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Comparing the Safety and Efficacy of Vildagliptin and Dapagliflozin as an Add on Therapy to Metformin in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Metformin is the first-line therapy for type 2 diabetes (T2D). Vildagliptin is a new oral antidiabetic drug that improves pancreatic islet cell reactions to glucose. Dapagliflozin is used with an appropriate diet and exercise plan to control high blood sugar in people with T2D. The combination therapy for T2D needs to be explored to improve the treatment strategy. **Aim:** In this study, we assessed the safety and efficacy of Vildagliptin and Dapagliflozin as an add-on therapy to Metformin in patients with T2D. **Materials and methods:** A Quasi-Experimental study conducted with 109 T2D patients was randomly assigned to Metformin plus Vildagliptin (n=56) or Metformin plus Dapagliflozin (n=53) for six months. Cardiometabolic parameters were collected at baseline and the end of treatment, and adverse events also monitored and recorded. The statistical analyses were performed using Microsoft Excel 2019 software. **Results:** Mean age of patients was 55.62 ± 8.1 years (Males 65.14%). Baseline characteristics did not differ between the two groups. After 6 months of follow-up, HbA1C significantly decreased in both Vildagliptin and Dapagliflozin groups (7.34 ± 0.20 % and 7.80 ± 0.35%, respectively). The systolic and Diastolic blood pressure was observed more or less similar in both treatment groups. Vildagliptin as an add-on therapy to Metformin result in a clinically meaningful reduction in the mean difference in Fasting Blood Sugar (FBS) 58.96 mg/dL and Postprandial blood sugar (PPBS) 104.11 mg/dL without an incidence of hypoglycaemia when compared with Dapagliflozin + Metformin. Vildagliptin with Metformin was observed with no incidence of serious adverse events when compared with Dapagliflozin therapy. **Conclusions:** Vildagliptin as an add-on therapy to Metformin observed more favourable effects on efficacy and safety perspective when compared to Dapagliflozin combination therapy for the treatment of T2DM.

Keywords
Dapagliflozin, Diabetes mellitus, type 2, Metformin, Safety and Efficacy, Vildagliptin.

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INTRODUCTION:

Diabetes is a persistent disease that arises either when the pancreas does not generate sufficient insulin or when the body cannot efficiently use the insulin it generates. Insulin is a hormone that controls blood glucose. Hyperglycaemia, also called raised blood glucose or raised blood sugar, is a general effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, particularly the blood vessels and nerves. [1]

Diabetes mellitus can be classified as Type 1 Diabetes mellitus, Type 2 Diabetes mellitus, Gestational diabetes, Maturity onset of diabetes in young, Neonatal Diabetes mellitus, and Latent autoimmune diabetes in adults. [2]

Diabetes mellitus occurs all through the world but is widespread mainly type 2 diabetes mellitus in developed and developing countries. The occurrence of diabetes has been progressively rising during the last few decades. International Diabetes Federation (IDF) approximates that close to 500 million people worldwide are right now living with diabetes, a number that is predictable to augment by an additional 30% in 2045. Diabetes, jointly with its host of micro and macrovascular difficulties, is an extensive cause of morbidity, Poor quality of life, and early mortality. It is projected that virtually 10% of worldwide all-cause mortality is related to diabetes. [3]

Metformin is one of the most widely prescribed first and second-line oral glucoselowering drugs.[4] It is a biguanide drug that reduces blood glucose levels by diminishing glucose production in the liver, lessening intestinal absorption, and rising insulin sensitivity. Metformin decreases both basal and postprandial blood glucose levels.[5] However, evidence suggests that, within three years of diagnosis, half of the patients with Type 2 diabetes require multiple therapies to achieve the glycaemic targets.[6]

Vildagliptin, a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor, improves glycaemic control by increasing α- and ß-cell responsiveness to glucose. Vildagliptin has also demonstrated a low risk of hypoglycaemia, a major limiting factor with glucose-lowering therapy. [7–8]

Dapagliflozin comes under the category of sodium-glucose co-transporter 2 (SGLT2) inhibitors. It lowers blood sugar by supporting the kidneys to get purge more glucose in the urine. Dapagliflozin is used along with diet and exercise, and sometimes with other medications, to lower blood sugar levels in adults with type 2 diabetes.[9]

This study assessed the efficacy, safety, and tolerability of vildagliptin compared with dapagliflozin, as an add-on therapy, in patients with Type 2 diabetes inadequately controlled with metformin monotherapy over six months.

MATERIALS AND METHODS:

The present Quasi-Experimental Study was conducted in the Department of Endocrinologists in a multi-specialty hospital in Coimbatore located in Tamil Nadu, India. The ethical approval was obtained from the Ethical Committee of the institution with approval number EC/AP/952/07/2022 dated 13th July 2022. The study was conducted for 6 months, from July 2022 to December 2022. Patients were included in the study after obtaining written signed consent from the patients after explaining the nature of the study. The existence of diabetes Mellitus is characterized according to World Health Organization (WHO), by examining capillary blood glucose via glucometer and/or plasma glucose.

