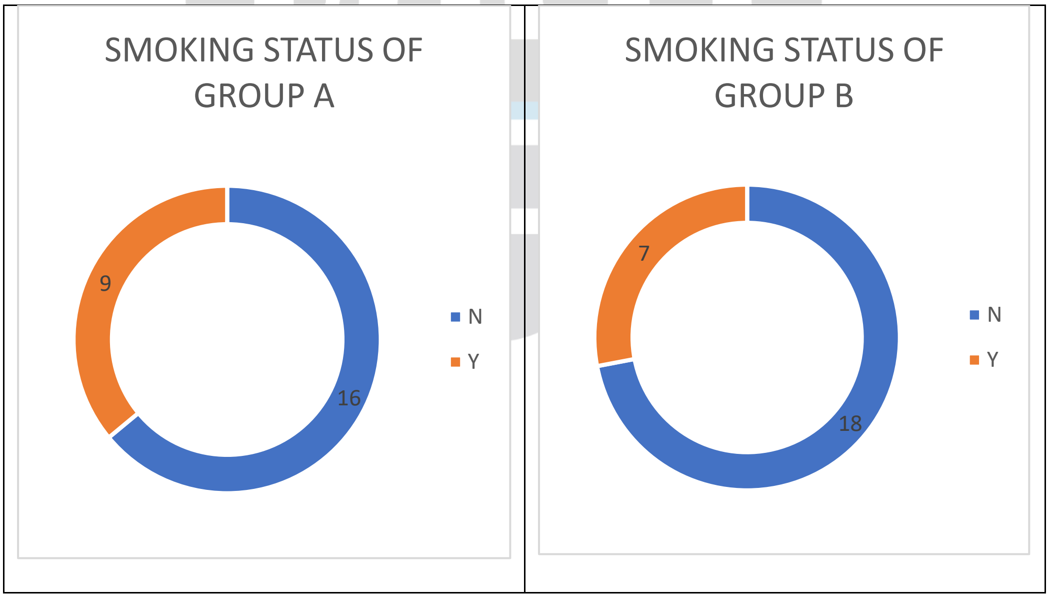


In Table 4 and Figure 4 shows Smoking status wise distribution of cases. In Group A,9(36%) were smokers and 16(64%) were Non smokers.In Group B, 7(28%) were Smokers and 18(72%) were Non smokers.More smokers are seen in Group A than the Group B.

TABLE-4 SMOKING STATUS WISE DISTRIBUTION OF CASES

SMOKING STATUS	GROUP A N=25 (%)	GROUP B N=25 (%)	TOTAL
SMOKER	9(36)	7(28)	16
NON-SMOKER	16(64)	18(72)	34

FIGURE -4 SMOKING STATUS WISE DISTRIBUTION OF CASES

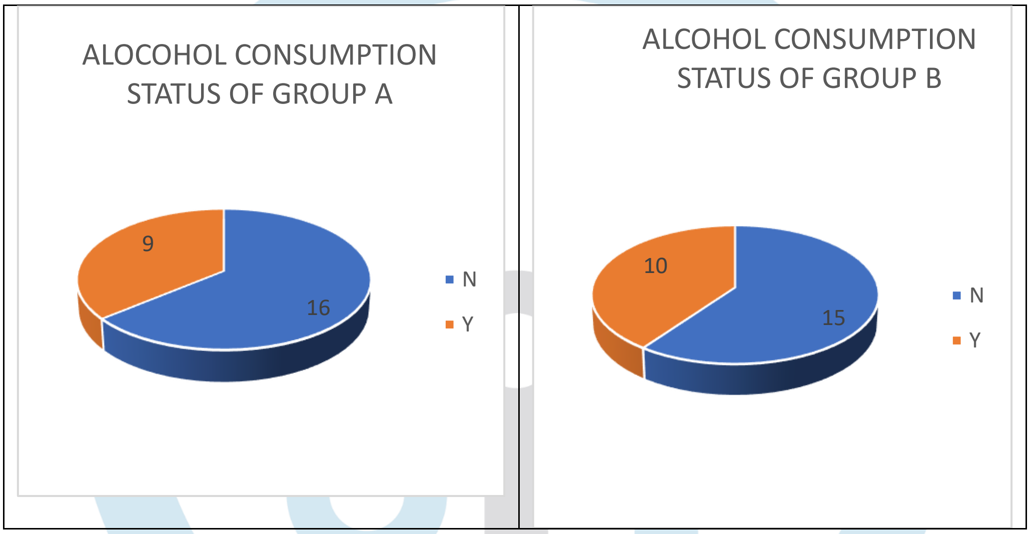


In Table 5 and Figure 5 shows the Alcoholic status wise distribution of cases. In Group A 9(36%) were Alcoholic and 16(64%) were Non Alcoholic. In Group B 10(40%) were Alcoholic and 15(60%) were Non Alcoholic. More Alcoholic prone are seen in Group A compare to Group B.

