

EFFICACY AND SAFETY OF DIPEPTIDYL PEPTIDASE-4 INHIBITOR COMPARED TO SULPHONYLUREA IN TYPE II DIABETES PATIENTS INADEQUATELY CONTROLLED WITH METFORMIN ALONE

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ABSTRACT

INTRODUCTION

Diabetes is a metabolic disorder marked by high blood glucose levels, and treatment often requires multiple drugs to achieve adequate glycemic control. In individuals with type 2 diabetes mellitus who do not respond to metformin, doctors may prescribe a dipeptidyl peptidase-4 inhibitor or a sulphonylurea as potential add-on therapy. The study was conducted to compare the efficacy and safety of the dipeptidyl peptidase-4 inhibitor with sulphonylurea.

MATERIAL AND METHODS

This was an interventional, comparative study involving 100 type 2 diabetic patients who visited the medicine department at Universal College of Medical Sciences. All the eligible patients were randomly divided into two treatment groups (50 each): Group A (sulphonylurea + metformin) and Group B (dipeptidyl peptidase-4 inhibitor + metformin). Treatment was provided for 18 weeks, and patients were investigated for blood glucose parameters like glycosylated hemoglobin, fasting blood glucose, postprandial glucose at baseline and after 18 weeks of follow-up, and questions regarding adverse reactions. The efficacy of the drugs between the two treatment groups was compared using an independent t-test.

RESULTS

Dipeptidyl peptidase-4 inhibitor plus metformin was found to be superior to sulphonylurea plus metformin in terms of HbA1c-lowering efficacy ($p=0.030$). A total of 13 (26%) patients in the sulphonylurea group reported unpleasant hypoglycemic events, compared to 3 (6%) in the dipeptidyl peptidase-4 inhibitor group ($p=0.006$). Patients treated with sulphonylurea gained weight over 18 weeks, but those on dipeptidyl peptidase-4 inhibitor lost weight ($p=0.043$).

CONCLUSIONS

Compared to sulphonylurea, adding a dipeptidyl peptidase-4 inhibitor to a metformin therapy significantly improves glycaemic control in type 2 diabetic patients who are not well controlled with metformin monotherapy, without producing hypoglycemia or weight gain.

KEYWORDS

Dipeptidyl peptidase-4 inhibitor, Efficacy, Metformin, Sulphonylurea, Type 2 DM.

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INTRODUCTION

Diabetes is a metabolic disorder marked by hyperglycemia, leading to various microvascular and macrovascular complications over time. Type 2 diabetes mellitus (T2DM) is the most common, and it arises when the body becomes insulin resistant or produces insufficient insulin. Although there is no exact statistics on diabetes patients in Nepal, the International Diabetes Federation-South East Region estimated that the prevalence of diabetes in adults was around 4% in 2019.¹ Treatment of T2DM often requires multiple drugs to achieve comprehensive disease control. Metformin is the first-line oral hypoglycemic medication when glycemic control cannot be achieved with lifestyle changes alone.² Sulphonylurea (SU) is the second most widely prescribed treatment category worldwide. SU increases insulin secretion by directly activating β -cells in the pancreas.³ However, the main downside of these medicines is hypoglycemia because of continued stimulation of insulin secretion with falling glucose concentrations.⁴ Another typical side effect is weight gain.⁵

If the cost permits, dipeptidyl peptidase-4 (DPP-4) inhibitor-gliptins are a second-line treatment that slows the inactivation of incretin hormones (glucagon-like peptide-1 and glucose insulinotropic peptides), increasing insulin synthesis and release while suppressing glucagon release.⁶ Furthermore, these DPP-4 inhibitors are well tolerated, with little risk of hypoglycemia and weight gain.⁷ Physicians must often choose between a DPP-4 inhibitor or a SU as prospective add-on alternatives in patients with T2DM inadequately controlled with metformin. Several studies had compared the efficacy and safety of DPP4 inhibitors with SU with mixed results.⁷⁻⁹ This study was conducted to compare the efficacy and safety of combined metformin and DPP-4 inhibitor with combined metformin and SU in Nepalese individuals with type 2 diabetes mellitus who had insufficient glycemic control when treated with metformin alone.

