Bioscene

Bioscene
Volume- 21 Number- 02
ISSN: 1539-2422 (P) 2055-1583 (O)
www.explorebioscene.com

Safety and Effectiveness of Dual Anti-Diabetic Therapy and its Clinical Outcome in Type Ii Diabetes Mellitus Patients: A Comparative Observational Study

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Abstract

Background and Objective: Combination of antidiabetic therapies were seen to be common in day-to-day life. This study was conducted to assess the effectiveness, safety and factors affecting clinical outcomes of dual antidiabetic therapy (Metformin + Vildagliptin & Metformin + Sitagliptin). **Methods:**This was a prospective longitudinal study carried out among Type 2 Diabetes patients in NIMS Hospital, Trivandrum for a period of 6 months which included data collection and follow up. The 112 subjects were classified based on inclusion and exclusion criteria out of which 7 subjects were lost to follow up hence a total of 105 patients were included in the study. **Results:**Combination of drugs (Metformin + Vildagliptin and Metformin + Sitagliptin) was found to be more prescribed in the age group of 52 to 59 years (41.5 %) and 60 to 69 (32.7%). The gender wise distribution was higher in females on both groups (62.9%). After 2 month treatment among the study variables HbA1C, PPBS, Total cholesterol, LDL, showed a statistical significant difference ($p < 0.05$). Metformin plus Vildagliptin (Group A) showed a significant reduction of HbA1C ($p= 0.01$), from baseline to follow up, whereas Metformin plus Vildagliptin (Group B) also showed a reduction in HbA1C ($p= 0.08$). Group A showed a significant reduction of PPBS ($p= 0.31$),LDL ($p= 0.21$) and T. Cholesterol ($p= 0.57$), from baseline to follow up, whereas Group B also showed a reduction ofPPBS ($p= 0.01$)LDL ($p= 0.01$)andT. Cholesterol ($p= 0.01$). No statistical significant difference was observed between both groups for Fasting Blood Sugar, Body weight, BMI,

Blood Pressure, Very Low Density Lipoproteins, High Density Lipoproteins, Triglycerides, eGFR, Urine Albumin Creatinine Ratio, Sr. Creatinine, Uric acid, Urine albumin and Urine creatinine. Tiredness was the most commonly reported adverse events in both groups. Adverse events include hypoglycemia, headache and UTI. Weight and comorbidities became a factor that can influence the efficacy of treatment in both groups (p=0.03 and p=0.04). **Interpretation and Conclusion:** Safety and effectiveness of Metformin with Vildagliptin and Metformin with Sitagliptin has identical characteristics. It can be concluded that both the combination of drugs were having same efficacy and safety in Type II Diabetic patients.

Key words: Type II Diabetes Mellitus, Safety, Effectiveness, Vildagliptin, Sitagliptin, Metformin, HbA1C

Introduction

Type II Diabetes Mellitus is a common multifactorial genetic syndrome, which is determined by several different genes and environment factors [(1)]. In Type II Diabetes Mellitus this mechanism breakdown, with the consequence that the two main pathological defects in Type II Diabetes are impaired insulin secretion through a dysfunction of the pancreatic beta cell and impaired insulin action through insulin resistance[(2)].Type II Diabetes Mellitus usually shows symptoms like frequent urination polyuria, polydipsia, polyphagia, weight loss, tiredness, blurred vision, wounds that are slow to heal, common infections and tingling at the extremities. Prevalence of Type II Diabetes Mellitus is contributed by interaction of risk factors which include combination of genetic, environment and metabolic factors. Type II Diabetes Mellitus has different complications, both microvascular and macro vascular complications. The American Association of Clinical Endocrinologist (AACE)/American College of Endocrinology (ACE) [(3)] and the American Diabetic Association (ADA) [(4)] Support a stepwise, progressive approach to pharmacotherapy. The recommended initial Type II Diabetes Mellitus management approach include lifestyle changes and monotherapy (usually with metformin) [(3 & 4)].

