EFFICACY OF CANAGLIFLOZIN AS AN ADD-ON TO TRIPLE DRUG TREATMENT WITH GLIMEPIRIDE, METFORMIN AND TENELIGLIPTIN

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ABSTRACT

BACKGROUND

Canagliflozin is a well-tolerated sodium-glucose transporter 2 inhibitor, with remarkable efficacy in providing glycaemic control in patients with type 2 diabetes mellitus (T2DM). However, limited evidence is available from national and international studies on the efficacy of the drug as an add-on to triple drug treatment for T2DM. The present study was aimed to evaluate the efficacy of canagliflozin (100 mg) as an add-on therapy in T2DM patients with inadequate disease control to triple drug treatment with glimepiride, metformin and teneligliptin.

MATERIALS AND METHODS

The prospective observational study was conducted in a clinical setting from Jan 2017 to March 2018. The study included T2DM patients showing inadequate disease control to triple drug treatment of glimepiride, metformin and teneligliptin. Clinical parameters such as body weight, HbA1c, systolic blood pressure, diastolic blood pressure, serum urea, creatinine, fasting and postprandial blood sugar levels were measured before and after the study. Comparison of pre- and post-treatment anthropometric and laboratory parameters were performed using paired t-test and Wilcoxon paired test.

RESULTS

The study included 51 patients with inadequately controlled T2DM, with an average age and BMI of 60 (47-68) and 23.78 (19.49-38.30) kg/m^2 respectively. A statistically significant difference was noted in the pre-and post-treatment measures of HbA1c, body weight, blood pressure, fasting and post-prandial blood sugar levels. The creatinine levels did not show significant variation following the treatment.

CONCLUSION

Canagliflozin has demonstrated significant efficacy when used as an add-on drug to triple drug treatment of glimepiride, metformin and teneligliptin in T2DM patients with inadequate disease control.

KEYWORDS

Canagliflozin, T2DM, HbA1c, triple drug treatment, metformin.

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BACKGROUND

Type 2 diabetes mellitus (T2DM), a chronic metabolic disease with multiple aetiologies, is gaining the status of potential epidemic in low- and middle-income countries. According to the World Health Organization (WHO), the disease has been projected to be the seventh leading cause of death globally by 2030.[1] Diabetes mellitus (DM) has been identified as one of the major causes for premature death, impaired quality of life, and disability, and the global health expenditure due to the disease is estimated to be around 673 billion dollars (comparable to 12% of total health expenditure).[2] As per 2017 reports of the International Diabetes Federation (IDF), over 72 million cases of DM were reported from India.[3]

SGLT2 inhibitors, a well-known class of drugs indicated for the management of DM, acts by inhibiting the glucose reabsorption in the proximal renal tubule.[4] Studies have demonstrated the effectiveness of these drugs in reducing the glycated haemoglobin levels (HbA1c) on an average by 0.5-0.8%, compared to the placebo, when used either as monotherapy or add-on therapy.[4] These drugs are also found to be effective in weight reduction(on an average by 2 kg), and decreasing the risk of hypoglycaemia and elevated blood pressure (at an average by 4 mmHg for systolic and 2 mmHg for diastolic pressure).[5] These clinical benefits have encouraged the use of SGLT2 inhibitors as an add-on therapy in patients with glycated haemoglobin level around 7-8%.[5]

Canagliflozin, a sodium-glucose transporter 2 (SGLT2) inhibitor, is a well-tolerated drug for the treatment of T2DM. The treatment assists in achieving a meaningful reduction in HbA1c, body weight and systolic blood pressure.[6] The drug acts as both SGLT2 inhibitor and P-glycoprotein inhibitor, and stimulates the excretion of glucose through urine, by

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suppressing glucose reabsorption by the kidney.[7] The drug has been first approved by the US Food and Drug Administration (FDA) in March 2013, for the treatment of T2DM in adults.[8,9] In August 2014, it has been approved for the combined use with metformin hydrochloride, as a fixed dose therapy for the treatment of T2DM.[8]

Several national and international studies have demonstrated the long-term effectiveness of canagliflozin as an add-on to dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists.[10,11] Canagliflozin is commonly used at daily doses of 100 and 300 mg.[12] The drug has demonstrated remarkable reduction in blood pressure, body weight and has lower risk of hypoglycaemia.[13] Kadowaki et al. (2018) have reported the long-term safety and efficacy of canagliflozin, as an add-on to teneligliptin, in Japanese T2DM patients with inadequate glycemic control.[14] Studies have also shown the significant efficacy of the drug, when used an add-on to double drug therapy in T2DM patients with inadequate disease control.[15] However, limited literature evidence is available on the efficacy of canagliflozin as an add-on to triple drug therapy. The present study evaluated the efficacy of canagliflozin (100mg) as an add-on therapy in T2DM patients with inadequate disease control to triple drug treatment with glimepiride, metformin and teneligliptin.