TABLE-5 ALCOHOL CONSUMING STATUS WISE DISTRIBUTION OF CASE

ALCOHOL CONSUMPTION STATUS	GROUP A N=25 (%)	GROUP B N=25 (%)	TOTAL
ALCOHOLIC	9(36)	10(40)	19
NON ALCOHOLIC	16(64)	15(60)	31

FIGURE- 5 ALCOHOL CONSUMING STATUS WISE DISTRIBUTION OF CASES

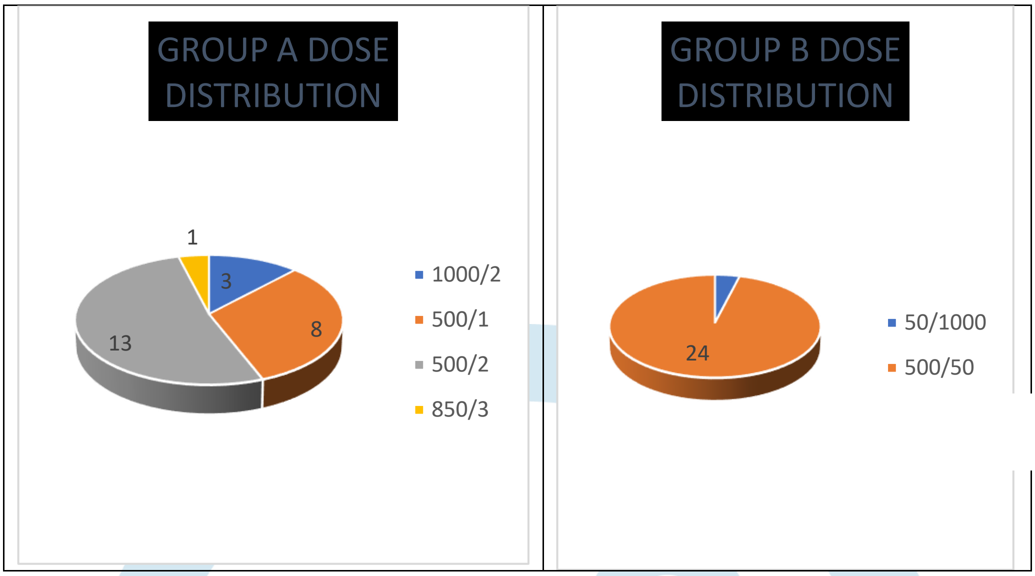


In Table 6 and Figure 6 shows the dose wise distribution of cases between the two groups.

