ORIGINAL ARTICLE

A Study on Safety and Efficacy of Sodium-glucose Cotransporter-2 Inhibitors as Adjuvant to Insulin Add-on Therapy in Uncontrolled Type 2 Diabetic Patients

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Abstract

Introduction: Inhibitors of sodium-glucose cotransporter-2 (SGLT-2) are proposed as a novel approach for the management of type 2 diabetes mellitus. SGLT-2 inhibitors have major advantages in terms of reducing HbA1c, blood sugar levels, body weight, and blood pressure and may potentially reduce the cardiovascular (CV) risk. The objective of the study is to assess the safety and efficacy of SGLT-2 inhibitors as an adjuvant to insulin add-on therapy in uncontrolled type 2 diabetic patients. **Materials and Methods:** The study was conducted in 100 patients with uncontrolled type 2 diabetes mellitus. 50 patients were received SGLT-2 inhibitor add-on therapy with gliclazide-metformin and insulin, and remaining 50 patients were received insulin add-on therapy with gliclazide metformin. The changes in fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), weight, body mass index (BMI), blood pressure, and CV risk of diabetic patients before the initiation of add-on therapy and after 6 months follow-up were measured. Diabetes-related complications such as foot ulcer, hypoglycemic episodes, and urinary tract infections were documented. **Results:** Patients on SGLT-2 inhibitors as adjuvant to insulin add-on therapy show better glycemic control, reduction in weight, BMI, blood pressure, and CV risk. In patients with SGLT-2 inhibitors add-on therapy, these were changes from baseline HbA1c (2.333%), FBS (82.97 mg/dL), and BMI (2.049 kg/m^2). In hypertensive patients, mean reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) was 15.12 mmHg and 6.40 mmHg, respectively. In non-hypertensive patients, mean reduction in SBP and DBP was 7.60 mmHg and 1.88 mmHg, respecively. The mean CV risk reduction was 6.046%. Among 50 patients, 3 developed urinary tract infection (UTI) and 1 developed hypoglycemia. In insulin add-on therapy patients, these were changes from baseline HbA1c, FBS, and BMI 1.029%, 39.98 mg/dL, and −1.584 kg/m^2, respectively. In hypertensive patients, SBP was 10.84 mmHg and DBP was 4.120 mmHg, and in non-hypertensive patients, mean reduction in SBP and DBP was −3.080 mmHg and −3.36 mmHg. The mean CV risk reduction was 0.866%. Of 50 patients, 5 developed UTI, 9 developed hypoglycemia, and 3 developed foot ulcer. **Conclusion:** SGLT-2 inhibitors are safe and effective for treatment in uncontrolled T2DM. The use of SGLT-2 inhibitors is very effective in glycemic control (reduction in HbA1c and FBS). The non-glycemic effects of SGLT-2 inhibitors include reduction in weight, BMI, and blood pressure. Therefore, glycemic and non-glycemic benefits contribute to an overall reduction in CV risk.

Key words: Diabetes mellitus, glycemic benefits, non-glycemic benefits, sodium-glucose cotransporter-2 inhibitor

INTRODUCTION

Diabetes mellitus continues to be a major non-communicable disease with global burden. Patients with diabetes have twice the risk for death than those without diabetes. Better glycemic control will help to reduce the risk of both microvascular and macrovascular complications due to diabetes mellitus. With an increase in the prevalence of uncontrolled type 2 diabetics, newer class of antidiabetic agents such as sodium glucose cotransporter-2 (SGLT-2) inhibitors was introduced. SGLT-2 inhibitors such as dapagliflozin and

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Received: 27-03-2018
Revised: 15-08-2018
Accepted: 01-09-2018

empagliflozin are approved to be used as monotherapy or in combination with metformin, sulfonylureas, or insulin.[1-3]

SGLT-2 inhibitors work by inhibiting SGLT-2 in the proximal convoluted tubules (PCT) to prevent reabsorption of glucose and facilitate its excretion in urine.[4,5] As glucose is excreted, its plasma levels fall leading to an improvement in all glycemic parameters. This mechanism of action is dependent on blood glucose levels and is independent of the actions of insulin. Thus, there are minimal potential for hypoglycemia and no risk of overstimulation or fatigue of the beta cells.[6]

The use of SGLT-2 inhibitors has major advantages in terms of reducing HbA1c and blood sugar levels and reduction in weight and blood pressures.[6,7] SGLT-2 inhibitors reduce weight by glucosuria. Glucosuria may signal the CNS to change appetite regulation.[8,9] SGLT-2 inhibitors reduce fat deposition by beta-oxidation of free fatty acids into triacylglycerol.[10] Blood pressure reduction by these agents is assumed to be related to its osmotic diuretic effect and vasodilation on nitric oxide release secondary to reduced oxidative stress.[11,12]