MATERIAL AND METHODS

The present study was an interventional, comparative study conducted among type 2 diabetic patients in the medicine department of Universal College of Medical Sciences-Teaching Hospital (UCMS-TH), Bhairahawa from July 2020 to December 2021 for 18 months, after taking approval from the Institutional Review Committee of UCMS-TH (UCMS/IRC/033/20). Patients with type 2 diabetes mellitus who were on metformin medication (≥ 1500 mg/day) at least for the last 3 months and had insufficient glycemic control (HbA1c levels $>7\%$ and $<10\%$) were included in the study. Patients were informed that their participation was voluntary, and written consent was taken.

The minimum number of participants per group was 25, calculated by applying the formula,

$$\text{Patient per group} = \frac{P1(1-P1)+P2(1-P2)}{(P2-P1)^2} \times (Z\alpha + Z\beta)^2$$

P1= assumed proportion that wish to detect in group 1 (Metformin + Sulphonylurea) = 0.42

P2= assumed proportion that wish to detect in group 2 (Metformin + DPP-4 inhibitor) = 0.30⁹

Z α = Z-score value at an alpha level of significance at 95 % confidence interval = 1.96

Z β = At 80% power of the test, the value of Z = 0.84

The calculated sample size was multiplied by 2 (25 X 2 = 50) to compensate design effect of 2. Hence, the final calculated sample size was 50 per group.

All the eligible patients were randomly divided into two groups (50 each): Group A (sulphonylurea + metformin) and group B (DPP-4 inhibitor + metformin). The standard dose of DPP-4 inhibitor (sitagliptin 100mg/day) and sulphonylurea (glimepiride 1mg/day) was added to the background metformin therapy (≥ 1500 mg/day) as an add-on. Treatment was provided for 18 weeks, and patients were contacted for a follow-up appointment. All of the patients were investigated for glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), and postprandial glucose (PPG) at baseline and after 18 weeks of follow-up, as well as adverse medication effects such as hypoglycemia and weight gain. The collected data was entered and coded in Microsoft Excel, then further analyzed after exporting to Statistical Package for the Social Sciences version 20. An independent t-test was used to compare the efficacy of the drugs and body weight change between two treatment groups whereas a dependent t-test was used for the comparison of the same within the group. A Chi-square test was used for the association of hypoglycemia as an adverse drug reaction. A p-value of less than 0.05 is considered statistically significant at a 95% confidence interval.

RESULTS

In both treatment groups, most individuals were between the ages of 41-60. The Sulphonylurea group had 27 (54%) male and 23 (46%) female patients, while the DPP-4 inhibitor group had 20 (40%) male and 30 (60%) female patients. Table 1 summarizes the baseline body weight and blood glucose values.

Table 1. Baseline parameters

Characteristics	Metformin + SU (n=50)	Metformin + DPP4-I (n=50)
Age (years), n (%)		
21-40	6 (12)	4 (8)
41-60	31 (62)	34 (68)
Above 60	13 (26)	12 (24)
Sex, n(%)		
Male	27 (54)	20 (40)
Female	23 (46)	30 (60)
Body weight (kg), Mean \pm SD	71.22 \pm 7.57	72.96 \pm 9.85
Blood glucose parameters (Mean\pmSD)		
HbA1c (%)	7.92 \pm .039	8.05 \pm 0.62
Fasting blood glucose (mg/dl)	155.39 \pm 33.03	163.48 \pm 28.77
Postprandial blood glucose (mg/dl)	231.40 \pm 51.16	248.22 \pm 56.14

SU: Sulphonylurea, DPP-4 I: Dipeptidyl peptidase inhibitor, HbA1c: Glycosylated hemoglobin

Both treatment groups significantly improved their HbA1c, FBG, PPBG, and weight from baseline ($p < 0.001$). There was a reduction in participants' body weight after 18 weeks in the DPP-4 inhibitor group, as compared to the weight gain in the Sulphonylurea group (Table 2).