In our study we observed combination of antidiabetic drugs; Metformin + Vildagliptin and Metformin + Sitagliptin. The Vildagliptin and Metformin combination had seen to be favorable for the beta cell function and it shows good safety and tolerability profile in comparison with other antidiabetic agents[(5)].This combination provide superior efficacy to monotherapy treatment and also indicates low risk of hypoglycemia[(6)]. Co administration of Metformin and Sitagliptin improves blood glucose control more than monotherapy with each drug separately and this also helps in preventing hypoglycemia and gastrointestinal side effects [(7)].

Materials and methods

Study design &setting

A Prospective, longitudinal study was conducted from November 2022 to April 2023 for 6 months during which 112 patients of Type 2 Diabetes Mellitus who took Metformin plus Vildagliptin and Metformin plus Sitagliptin combination on the study period were enrolled. The study was conducted among Type II Diabetics in Endocrinology department at NIMS hospital Neyyattinkara, Trivandrum, Kerala, India. Ethical approval was taken from Institutional Ethical Committee dated 12th November 2022. All procedures followed ethical standards on human experimentation i.e., data collection.

Participants

The purposive sampling technique was used to get a sample size of 112 cases. The participants were enrolled based on the inclusion and exclusion criteria. The inclusion criteria include Age between 30 – 80 years, Type II Diabetes Mellitus patients, HbA1c greater than 6.5%, Dual Oral hypoglycemic therapy (Metformin + Vildagliptin and Metformin + Sitagliptin), those who were willing to participate in the study and exclusion criteria include patientstreated with insulin and steroids, history of pregnancy, lactation & gestational diabetes.

Baseline and Follow-Up Assessment

Baseline data were collected and follow up of the patient was done at an interval of 2 months.

Statistical Analysis

All the data were collected in a structured proforma and entered in MS Excel Spreadsheet.Baseline characteristics of the study population were analyzed using descriptive statistics.Changes in variables, factors affecting clinical outcome and adverse events were analyzed using statistical package for social sciences (SPSS) version 23. A p value < 0.05 was considered significant. For categorical variables chi square test was applied and for interval or ratio scale, student's t test was used.

Results

Among the 112 study participants, 7 were lost to follow up and the allocation of study subjects and characteristics is shown below in Figure 1.