MATERIALS AND METHODS

The prospective observational study included subjects with inadequate control of T2DM (glycated haemoglobin (HbA1c) of >7.5%) to triple drug treatment with glimepiride, metformin and teneligliptin, enrolled in a clinical setting from Jan 2017 to March 2018. Informed consent was obtained from all the participants. The inclusion criteria considered were: subjects aged between 30-70 years and patients with glycated haemoglobin (HbA1c) of >7.5%. The study excluded subjects with serious complications such as significant osmotic symptoms, acute myocardial infarction, cerebrovascular accident, urinary tract infection, and pneumonia. The demographic details of the study subjects such as age, gender and body mass index (BMI) were recorded, and they received 100 mg of canagliflozin per day, along with the tripe drug treatment, glimepiride, metformin and teneligliptin, for a period of three months. The following clinical and anthropometric parameters were measured at baseline and three months after the treatment: weight, systolic and diastolic blood pressure, serum urea, serum creatinine, HbA1c and fasting (FBS) and postprandial blood sugar (PPBS) levels. The outcome measures considered were weight loss and changes in blood pressure, FBS, PPBS and HbA1c over time from baseline.

Statistics

Data with normal distribution were represented as mean ± SD, without normal distribution as median (range), and categorical data as counts. Comparison of pre- and post-treatment anthropometric and laboratory parameters was performed using paired t-test for normal data and Wilcoxon paired test for data without normal distribution. P value <0.05 was considered as statistically significant. Delta analysis was performed for comparison of pre-and post-data, and to quantify the data as: increased, decreased and stable (remained unchanged). All the statistical analyses were performed using Medcalc software version 14.8.1 (MedCalc Software, Ostend, Belgium).

RESULTS

The study included 51 patients with inadequately controlled T2DM, as per the HbA1c status. The descriptive details of the study participants are given in table 1. The mean (SD) age noted was 60(47-68) with a male to female ratio of 1:0.88. The median (range) of BMI was 23.78 (19.49-38.30) kg/m^2.

The details of comparison of pre- and post-treatment clinical and laboratory parameters are given in table 2. Statistically significant difference between the pre- and post-treatment levels of weight, systolic BP, diastolic BP, urea, FBS, PPBS and HbA1c was noted. However, creatinine levels were not significantly different.

The results of delta analysis, performed for pre- and post-treatment clinical and laboratory parameters, are given in table 3. Pre- and post-treatment weight showed increase in 13 patients, decrease in 29 patients and stable in 9 patients. Systolic BP increased in 11 patients, decreased in 38 patients and was stable in 2 patients. Diastolic BP increased in 10 patients, decreased in 40 and was stable in 1 patient. Decrease in urea levels was noted in 38 patients, while it increased in 9 patients and remained stable in 4 patients. Creatinine increased in 18 patients, decreased in 21 patients and remained unchanged in 12 patients. The study has noted an overall decrease in the post-treatment sugar levels of FBS, PPBS and HbA1c.

Parameters	Values*
Age (yrs.)	60(47-68)
Gender (M/F)	27/24
BMI	23.78(19.49-38.30)

Table 1. Descriptive Statistics for Demographic and Anthropometric Variables of the Subjects

*Data without normal distribution as median (range) and categorical data as counts.

Parameters	Pre-treatment/Baseline*	Post-treatment/After 3 months*	P value
Weight (n=51)	64.63 ± 7.44	64.01 ± 7.22	0.0032
Systolic BP (n=51)	136 (110-190)	134 (108-154)	< 0.0001
Diastolic BP (n=51)	82 (64-98)	80 (60-90)	< 0.0001
Urea (n=51)	27.23 ± 6.49	25.25 ± 5.94	< 0.0001
Creatinine (n=51)	1 (0.6-1.3)	0.9 (0.4-3.5)	0.6154
FBS (n=50)	154 (94-204)	121.5 (84-170)	< 0.0001
PPBS (n=50)	284 (184-360)	175 (144-310)	< 0.0001
HbA1c (n=50)	8.10 (7.40-9.60)	7.0 (6.50-9.10)	< 0.0001

Table 2. Comparison between Pre-and Post-Treatment Levels of Anthropometric and Laboratory Parameters in the Subjects

*Data with normal distribution are represented as mean ± SD, without normal distribution as median (range) and categorical data as counts

Parameters	Increase	Decrease	Stable
Pre- and Post-treatment			
Weight	13	29	9
Systolic BP	11	38	2
Diastolic BP	10	40	1
Urea	9	38	4
Creatinine	18	21	12
Baseline and after 3 months			
FBS	0	50	0
PPBS	0	50	0
HbA1c	1	47	2

Table 3. Delta Difference between Pre- and Post-Treatment Levels of Anthropometric and Laboratory Parameters

Pre- and post-treatment delta analysis was performed. In this analysis results are quantified as increase, decrease, and remained unchanged.