Table 2. Efficacy parameters

Parameters (Mean±SD)	Treatment group	Baseline	After 18 weeks	p-value
HbA1c (%)	M+SU	7.92±0.39	7.27±0.38	<0.001*
	M+DPP4-I	8.05±0.62	7.04±0.60	<0.001*
FBG (mg/dl)	M+SU	155.39±33.03	135.66±23.30	<0.001*
	M+DPP4-I	163.48±28.77	141.28±19.94	<0.001*
PPBG (mg/dl)	M+SU	231.40±51.16	170.80±27.82	<0.001*
	M+DPP4-I	248.22±56.14	179.44±34.69	<0.001*
Weight (kg)	M+SU	71.22±7.57	74.28±7.46	<0.001*
	M+DPP4-I	72.96±9.85	70.66±10.02	<0.001*

Dependent t-test, *Significant. M: Metformin, DPP4-I: Dipeptidyl peptidase inhibitor, SU: Sulphonylurea, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, HbA1c: Glycosylated hemoglobin

The baseline HbA1c, FBG, PPBG, and body weight did not differ significantly across the treatment groups ($p=0.05$). Similarly, after 18 weeks, the difference in FBG and PPBG reduction between the two groups was not statistically significant ($p > 0.05$). However, compared to the Sulphonylurea group, the DPP-4 inhibitor group had a considerably higher ($p=0.030$) mean reduction in HbA1c after 18 weeks (Table 3).

Table 3. Efficacy parameters

Parameters (Mean±SD)	Follow up (weeks)	M+SU (n=50)	M+DPP4-I (n=50)	p-value
HbA1c (%)	Baseline	7.92±0.39	8.05±0.62	0.240
	After 18 weeks	7.27±0.38	7.04±0.60	0.030*
FBG (mg/dl)	Baseline	155.39±33.03	163.48±28.77	0.195
	After 18 weeks	135.66±23.30	141.28±19.94	0.198
PPBG (mg/dl)	Baseline	231.40±51.16	248.22±56.14	0.121
	After 18 weeks	170.80±27.82	179.44±34.69	0.173
Weight (kg)	Baseline	71.22±7.57	72.96±9.85	0.325
	After 18 weeks	74.28±7.46	70.66±10.02	0.043*

Independent t-test, * Significant. M: Metformin, DPP4-I: Dipeptidyl peptidase inhibitor, SU: Sulphonylurea, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, HbA1c: Glycosylated hemoglobin.

A total of 16 subjects reported hypoglycemic symptoms. As seen in table 4, 13 (26%) patients in the sulphonylurea group experienced hypoglycemia, compared to 3 (6%) in the DPP-4 inhibitor group, which is statistically significant ($p=0.006$).

Table 4. Experience of hypoglycemia as an adverse drug reaction

	M+SU (n=50)	M+DPP4-I (n=50)	p-value
Hypoglycemic symptoms (%)	13 (26)	3 (6)	0.006*

Chi-square test, *Significant. M: Metformin, DPP4-I: Dipeptidyl peptidase inhibitor, SU: Sulphonylurea

DISCUSSION

In this prospective comparative study conducted at UCMS-TH in type 2 diabetic patients over an 18-week treatment period, the add-on efficacy and safety of dipeptidyl peptidase-4 Inhibitor in lowering plasma blood glucose was compared to that of sulphonylurea in patients with inadequate glycaemic control on metformin monotherapy.

The major goal of treatment is to maintain glycemic control by keeping the HbA1c level below 7% to reduce the risk of microvascular and macrovascular problems without putting patients at risk of hypoglycemia. Metformin, coupled with lifestyle adjustments, should be considered a first-line medication in patients with type 2 diabetes, according to the American Diabetes Association guidelines. If first-line therapy fails to control diabetes, drugs such as insulin, sulphonylureas, thiazolidinediones, gliptins, GLP-1 analogs, or gliflozins may be used.¹⁰

Sulphonylureas remain a cornerstone in treating type 2 diabetes, despite the recent approval of numerous novel categories of anti-diabetic medicines. In our clinical settings, Sulphonylureas, particularly glimepiride, are the most preferred first add-on to Metformin due to their efficacy, safety, and economical.¹¹ However, sulphonylureas like glimepiride produce pharmacologically active metabolites, which may prolong the duration of action and raise the risk of hypoglycemia.¹² In addition, Sulphonylureas can lose their effectiveness over time and cause an increase in body weight.⁵