SGLT-2 inhibitors have proven benefits in reducing adverse cardiovascular (CV) outcomes. The mechanism of SGLT-2 inhibition such as calorie restriction mimetics (CRM) and pro-ketogenic effect explains their CV benefits. The CRM effect is mediated through modulation of the adenosine monophosphate-activated protein kinase pathway. Proketogenic effect is based on the ketogenic potential of SGLT-2 inhibitors which increase the production of ketone bodies: 3-Hydroxybutyrate, acetoacetate, and acetone in the liver, by increasing glucagon levels and by reducing the insulin:glucagon ratio.[13,14] The objectives of the study were to evaluate the beneficial effects and the side effects of SGLT-2 inhibitors in uncontrolled type 2 diabetes mellitus.

MATERIALS AND METHODS

The study was approved by the Institutional Human Ethics Committee, PSG Institute of Medical Sciences and Research (Proposal no: 17/036). The study was conducted in outpatients in the Department of Endocrinology and Department of General Medicine, PSG Hospitals, Coimbatore, for 6 months. This is an observational study done to evaluate the safety and efficacy of SGLT-2 inhibitors as adjuvant to insulin add-on therapy in uncontrolled type 2 diabetic patients. Parameters such as fasting blood sugar (FBS), HbA1c, weight, body mass index (BMI), and blood pressures were taken into consideration. A total subject of 100 were recruited for the study and divided into two treatment groups. 50 patients comes under Group 1 (patients on SGLT-2 inhibitor [empagliflozin 25 mg/dapaglifozin 10 mg] + metformin-gliclazide 40/500 mg + insulin [human mixtard, mean dose is 24.1 U]) and remaining 50 comes under Group 2 (patients on insulin [human mixtard, mean dose is 28.6U] + metformin-gliclazide 40/500 mg). In Group 1, SGLT-2 inhibitor is the add-on therapy whereas in Group 2, it is insulin.

Inclusion criteria of the study include age above 18 years and patient with poor diabetic control (HbA1c level above 7.5%) and on regular follow-up. Exclusion criteria include type 1 diabetes mellitus, renal failure patients, psychiatric patients, pediatric patients, gestational diabetes mellitus, and patients not willing to participate. SGLT-2 inhibitors are approved only for type 2 diabetes mellitus, and its safety and efficacy are not established in age below 18 years. The blood glucose lowering effect of SGLT-2 inhibitors is reduced in renal disease.

The changes in FBS, HbA1c, weight, BMI, blood pressure, and CV risk of diabetic patients before the initiation of add-on therapy and after 6 months follow-up were assessed using data collection form. CV risk score reduction was assessed using Framingham risk score calculator developed by Framingham Heart Study, Boston University. 10 years' CV risk calculator was used which is based on BMI. Adverse drug reactions occurred during the treatment were documented during every follow-up. Statistical analysis was performed using PRISM software. Student *t*-test (paired *t*-test) was used to compare the effect of add-on therapy.

RESULTS AND DISCUSSION

A total of 121 patients were recruited based on inclusion and exclusion criteria. 21 patients were dropped out during the study period due to irregular follow-up. Demographic and clinical details of patients were recorded. Group 1 had 27 males and 23 females, whereas Group 2 had 29 males and 21 females. In both groups, 25 were hypertensive patients on standard treatment, whereas 25 were nonhypertensive patients. BMI based on classification is presented in Figures 1 and 2.

Diabetic profile of patients is depicted in Table 1. HbA1c and FBS of patients were recorded on the day of add-on therapy (baseline) and then every 6 weeks for 6 months.

In Group 1, the mean difference in HbA1c was 2.333% and that of FBS was 82.97 mg/dL. In Group 2, the mean difference in HbA1c was 1.029% and that of FBS was 39.98 mg/dL. Both HbA1c and FBS show statistically significant reduction after 6 months of add-on therapy in both Group 1 (*P* value for both HbA1c and FBS is <0.0001) and Group 2 (*P* value for HbA1c and FBS is 0.0017 and 0.0043, respectively).

Weight and BMI of patients are presented in Figure 3.