We included T2D patients with ages greater than or equal to 18 years, both gender, patient-initiated with Metformin, patients with HbA1c > 7% and < 12%, patients with Body Mass Index (BMI)>20 kg/m2, and patients with estimated Glomerular Filtration Rate (eGFR) > 30ml/min. We excluded patients with Type-I Diabetes mellitus, patients with a recent history of surgery, gestational diabetes, low body mass index, and patients with eGFR < 30ml/min.

This quasi-experimental study included about 120 patients. The enrollment of patients was done based on inclusion criteria. All the demographic data and other baseline details were collected from the patient's record. The combination of Vildagliptin plus Metformin for group A (60 patients) and Dapagliflozin plus Metformin for group B (60 patients) was initiated. Due to practical challenges, we were able to take only 109 patients' follow-up data (Group A – 56 patients, and Group B 53 patients). The follow-up data were collected in the data collection form which includes Systolic and diastolic Blood Pressure, FBS, PPBS, HbA1c, and body weight.

Adverse events of both groups were monitored and recorded. After that, the data were analysed.

Statistical Analysis:

The statistical analyses were performed using Micro Soft excel 2019 software. The p value<0.05 was considered statistically significant. Paired student t-test was used to check the glycaemic variability before and after treatment with both combination therapies.

RESULTS:

In our Quasi-experimental study, a total of 120 T2DM patients were included and randomly assigned to

either combination of Vildagliptin plus Metformin, named group A (60 patients), or Dapagliflozin plus Metformin, named group B (60 patients) based on the inclusion and exclusion criteria. Of these, 109 (90.83%) completed the study (Vildagliptin: n = 56, 93.33%; Dapagliflozin: n= 53, 88.33%).

The patient baseline demographics and baseline characteristics were comparable between both treatment groups which is presented in Table 1. Overall, the mean age of the population was 55.62 ± 8.1 years, with that 70.8% lying in the age group of 50 to 60 years, male participants were dominant (65.14%). Approximately half of the patient population in both the treatment groups was obese (BMI >30 kg⁄m2) and there was little variation in the average duration of Type 2 diabetes (vildagliptin: 2.7 years; gliclazide: 3.1 years).

The baseline mean of HbA1c was 9.2 % in both groups and Systolic and Diastolic blood pressure also comparable. The mean FBS (vildagliptin: 193.28 mg/dL; Dapagliflozin: 188.13 mg/dL) and PPBS ((vildagliptin: 275.52 mg/dL; Dapagliflozin: 254.39 mg/dL) were also analogous in both groups.

Table 1: Patient demographics and baseline characteristics

Variables	Group A Vildagliptin and Metformin (n = 56) (Mean ± SE)	Group B Dapaglifozin and Metformin (n = 53)(Mean ± SE)
Age (years)	54±4.8	56±5.2
Male (n(%))	33 (58.93%)	38 (71.70%)
Female (n(%))	23 (41.07%)	21 (28.30%)
Duration of T2DM(Years)	2.7±1.2	3.1±0.9
HbA1c (%)	9.53 ± 1.94	8.96 ± 1.704
Weight (kg)	70.66 ± 14.33	64.8 ± 14.88
Systolic BP (mmHg)	122.43 ± 14.69	120 ± 11.15
Diastolic BP (mmHg)	77.70 ± 10	78.68 ± 9.05
FBS (mg/dL)	193.28 ± 83.36	188.13 ± 74.44
PPBS (mg/dL)	275.52 ± 93.64	254.39 ± 67.19

The cardiometabolic parameters of both groups, at the endpoint, are presented in Table 2. The mean HbA1c reduction for both groups was significant when compared to the baseline. However, Group A showed more reduction in the mean HbA1c percentage, and the mean change was a 2.19 % reduction from the baseline. A significant reduction of weight has been observed with group B, and at the same time weight neutrality was observed with group A. There is no remarkable change in the Systolic and Diastolic blood pressure when compared to the baseline for both the groups.

There was a remarkable reduction in the FBS in both groups however Group A observed slightly higher efficacy. Even though the level of PPBS from both the groups was observed with a significant change from the baseline, Group A exhibited a highly favorable reduction in the level of PPBS compared to Group B.

Table 2: Mean changes in cardiometabolic parameters at the endpoint

Parameters	Group A Vildagliptin + Metformin (n = 56)			Group B Dapagliflozin + Metformin (n= 53)		
	On admission	Follow up	Change	On admission	Follow up	Change
Weight (kg)					65.77 ± 3.08	−4.04
Systolic BP (mmHg)	122.43 ± 14.69	121.70 ±9.12	−0.73	123.22 ± 11.15	119 .87 ± 9.55	−3.35
Diastolic BP (mmHg)	77.71 ± 10.1	77.82 ± 6.34	+0.11	78.68 ± 9.05	74.11 ± 5.02	−4.57
FBS (mg/dL)	193.28 ± 83.36	134.32 ± 6.60*	−58.96	188.13 ± 74.44	145.68 ± 6.65*	−42.45
PPBS (mg/dL)	275.32 ± 93.64	171.21 ± 4.52*	−104.11	254.39 ± 67.19	195.94 ± 10.85*	−58.45
HbA1c (%)	9.53 ± 1.94	7.34 ± 0.20*	− 2.19	8.96 ± 1.704	7.80 ± 0.35 *	−1.16
	70.66 ± 14.33	70.24 ± 2.65	−0.42	69.81 ± 14.88		

Adverse events were summarized in Table 3. None were reported hypoglycaemic events from either group throughout the study period. Dehydration is a common side effect in both groups. There was no

serious adverse event in Group A. Group B reported the Urinary Tract Infection from a patient and it was treated. And there was no discontinuation due to adverse events or death observed.