As a result, new alternative therapies are being investigated. GLP-1 is a hormone that promotes insulin secretion, lowers glucagon secretion, enhances beta-cell activity, and slows stomach emptying in response to hyperglycemia. GLP-1 production is decreased in type 2 diabetic patients. DPP-4 quickly degrades GLP-1 after it is generated. The bioavailability of the GLP-1 hormone is prolonged by inhibiting the enzyme with DPP-4 antagonists, such as sitagliptin.¹³ DPP-4 inhibitors are a novel family of medications that aid with glucose homeostasis by enhancing the action of endogenous incretin without increasing the risk of hypoglycemia and weight gain.¹⁴

Our study result showed that sulphonylurea and DPP-4 inhibitor significantly ($p < 0.001$) lowered HbA1c, FBG, PPBG after 18 weeks. However, the DPP-4 inhibitor was superior to sulphonylurea in terms of HbA1c-lowering efficacy ($p=0.030$). The prior studies comparing glimepiride and Sitagliptin as an add-on to metformin have found similar outcomes. Patients who received sitagliptin add-on to

Metformin had a higher HbA1c reduction and a lower chance of insulin initiation than those who received sulphonylurea.¹⁵⁻¹⁸ Incretin-based treatments, such as GLP-1 agonists and DPP-4 inhibitors, are particularly successful in Asian type 2 diabetic patients.¹⁹ A higher HbA1c reduction could have been related to a decrease in hypoglycemia episodes and, as a result, a significant reduction in defensive eating behavior.

Studies by Srivastava S et al⁸ and Devarajan TV et al⁹ had opposite findings. The combination of glimepiride and metformin showed a substantial reduction in Glycemic parameters compared to sitagliptin and metformin. But secondary glycemic end measures such as FBG and PPBG showed no statistically significant changes, in parallel with the findings of the studies.^{16,20}

There was a clinically significant difference ($p=0.006$) in the percentage of patients reporting hypoglycemia: 26% of patients in the sulphonylurea group reported unpleasant hypoglycemic events, compared to 6% in the DPP-4 inhibitor group. In previous head-to-head trials, sitagliptin was found to have a much-decreased incidence of hypoglycaemic episodes compared to sulphonylureas like glimepiride when added to metformin monotherapy.^{7,8}

Dipeptidyl peptidase-4 (DPP-4) inhibitors, unlike indiscriminate insulin secretagogues like SUs, regulate glucose-dependent insulin release and are therefore not likely to induce hypoglycemia. Furthermore, the DPP-4 inhibitor has been demonstrated to preserve glucagon counter-regulation during hypoglycemia.²¹ Aside from an increased risk of hypoglycemia in patients taking glimepiride, both sitagliptin and glimepiride were generally well tolerated.

There was also a significant difference in weight gain between the therapy groups ($p=0.043$). Patients on stable dosages of metformin treated with glimepiride gained weight over 18 weeks, but those on sitagliptin lost weight, supported by the studies. In addition to being antihyperglycemic, incretins also lower gastrointestinal motility, which, along with enhanced satiety, results in weight loss.²² DPP-4 inhibitors have the edge over other oral glucose-lowering medications such as sulphonylureas in weight loss and considerable improvement in glycaemic control.⁷

DPP-4 inhibitors are relatively new medications, and their cost remains a barrier to their widespread usage, especially in developing countries like Nepal. Glycemic control improvements may minimize the risk of diabetes-related complications, and when combined with a lower risk of hypoglycemia, DPP-4 Inhibitors may offer considerable health-economic benefits over sulphonylureas.

The limitation of the current study is that it included 50 patients in each group; thus, a bigger cohort and longer follow-up beyond 18 weeks are needed to determine the safety and efficacy of the treatment. Under the therapeutic group of SU and DPP-4 inhibitors, a single medicine and standard dose (sitagliptin 100 mg/day and glimepiride 1 mg/day) was employed. Another limitation is that the study examines two

classes of drugs with different mechanisms of action: SU and DPP-4 inhibitor.

CONCLUSION

The findings of this trial suggest that adding a dipeptidyl peptidase-4 inhibitor to a metformin therapy significantly improves glycaemic control in type 2 diabetic patients who are not well controlled with metformin monotherapy, without producing hypoglycemia or weight gain, compared to sulphonylurea.

CONFLICT OF INTEREST

None.

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