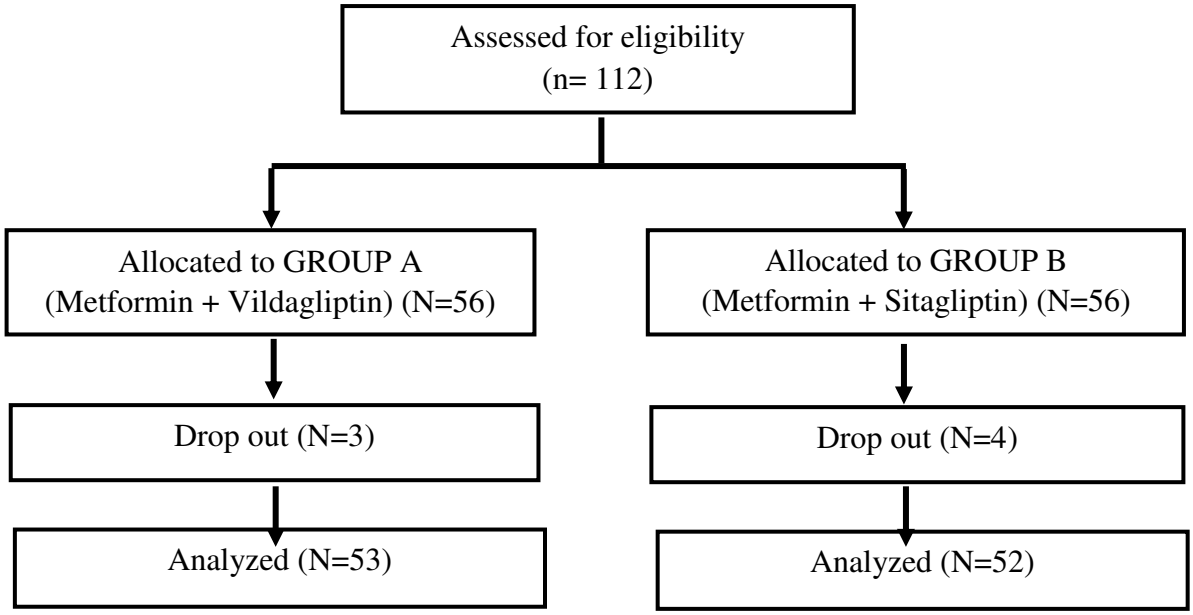

Fig. 1. Allocation of drop out subjects

A total of 105 patients were analyzed during the study. Combination of drugs (Metformin + Vildagliptin and Metformin + Sitagliptin) was found to be more prescribed in the age group of 52 to 59 years (41.5 %) and 60 to 69 (32.7%). The mean age was found to be 56.50 ± 10.5. The gender wise distribution was higher in females on both groups(62.9%). After 2 month treatment among the study variables HbA1C, PPBS, Total cholesterol, LDL, showed a statistical significant difference ($p < 0.05$). Group A showed a significant reduction of HbA1C ($p= 0.01$), from baseline to follow up, whereas Group B also showed a reduction in HbA1C ($p= 0.08$). Group A and Group B showed a significant reduction of PPBS, from baseline to follow up [Group A ($p= 0.31$)&Group B ($p= 0.01$)]. Similarly both groups showed a significant reduction of Total Cholesterol,from baseline to follow up [Group A ($p= 0.57$) & Group B ($p= 0.01$)]. Group A and Group B showed a significant reduction of LDL, from baseline to follow up [Group A ($p= 0.21$) & Group B ($p= 0.01$)]. No statistical significant difference was observed between both groups for FBS, Body weight, BMI, Blood Pressure, Very Low Density Lipoproteins, High Density Lipoproteins, Triglycerides, eGFR, Urine Albumin Creatinine Ratio, Sr. Creatinine, Uric acid, Urine albumin and Urine creatinine. Tiredness was the most commonly reported adverse events in both groups with and average causality assessment of 2.6 ± 0.44. Adverse

events include tiredness, hypoglycemia, headache, UTI. Weight and comorbidity became a factor which can influence the efficacy of treatment in both groups (p=0.03 and p=0.04) respectively for group A + group B.The result of our study shows both the combination of the drugs have equal efficacy and safety profile.

Discussion

The current study highlighted the comparison of effectiveness and safety of dual antidiabetic therapy among Type 2 diabetic mellitus patients.The mean age of group A was found to be 56.30 ± 10.50 and group B was 56.70 ± 10.51. Which was comparable to the study conducted by *Li Zang et al*[8]. In group A, 60.3% were females and 39.6% were males, while in group B 65.3% were females and 34.6% were males. Similar study by *Asima Khan et al* [9], found that women comprised 58.5% of the study population which was comparable tothis study with 62.9% of females. In the baseline data, 27 patients of group A had weight in the range of 60-69kg while in group B 21 patients were in the range of 70-79kg. In the follow up data, 26 patients of group A had weight in the range of 60-69kg while in group B 21 patients of group B were in the range of 70-79kg. The mean weight of the two groups were 66.24 ± 10.46kg.

In thisstudy, group B had higher BMI in baseline as well as in follow up compared to group A.Similar study conducted by *LI Zang* [8]found that BMI was higher infirst group (Vildagliptin and Metformin) 26.4 ± 3.9 kg/m^2 and 25.3 ± 3.4kg/m^2 in second group (Comparator group).Among 105 patients, the most prominent comorbidity was Dyslipidemia (15%), and it was found to be significant (p= 0.04).In this study, group A had higher frequency of dyslipidemia(45.5%), when compared to group B(33.3%) which is followed by hypertension (group B 33.3%) and Nonalcoholic fatty liver disease (NAFLD) (group B 33.3%).Other comorbidities include hypothyroidism and BPH in lesser frequency.