In Group 1, mean baseline weight (79.36±18.41) was reduced to 73.94±15.34. In Group 2, mean baseline weight (61.63±9.828) was increased to 65.82±12.90. In Group 1, mean baseline BMI (29.95±6.590) was reduced to

27.90±5.589. In Group 2, mean baseline BMI (23.55±4.022) was increased to 25.13±5.011. In Group 1, the mean difference in weight was 5.421 kg and that of BMI was 2.049 kg/m^2. In Group 2, the mean difference in weight was −4.192 kg and that of BMI was −1.584 kg/m^2. Both weight and BMI show statistically significant reduction after 6 months of add-on therapy in Group 1 ($P < 0.0001$), whereas Group 2 shows statistically significant increase after 6 months of add-on therapy (P value for weight and BMI is 0.0004 and 0.0003, respectively).

SBP and diastolic blood pressure (DBP) in hypertensive patients on standard treatment are presented in Table 2.

In Group 1, the mean difference in SBP was 15.12 mmHg and that of DBP was 6.40 mmHg. In Group 2, the mean difference in SBP was 10.84 mmHg and that of DBP was 4.120 mmHg. Both SBP and DBP in hypertensive patients on standard treatment show statistically significant reduction after 6 months of add-on therapy in Group 1 (P value for SBP and DBP is <0.0001 and 0.0075, respectively), whereas in Group 2, SBP shows statistically significant reduction ($P = 0.0103$) and DBP shows non-significant reduction after 6 months of add-on therapy ($P = 0.0566$).

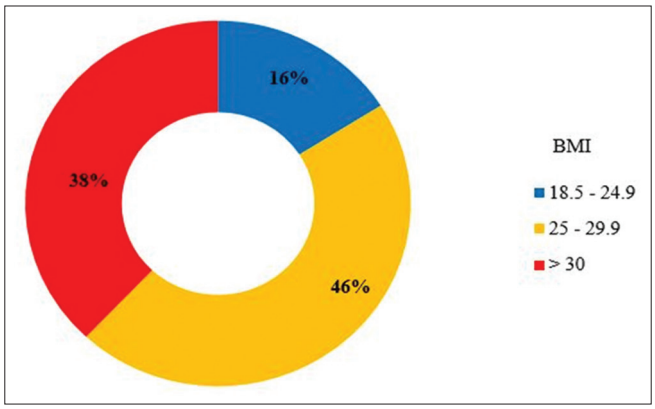

Figure 1: Group 1: Body mass index based on classification ($n = 50$)

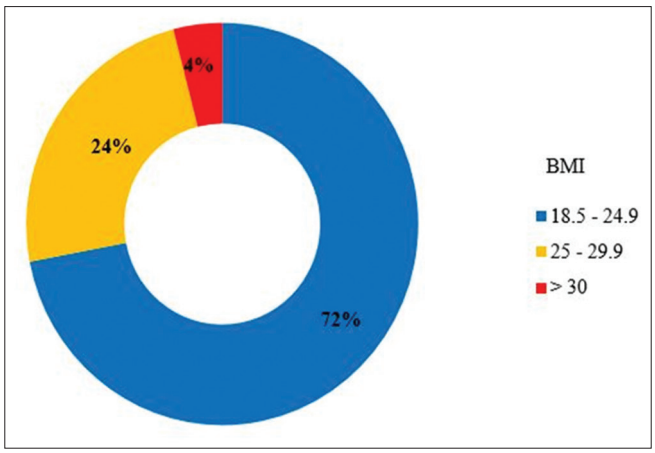

Figure 2: Group 2: Body mass index based on classification ($n = 50$)

Blood pressure in non-hypertensive patients is presented in Table 3.

In Group 1, the mean difference in SBP was 7.60 mmHg and that of DBP was 1.88 mmHg. In Group 2, the mean difference in SBP was −3.080 mmHg and that of DBP was −3.36 mmHg. Both SBP and DBP in non-hypertensive patients show statistically significant reduction after 6 months of add-on therapy in Group 1 (P value for SBP and DBP is 0.0005 and 0.0289, respectively), whereas Group 2 shows statistically non-significant increase in SBP and DBP after add-on therapy (P value for SBP and DBP is 0.3303 and 0.0731, respectively).

CV risk score of patients is presented in Figure 4.

In Group 1, mean baseline CV risk score (32.70±19.89) was reduced to 26.65±17.46 and the mean difference was 6.046%. In Group 2, mean baseline score (30.78±19.26) was reduced to 29.92±17.54 and the mean difference was 0.866%. Group 1 shows statistically significant reduction in CV risk ($P < 0.0001$) after 6 months of add-on therapy, whereas Group 2 shows non-significant reduction after add-on therapy ($P = 0.4188$).

Incidence of adverse events is presented in Table 4.