TABLE 6- DOSE WISE DISTRIBUTION OF CASES

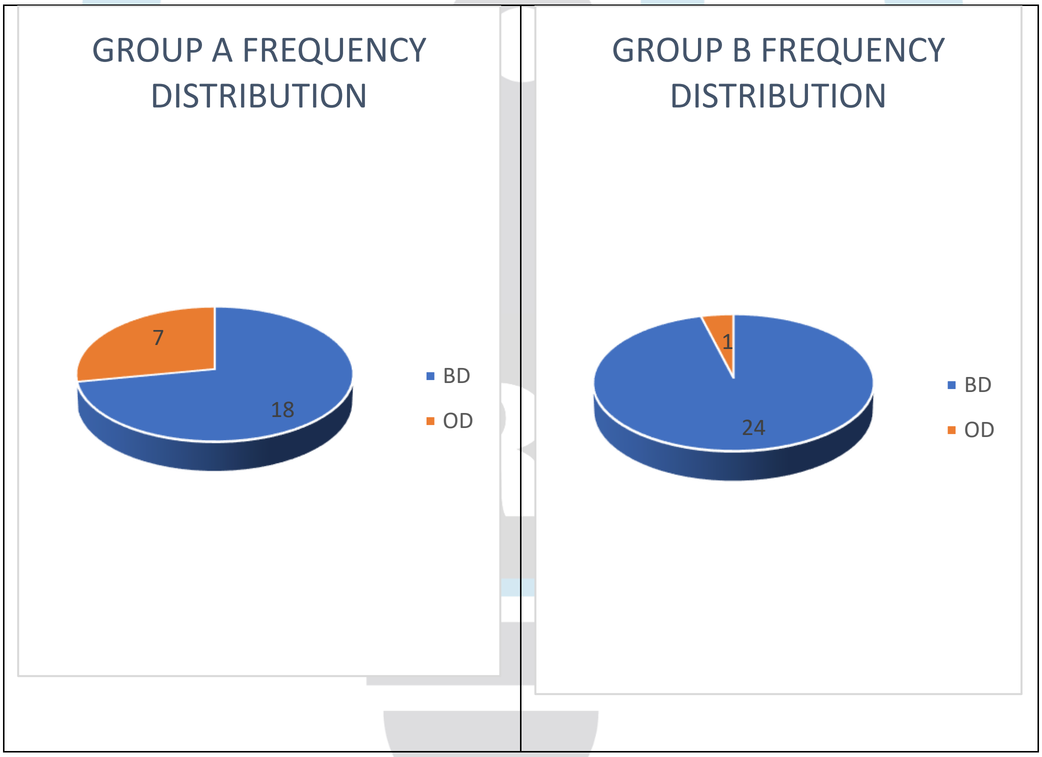
GROUP	DRUGS AND DOSE		FREQUENCY N=25(%)
GROUP-A	METFORMIN GLIMEPIRIDE	1000/2	3(12)
		500/1	8(32)
		500/2	13(52)
		850/3	1(4)
GROUP-B	METFORMIN VILDAGLIPTIN	1000/50	1(4)
		500/50	24(96)

FIGURE 6-DOSE DISTRIBUTION WISE OF CASES



In Table 7 and Figure-7 shows the frequency wise distribution of cases between the two groups.In Group A,18(72) are on BD Frequency and 7(28) are on OD frequency.In Group B 24(96) are on BD frequency and 1(4) are on OD frequency.

FIGURE-7 FREQUENCY WISE DISTRIBUTION OF CASES



In the present study, Table 8,9,10 shows the glucose Triad's levels were compared between the group for group A on admission was found to be 146.4 ± 53.58 and for group B 173.6± 55.647 was found to be with P value 0.0847.On discharge for group A FBS level were 144.36 ± 53.65 and group B 168.72 ±48.266 with P value0.0979 respectively. Within the group FBS for group A on admission and discharge was found to be be 146.4 ± 53.58 and 144.36 ± 53.65.P value was found to be 0.8936.For group B FBS level on admission and discharge was found to be 173.56 ±55.647 and 168.72 ±48.266 with P value was found to be 0.743 respectively.

When RBS levels were compared between the group for group A on admission was found to be 206.95 ± 62.01 and for group B was found to be 223.68± 66.1 with P value 0.3607, and on Discharge for group A RBS level were 191.88 ±

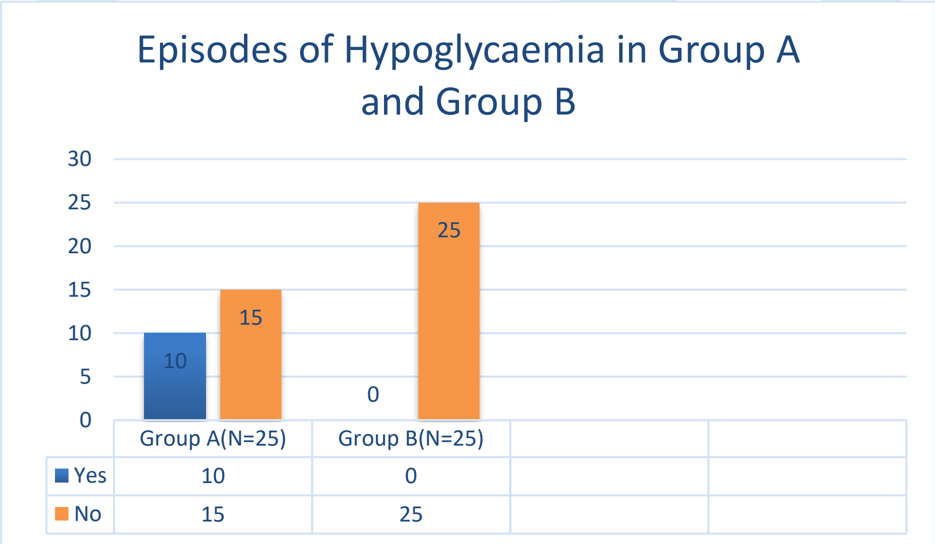
40.43 and group B 219.16 ± 69.553 with P value0.0965 respectively. Within the group RBS for group A on admission and discharge was found to be 206.95 ± 62.01 and 191.88 ± 40.43 with P value was found to be 0.319 respectively .For group B RBS level on admission and discharge was found to be 223.68 ±66.1 and 219.16 ±69.553 with P value was found to be <00001 respectively.Between the groups in Group A,HBA1c was found to be 8.992 ± 1.68 and for group B HBA1C was found to be 10.316±2.058.P value was found to be 0.0162There was significant reduction in both groups .These study result are similar with the study conducted by *Nishant t et al.*