In this study, higher HbA1c was in the range of 6.5-9.0. In the baseline data, 42 patients (79.2%) in of group A was in 6.5-9.0 ranges of HbA1c while in group B it was found to be 37 patients (71.2%). But during follow up, 47 (88.7%) of patients in group A were in 6.5-9.0 and 43 patients (82.7%) in group B.In the range of 9.5-13.0, 11 patients (20.8%) of group A during baseline and 6 (11.3%) patients during follow up were included and in Group B had 15 patients (28.8%) during follow up and 9 patients (17.3%) during follow up were included. Among study participants, in group A during baseline, 34 (64.2%) of patients had ≥ FBS 126mg/dLwhile on follow up it was found to be 38 patients (71.7%). In case of group B, 42 (80.8%) of patients had ≥ FBS 126mg/dLwhile on follow up it was found to be 41 patients (78.8%). When comparing both the groups, Group B had slight reduction in FBS.In the study participants, majority of them were distributed in PPBS≥ 120 mg/dL. In this study, group A during baseline, 45(84.9%) of patients had ≥ PPBS 120mg/dLwhile on follow

up it was found to be 47 patients (88.7%). In case of group B, 51 (98.1%) of patients had ≥PPBS 120mg/dLwhile on follow up it was found to be 49 patients (94.2%).

In this study, most of the patients were distributed inthe total cholesterol value of ≥ 120 mg/dL. Among 105 participants, in group A during baseline, 34 (64.2%) of patients had total cholesterol ≥ 200mg/dLwhile on follow up it was found to be40 patients (75.5%). In case of group B, 27(51.9%) of patients had ≥ 200mg/dLwhile on follow up it was found to be 38 patients (73.1%). When comparing two groups, both the groups had increased the total cholesterol. In this study participants,most of them were distributed in the LDL value of < 100mg/dL. Group A during baseline, 24 (45.3%) of patients had < 100mg/dLwhile on follow up it was found to be 25 patients (47.2%). In case of group B, 17 (32.7%) of patients while on follow up it was found to be 23 patients (44.2%). Majority of them were included in the HDL value of >40mg/dL.

Among the study participants, in group A during baseline, 33(62.3%) of patients had ≥ FBS 126mg/dLwhile on follow up it was found to be 39 patients (73.6%). In group B, 42 (80.8%) of patients had > 40mg/dLwhile on follow up it was found to be 42 patients (80.8%).When comparing both the groups, group A had increased number of patients but in case of group B, there was no change. In the present study, majority of them were distributed in the VLDL value of≤ 30mg/dL. In this study, group A during baseline,36 (67.9%) of patients had ≤30mg/dL while on follow up it was found to be 45 patients (84.9%) and in case of group B, 36(69.2%) of patients had ≤30mg/dL while on follow up it was found to be 34 patients (65.4%). When comparing both the groups, group A had increased the number of patients after follow up. Among the study participants, most of the subjects were included in triglycerides <150mg/dL. At baseline, triglycerides of 35 patients (66%) of group A was in the range of < 150mg/dLbut after the follow up it was 44 patients (83%). In case of group B, 34 of patients (65.4%) were found in baseline and 35 patients (67.3%) during the follow up. When comparing both the groups, triglycerides of group A as well as group B had increased number of patients during follow up.

In this study, eGFR of most of the patients were included in the range of ≥ 90 ml/min in both groups. At baseline, ≥ 90 ml/min ranges of eGFR 30 patients (56.6%) were found in group A but after the follow up it was changed to 36 patients (67.9%). In group B, 31 patients (59.6%) were found in baseline and in follow up 36 patients (69.2%). When comparing both the groups on eGFR, group A had increased number of patient but in case of group B, there was increased number of subject after the follow up. Majority of subjects were in the interval of 140-159 mmHg SBP and interval of 80-89 mmHg DBP. In group A, in baseline 26 (49.1%) ofpatients had BP measurement of 140-159mmHg SBP and during follow up 7 patients (13.3%). And in group B, 23(44.2%) ofpatients had BP measurement of 140-159mmHg SBP and during follow up and17 patients (32.7%). In group A, in baseline 23 (43.4%) ofpatients had

BP measurement of 80-89mmHg DBP and during follow up 26 patients (49.1%). And in group B, 15(28.8%) ofpatients had BP measurement of 80-89mmHg DBP and during follow up and 21 patients (32.740.4%). When comparing both groups, in SBP both groups had reduced the number of patients and in DBP had slight elevation in patient's number which is shown in Table 1.