DISCUSSION

Canagliflozin, the first approved SGLT2 inhibitor to improve glycemic control in adult US patients with T2DM, has been known to increase urinary glucose excretion by SGLT2 inhibition and to facilitate intestinal SGLT1 inhibition, contributing to the overall reduction in the HbA1c levels.[16,17] SGLT2 facilitates the reabsorption of filtered glucose from the early proximal tubule by around 90%. Therefore, the inhibition of SGLT2 transporter molecules, significantly reduces the reabsorption of filtered glucose, thereby increasing the renal excretion of glucose.[18] Accumulating evidence has demonstrated the efficacy of the drug as mono and add-on therapy, for treating T2DM. Wilding et al. (2015), based on a post-hoc analysis, have concluded that canagliflozin can provide glycemic improvement across a range of baseline HbA1c.[19] The drug has been indicated as an effective therapeutic option for individuals aged 75 and more. A randomized phase 3 trial by Sinclair et al. (2016) has reported that canagliflozin can improve the glycemic control, blood pressure and body weight in individuals aged ≥75 years.[20] The drug has been shown to be effective in reducing body weight and improving glycemic control, when used in combination with insulin.[21]

Gavin et al. (2015) have reported that the drug can provide improved outcomes, such as reduction in HbA1c, body weight and systolic blood pressure in T2DM patients, independent of racial background.[22] Several studies conducted on Indian T2DM patients have also demonstrated the effectiveness of the drug in enabling glycemic control and reducing body weight. Kumar et al. (2016) have reported a -0.88% and -0.74% reduction in HbA1c in Indian T2DM patients treated with 300 mg and 100 mg of canagliflozin respectively.[23] Kaur et al. (2015) have evaluated the efficacy of canagliflozin as combination therapy in T2DM with inadequate glycemic control. The researchers have noted that, despite early regimen of glucose lowering agents, the subjects on canagliflozin had significant reduction in the levels of HbA1c, fasting plasma glucose and body weight compared to the placebo.[24] Literature evidence suggests that the addition of SGLT2 inhibiters, such as canagliflozin to metformin therapy in T2DM patients, can provide significant efficacy compared to the combination with non-SGLT2 inhibitors.[25]

Several studies have evaluated the efficacy of canagliflozin as an add-on to double drug treatment for achieving glycemic control in T2DM patients. Wilding et al. (2013) have investigated the efficacy of canagliflozin as an add-on to metformin and sulfonylurea in T2DM patients in a 52-week randomized, double-blind, placebo-controlled, phase 3 trial. The researchers have found that the addition of canagliflozin to the double drug treatment significantly reduced HbA1c levels, fasting blood glucose and body weight, at doses of 100 and 300 mg compared to the placebo.[15] Similar observations were reported by Schernthaner et al. (2013) on comparison of the efficacy of canagliflozin as an add-on to metformin and sulfonylurea in T2DM patients. The study demonstrated that the drug is superior to sitagliptin in decreasing A1C, fasting plasma glucose levels, body weight and systolic blood pressure.[26] Forst et al. (2014) have evaluated the efficacy of canagliflozin as an add-on to metformin and pioglitazone in T2DM patients with inadequate disease control, and reported similar findings as that of Wilding et al. (2013).[27] The authors have noted significant reduction in body weight, fasting blood glucose levels and systolic blood pressure. Additionally, the drug has been shown to be effective in

treating T2DM patients with inadequate glucose control to metformin and sitagliptin.[28] Moreover, several studies have recommended the use of fixed dose combination of canagliflozin and metformin across a broad range of patients with T2DM.[29]

The present prospective observational study, conducted on 51 T2DM patients with inadequate disease control to triple drug treatment with glimepiride, metformin and teneligliptin, has demonstrated that the addition of canagliflozin to the triple drug treatment can significantly reduce the body weight, HbA1c, systolic and diastolic blood pressure, urea, FBS and PPBS. Limited studies are available, both at the national and international levels, on the evaluation of the efficacy of canagliflozin as an add-on to triple drug therapy for the treatment of T2DM.

The present findings hold immense relevance, as the study is first-of-its-kind reporting the efficacy of canagliflozin as an add-on therapy to triple drug treatment with metformin, teneligliptin and glimepiride in T2DM patients with inadequate disease response.

The limitations of the study include smaller sample size, single-center based and non-randomized study design. Hence the observations of the study cannot be generalized. The present study has also not evaluated the safety of the drug as an add-on to the triple drug therapy. The study warrants prospective cohort studies involving larger sample size to explore the long-term efficacy of the drug on disparate population to corroborate the present study findings.

CONCLUSION

The present study suggests canagliflozin as an effective add-on oral therapeutic option in T2DM patients showing inadequate control to triple drug treatment of glimepiride, metformin and teneligliptin. The drug can provide remarkable reduction in HbA1c levels, weight, blood pressure, fasting and post-prandial blood sugar levels, and urea within shorter treatment duration.

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