In table 11 and Figure shows the episodes of hypoglycemia in both Groups

TABLE 11.COMPARISON OF EPISODES OF HYPOGLYCAEMIA IN BOTH GROUPS

Episodes of Hypoglycemia	Group A(N=25)	Group B(N=25)
Yes	10	0
No	15	25

FIGURE 11.COMPARISON OF EPISODES OF HYPOGLYCAEMIA IN BOTH GROUPS



Discussion

Diabetes is a complicated, long-term ailment that is a major global health concern as well as one in India. Diabetes is the most difficult patient to treat since it progresses over time and causes more and more problems with antidiabetic medication. As treatment with a single oral hypoglycemic drug frequently results in suboptimal outcomes, many individuals with type 2 diabetes require more than two of these medications. An ideal strategy for managing diabetes early on would be combination therapy. The combined treatments work well to reduce side effects and the dosage of antihyperglycemic medications. Therefore, comparing the effectiveness of vildagliptin with metformin and glimepiride was the goal of the current investigation.

In the present study The demographic and clinical measurements in both the groups i.e., group A(Metformin glimipiride) and group B(Metformin vildagliptin) of randomized patients are mentioned below.

Demographic Characteristics of the Study Subjects: During 6 months period a total of 50 cases were collected and analysed. Age distribution of patients is summarized in Table 1 and Figure 1. In Group A, the mean average age was 64.12.In Group B, the mean average age was 55.84.Among 50 patients, out of 25 patients belonging to Group A, 7 were male, 18 were female. Out of 25 patients belonging to Group B,11 were male, 14 were female. It has been shown in

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In the present study ,Table 8,9,10 shows the glucose triad.Between the groups in Group A,HBA1c was found to be 8.992 ± 1.68 and for group B HBA1C was found to be 10.316±2.058.P value was found to be 0.0162There was significant reduction in both groups .These study result are similar with the study conducted by Nishant t et al.

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CONCLUSIONS

American Diabetic Association guidelines have recommended Metformin as first line drug to be used in type II Diabetes mellitus patients. If there is glycemic variability with Metformin, add-on drugs like Sulphonylureas, DPP-4 Inhibitors or other OHA's or insulin to be considered depending on the clinical scenario.

Sulphonylureas are one of the most potent oral antidiabetic agents. Due to good efficacy, safety, and cost-effectiveness, Sulphonylureas, especially modern ones like Glimepiride, are the most preferred first add-on to Metformin in Indian clinical settings.It has dual mode of action – reduces insulin resistance and improves glucose utilization through glucose transporter -4 resulting in potent glycemic reduction with minimal risk of hypoglycemia or weight gain. Dipeptidyl peptidase inhibitors are a well-established class of oral agents having moderate efficacy with a good overall safety profile including low risk of hypoglycemia and weight neutrality.Hence the study concluded that both groups work effectively in a same manner.Metformin vildagliptin appeared to be equally effective to that of metformin glimepiride and it resulted in better adverse event profile with lower risk of hypoglycemia

Limitation:

- As the sample size is small, the inference of the study has limited value.
- Duration of study and Sample size was not enough for single centered study and validity would be more if it is Multi centered Study
- The study was carried out in Inpatient department and not involved Outpatients with Type 2 Diabetic mellitus.

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