Table 1:Comparison of effectiveness

Variables	**Baseline**	**Follow Up**	**Mean Changes from Baseline**	**p- Value**
HbA1C (%) Mean ± SD				
Group A	8.40 ± 1.65	7.83 ± 1.37	0.57 ± 0.28	**0.01***
Group B	8.79 ± 1.5	8.63 ± 1.1	0.16 ± 0.4	0.08
FBS (mg/dl) Mean ± SD				
Group A	169.38 ± 56.30	165.58 ± 44.46	3.79 ± 11.84	0.57
Group B	192.56 ± 62.2	184.19 ± 67	8.36 ± -4.8	0.27
PPBS (mg/dl) Mean ± SD				
Group A	195.02 ± 64.42	185.58 ± 54.35	9.43 ± 10.27	0.31
Group B	222.25 ± 61.6	200.83 ± 56.1	21.42 ± 5.5	**0.01***
Body Weight (kg) Mean ± SD				
Group A	64.24 ± 8.20	64.00 ± 8.28	0.24 ± -0.08	0.53
Group B	68.46 ± 11.45	68.07 ± 11.24	0.39 ± 0.21	0.29
BMI (kg/m²) Mean ± SD				
GroupA	24.66 ± 2.90	24.58 ± 3.08	0.08 ± -0.18	0.66
Group B	25.55 ± 4.15	25.43 ± 4.01	0.11 ± 0.14	0.38
Blood pressure (mmHg) Mean ± SD				
GroupA	136/79 ±18.3/13.3	131/77 ±14.7/9	3.63 ± 5	0.28
Group B	144/86 ± 21/14	142/86 ±14.7/11	1.82 ± 3.7	0.44
T. CHOL (mg/dL) Mean ± SD				
Group A	188.40 ± 45.71	183.08 ± 82.2	5.32 ± -36.49	0.57
GroupB	196.98 ± 45.9	183.94 ± 36.6	13.03 ± 9.3	**0.01***
LDL (mg/dL) Mean ± SD				
Group A	106.81 ± 41.10	100.98 ± 36.84	5.83 ± 4.26	0.21
GroupB	114.21 ± 43.6	103.46 ± 36.7	10.75 ± 6.9	**0.01***
VLDL (mg/dL) Mean ± SD				
Group A	26.09 ± 9.06	27.64 ± 11.08	-1.57 ± -2.02	0.27

GroupB	30.81 ± 18.1	30.31 ± 13.7	0.50 ± 4.4	0.62
HDL (mg/dL) Mean ± SD				
Group A	53.94 ± 27.28	52.00 ± 22.29	1.94 ± 4.99	0.29
GroupB	54.37 ± 18.4	52.75 ± 16.1	1.62 ± 2.3	0.38
Triglycerides (mg/dL) Mean ± SD				
Group A	129.34 ± 49.49	129.32 ± 56.79	0.02 ± -7.3	0.99
GroupB	144.92 ± 75	138.50 ± 49.3	6.42 ± 25.7	0.26
eGFR (ml/L) Mean ± SD				
Group A	101.51 ± 29.06	101.40 ± 27.28	0.11 ± 1.78	0.94
GroupB	98.75 ± 21.3	87.71 ± 21.3	1.04 ± 0	0.27
UACR (mg/gm) Mean ± SD				
Group A	28.65 ± 31.81	29.35 ± 36.85	-0.23 ± -5.04	0.92
Group B	84.52 ± 23.13	86.93 ± 24.68	-2.41 ± -1.55	0.15
Serum Creatinine (mg/dL) Mean ± SD				
GroupA	1.42 ± 0.8	1.34 ± 0.70	0.08 ± 0.1	0.40
Group B	0.74 ± 0.16	0.75 ± 0.15	-0.02 ± 0.01	0.09
Uric Acid (mmol/L) Mean ± SD				
Group A	3.98 ± 1.1	4.01 ± 1.0	-0.09 ± 0.1	0.13
GroupB	4.45 ± 1.3	4.54 ± 1.1	-0.34 ± 0.2	0.64
Urine Albumin (µg/ml) Mean ± SD				
Group A	20.12 ± 15.89	18.89 ± 12.49	1.23 ± 3.4	0.33
Group B	21.67 ± 18.0	22.97 ± 18.4	- 1.29 ± 0.4	0.31
Urine Creatinine (µmol/kg) Mean± SD				
Group A	80.06 ± 52.44	80.28 ± 50.35	-0.22 ± 2.09	0.92
Group B	88.72 ± 41.73	86.93 ± 38.29	1.79 ± 3.44	0.15