CONCLUSION

SGLT- 2 inhibitors are safe and effective treatment in uncontrolled type 2 diabetes mellitus. The use of SGLT-2 inhibitors is very

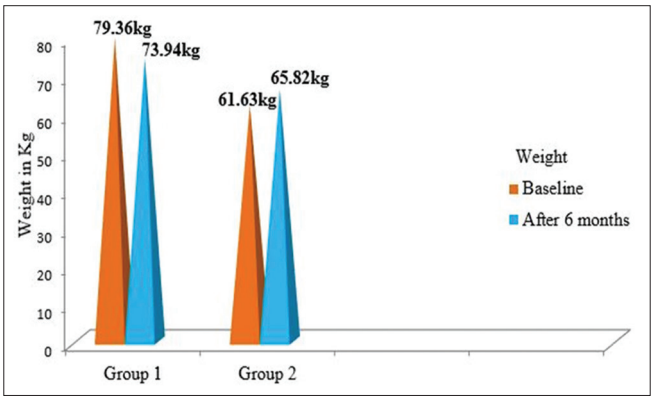

Figure 3: Comparison of mean weight

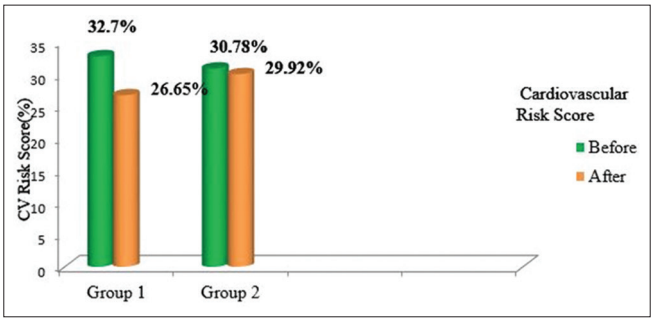

Figure 4: Comparison of mean cardiovascular risk score

Table 1: Diabetic profile of the patients

Time period	Group 1 (*n*=50) (mean±SD)		Group 2 (*n*=50) (mean±SD)	
	HbA1c	FBS	HbA1c	FBS
Baseline	10.19±1.574	213.8±64.75	10.08±2.202	197±80.72
1st follow-up	-	179.5±57.78	-	181±75.71
2nd follow-up	9.27±1.427	165.6±46.67	9.425±1.899	167.1±55.38
3rd follow-up	-	146.6±33.74	-	158.7±54.62
Last follow-up (after 6 months)	7.852±1.358	130.9±32.09	9.046±2.119	157±57.05

Table 2: Blood pressure in hypertensive patients on standard treatment

Time period	Group 1 (*n*=50) (mean±SD)		Group 2 (*n*=50) (mean±SD)	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
Baseline	143.4±12.10	85.92±11.28	145.5±21.26	85.36±10.77
1st follow-up	136.7±12.68	82.36±5.83	141.8±21.11	82.12±10.52
2nd follow-up	133.4±8.779	80.88±4.576	140.7±18.94	81.44±8.903
3rd follow-up	129.1±6.673	79.60±3.149	136.8±17.09	80.12±10.01
Last follow-up (after 6 months)	128.3+8.405	79.52+3.537	134.7+15.8	81.24+8.197

Table 3: Blood pressure in non-hypertensive patients

Time period	Group 1 (*n*=50) (mean±SD)		Group 2 (*n*=50) (mean±SD)	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
Baseline	132.6±8.827	80.20±5.354	123.5±14.77	74.8±6.764
1st follow-up	128.3±8.188	78.12±5.622	120.4±14.83	72.24±9.293
2nd follow-up	126.6±7.572	78.56±5.591	121.7±12.10	73.80±7.182
3rd follow-up	124.6±7.083	78.20±5.307	122.9±11.70	74.89±6.504
Last follow-up (after 6 months)	25±7.106	78.32±5.498	126.6±14.98	78.16±8.25

Table 4: Incidence of adverse events

Treatment group	Foot ulcer (%)	Hypoglycemia (%)	UTI (%)
Group 1 (*n*=50)	0 (0)	1 (2)	3 (6)
Group 2 (*n*=50)	3 (6)	9 (18)	5 (10)

UTI: Urinary tract infection

effective in glycemic control (reduction in HbA1c and FBS). The non-glycemic effects of SGLT-2 inhibitors include a reduction in weight, BMI, and blood pressure. The glycemic and non-glycemic benefits contribute to an overall reduction in CV risk. These benefits promise a definite well-tolerated therapy with SGLT-2 inhibitors as adjuvant to insulin add-on therapy in uncontrolled type 2 diabetes patients.

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Source of Support: Nil. **Conflict of Interest:** None declared.