Table 3. Incidents of Adverse Events

Parameters	Group A Vildagliptin + Metformin	Group B Dapagliflozin + Metformin
Adverse events	Abdominal pain (3%) Itching in head and arms (6%) Tiredness (7%) Blurred vision (2%) Dehydration (12%) Dizziness (4%)	Nocturia (3%) Loss of appetite (7%) Dehydration (15%)
Serious adverse events	Nil	Urinary Tract Infection (n =1)
Discontinuation due to AEs	Nil	Nil
Deaths	Nil	Nil

DISCUSSION:

In our study, the patient baseline demographics and baseline characteristics were comparable between both treatment groups. Glucose-lowering therapy is concerned with weight gain. Weight neutrality has been observed with the vildagliptin plus metformin group in our study. The same kind of outcome has been observed in vildagliptin trials both in monotherapy and add-on settings. [10 –13]

A significant reduction of weight has been observed with the dapagliflozin plus metformin group. This observation is consistent with a study reported by Bolinder et al 2012. The decrease in body weight is the result of two major effects of SGLT2 inhibition: caloric loss due to glucose excretion and loss of body water due to osmotic diuresis.[14]

There was no remarkable change in the Systolic and Diastolic blood pressure when compared to the baseline for the vildagliptin combination. Smaller decreases from baseline were observed in mean systolic and diastolic blood pressure with dapagliflozin therapy. Our results were consistent with Bailey et al 2013. [15]

After 6 months of treatment, vildagliptin was inferior to dapagliflozin in combination with metformin in achieving HbA1c reduction in patients inadequately controlled with metformin monotherapy. Although both treatments were generally well tolerated, there was a remarkable reduction in the FBS in both groups however, vildagliptin plus metformin was observed with slightly higher efficacy. Even though the level of PPBS from both the groups was observed with a significant change from the baseline, vildagliptin plus metformin exhibited a highly favorable reduction in the level of PPBS compared to Dapagliflozin plus metformin. Regarding safety, none reported hypoglycaemic events from either group throughout the study period. Dehydration is a common side effect in both groups. There was no serious adverse event in Group A. Group B reported the Urinary Tract Infection from a patient and it was treated. And there was no discontinuation due to adverse events or death observed.

The efficacy and safety of vildagliptin as monotherapy and as an add-on or combination with metformin has been demonstrated. [16–17] Therapy with vildagliptin in combination with metformin is a balanced approach as both have complementary mechanisms of action. Metformin reduces hepatic glucose output and improves insulin sensitivity, whereas the DPP-4 inhibitor increases glucagon-like peptide-1 (GLP-1) levels, which stimulate insulin secretion and inhibit glucagon secretion. [18–21] Furthermore, mechanistic studies have suggested that DPP-4 inhibitors such as vildagliptin may be particularly effective when combined with metformin because of its synergistic effect of raising plasma levels of active GLP-1.[22]

Additionally, in prior clinical studies, vildagliptin added to ongoing metformin monotherapy significantly improved fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). These effects were associated with an improvement in measures of B-cell function, no weight gain, and no increase in the incidence of hypoglycemia.[23] A good efficacy and safety profile coupled with a low risk of hypoglycemia could make vildagliptin an appealing option as a glucose-lowering agent.

The durability of type 2 diabetes therapy is typically limited by the natural history of the disease such that the progressive decline in β-cell function superimposed upon insulin resistance restricts the continuing efficacy of interventions that are dependent on insulin production or insulin action.[24] The present study demonstrates the increased glycemic control in the vildagliptin treatment group as add-on therapy with metformin compared to the dapagliflozin for short time use that

is for 6 months of the study period. The low rate of adverse events indicates a favorable tolerability profile that makes vildagliptin an important addition to the treatment strategy. However, a long time study period with a larger population might be done to ensure the safety and efficacy of vildagliptin as an add-on therapy with metformin.

CONCLUSION:

In conclusion, in patients with Type 2 diabetes inadequately controlled with metformin monotherapy, the addition of the vildagliptin provides more favorable HbA1c-lowering efficacy after 6 Months of treatment compared with the addition of over dapagliflozin. By considering a safety perspective vildagliptin does not produce any serious adverse events. This finding has important clinical implications in helping to identify add-on therapy with metformin to efficiently control the glycemic level in type 2 diabetic Mellitus patients.

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