Throughout the study, mean HbA1c was lower in patients treated with group A (Vildagliptin plus Metformin) than in those treated with group B (Sitagliptin plus Metformin). Mean HbA1C difference was 0.57 ± 0.28 (p= 0.01) in group A and 0.16 ± 0.4 (p= 0.08) in group B.The mean change within the treatment groups for PPBS from the baseline to the follow up was statistically significant in both study groups. Group A showed a reduction in PPBS (p= 0.31), from 195.02 ± 65.77 at base line to 185.5 ± 55.20. Whereas group B showed a reduction in PPBS (p= 0.01), from 222.25 ± 61.58 at baseline to 200.83 ± 56.15 as shown in Table 1.This was similar to *Asima Khan* et al[9], concluded the reduction of PPBS levels.

Group A showed a reduction in cholesterol (p= 0.57), from 188.40 ± 47.18 at base line to 183.08 ± 85.62. Whereas group B showed a reduction in cholesterol (p= 0.01), from 196.98 ± 45.93 at baseline to 183.08 ± 36.63 as shown in Table 1. The mean

change within the treatment groups for cholesterol from the baseline to the follow up was statistically significant in both groups. Among lipid profile a greater mean reduction in LDL value was observed in the group B (10.75 ± 6.89), p= 0.01 than in group A (5.83 ± 4.48), p= 0. 21, which can be found in Table 1 similar study by *Eu Jeong Ku*[10]showed reduction in LDL in one group (Empagliflozin group).

Comparison of safety

Tiredness, headache, UTI and hypoglycemia were the adverse events reported in 5 study participants(Table 2).

Table 2: Comparison of safety

Adverse Events	**Group A (Metformin+Vildagliptin)**		**GROUP B (Metformin+Sitagliptin)**		**p-Value**
	N=10	**%**	**N=10**	**%**	
Tiredness	2	0.2	3	0.3	0.65
Headache	0	0	1	0.1	1.0
Urinary Tract Infection	1	0.1	0	0	1.0
Hypoglycemia	2	0.2	1	0.1	0.56

Safety outcome assessment included reporting of adverse events (AE). In this study, out of 105 patients, 5 patients reported adverse events in both groups. All adverse events were not severe. Tiredness was the most commonly reported AE in both groups with and average causality assessment of 2.6 ± 0.44. Adverse Events include tiredness, hypoglycemia, headache, UTI (Table2).

Vildagliptin and Sitagliptin now been examined in a large number of subjects and shown to be tolerable and safety, both in short term studies and in studies up to one year duration (*Lukashevich V et al*[11], *Kothny W et al*[12], *Scott R et al*[13]).

Factors affecting clinical outcome

In our study, weight can also be considered as a factor which can influence efficacy of treatment in both groups. The mean weight of group A 64.07 ± 8.36 Kg and group B was 68.40 ± 11.89 Kg. The total mean weight calculated as 66.24 ± 10.46 Kg with a statistical significant difference (p value = 0.03).

Medication adherence was calculated by using Medication Adherence Rating Scale (MARS). Scoring scale in MARS include 0-4 (low adherence), 5-7 (medium adherence) and 8-10 (high medication adherence).

Medication adherence is one of the factor which can affect the clinical outcome. The variables selected for medication adherence were age, gender, HbA1C. In group A under the age group 50 to 60 years was having highest adherence and lowest belongs to less than 50 years and group B having highest adherence in the age group of greater than 60 years and low adherence in 50 – 60 years age group. Whereas under the gender distribution, female had higher medication adherence in both study population (Table 4).

Acknowledgement
We acknowledge the expert opinion of Dr.Sasikumar Director of NICER (NIMS Center of Endocrinology and Research), NIMS Medicity for his valuable suggestions.

Financial support and sponsorship: None
Conflicts of Interest: None

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