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Research Article

A PROSPECTIVE INTERVENTIONAL COMPARATIVE LONG-TERM STUDY ON THE EFFICACY OF CANAGLIFLOZIN AND DAPAGLIFLOZIN IN A TERTIARY CARE HOSPITAL FOR A SPAN OF 1 YEAR

DHANUSH BELLAPU[1]*, RONALD DARWIN[2]

[1]Department of Pharmacy Practice, School of Pharmaceutical Sciences, VISTAS, Chennai, Tamil Nadu, India. [2]Department of Pharmacology, School of Pharmaceutical Sciences, VISTAS, Chennai, Tamil Nadu, India.
***Corresponding author: Dhanush Bellapu; Email: bellapudhanush@gmail.com**

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ABSTRACT

Objectives: This study mainly focuses on the comparison between the efficacy of canagliflozin and dapagliflozin by observing the prolonged effects, quality of life of patients, and comparing them with patients prescribed antihyperglycemic agents other than sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

Methods: This prospective interventional comparative study was conducted among 3452 patients admitted to the general medicine and endocrine department, Anu Group of Hospitals, Vijayawada, for 1 year, by eluding the patient's fasting blood sugar, postprandial blood sugar, renal function test, Hemoglobin A1c, blood pressure, and the finding severity score of adverse drug reaction (ADR) using the Naranjo scale during the study.

Results: The most common ADRs after utilizing canagliflozin was hypotension and dapagliflozin wes dehydration. The Chi-square test for patients with ADR's after using canagliflozin versus dapagliflozin used to treat type 2 diabetes. 9.12529 is the calculated Chi-square value at 5° of freedom and 5% level of significance ($p<0.1042$ – not significant). This shows that there was a slight difference but similar effects using canagliflozin versus dapagliflozin. The positive effect after treatment was weight reduction, which was greater in canagliflozin. Negative effects were hypotension, dehydration, infections, polyuria, and ketoacidosis, which were greater in canagliflozin.

Conclusion: We concluded that females were affected by urinary tract infection and vaginal infection. Efficacy was similar in control, canagliflozin, and dapagliflozin, but it may be a cost-related burden.

Keywords: Sodium-glucose cotransporter-2 inhibitors, Canagliflozin, Dapagliflozin, Effectiveness.

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INTRODUCTION

A significant and growing worldwide health issue is diabetes. There are presently 387 million afflicted persons across the world, with an 8.3% prevalence [1]. By 2035, there will be 592 million individuals worldwide with type 2 diabetes, of which more than 45% are undiagnosed. It is anticipated that 316 million more individuals have reduced glucose tolerance, and maximum among them will be developing type 2 diabetes [2,3]. For instance, the incidence of diabetes is 6.0% in the UK and affects 3.2 million people, but it is 12% in the USA. Aging inhabitants, expeditious cultural and community changes (such as substantial urbanization and diet modifications), sedentary lifestyle, and excess body mass are a few of the many factors contributing to this epidemic. For instance, Scotland has over 50% obese and 30% overweight type 2 diabetes patients, showing that weight loss should be a top focus for both avoidance and mitigation. Nearly 60% of type 2 diabetes patients are above the age of 65, and prevalence rates are greater among older people (around 15% are afflicted) [4-6].

Elderly patients frequently have several comorbidities, greater risks of negative medication outcomes and low glycemic values, and further needs for fitness and social care support. This has management issues connected with it. To treat type 2 diabetes mellitus (T2DM), inhibitors of sodium-glucose cotransporter-2 (SGLT-2) were first created because they can reduce blood sugar levels by increasing the excretion of glucose in the urine [1,7,8]. When compared to the several other medications accessible to the physician to treat T2DM, SGLT-2 inhibitors affect the kidneys, which are crucial for maintaining glucose homeostasis because they filter and reabsorb glucose in the proximal convoluted tubules (PCT). Approximately 180 g of glucose is percolated daily by the kidneys. The high-capacity, low-affinity SGLT-2 reabsorbs 80–90% of the glucose that was filtered by the plasma in the early PCT [4].

Plasma glucose levels related to glucose filtration and reabsorption are directly proportional to each other. Due to persistent hyperglycemia and increased activity, mRNA expression of SGLT-1 and SGLT-2 was raised in animal models of T2DM. This alters how the kidneys handle glucose and raises the maximal threshold for glucose reabsorption, which eventually conserves glucose and worsens hyperglycemia [9].

The inhibitors of SGLT-2 were a relatively new category of antihyperglycemic medication used in the therapy of T2DM [10-13]. It has a different mechanism of action, which targets the kidneys by inhibiting glucose reabsorption up to 90%. In addition to its action on glucose control, its efficiency is associated with natriuresis and diuresis, weight loss, blood pressure (BP) control, depletion of diabetes-related ventricular remodeling, and probable cardiovascular benefits [14]. Empagliflozin, canagliflozin, and dapagliflozin are the three U.S. Food and Drug Administration (FDA) approved inhibitors of SGLT-2 [15]. The most common convolutions of SGLT2 inhibitors are polyuria, volume depletion, and genitourinary infections. Recently, the FDA has notified about the cases of Fournier's gangrene related to SGLT2 inhibitor usage [16,17]. Other rare side effects are euglycemic diabetic ketoacidosis and hypoglycemia, particularly when inhibitors of SGLT2 were concurrently given with insulin or sulfonylureas [18,19].

Some randomized control trials proved that SGLT-2 inhibitors reduce the hemoglobin A1c (HbA1c) levels by 0.5–1.1%. These medications can also reduce cardiovascular and nephrological-related issues [20-22]. The pleiotropic effects of SGLT-2 inhibitors, rather than hypoglycemic

effects, are useful in the treatment of patients suffering from diabetic nephropathy by maintaining the renal glucose levels [23,24].

SGLT-2 inhibitors can be used in a wide range of patients' diabetic comorbidities, such as cardiovascular diseases, chronic kidney disease (CKD), and heart failure, along with patients with a lesser glomerular filtration rate of 30 mL/min/1.73 m^2 [25]. SGLT-2 inhibitors are more effective in Asian patients when compared to white patients [26-28].

This study was conducted to know the effectiveness in the patients with T2DM by giving canagliflozin and dapagliflozin as an add-on therapy.

METHODS

Source of data and study design

This is a prospective interventional comparative study designed to evaluate and compare the clinical outcomes of patients with diabetes mellitus who are treated with different SGLT-2 inhibitors – canagliflozin and dapagliflozin – as add-on therapies, against a control group receiving standard antidiabetic treatment as per Indian Council of Medical Research (ICMR) guidelines.

The primary goal is to assess the comparative efficacy and safety of these interventions based on the number and combination of antihyperglycemic agents used in treatment regimens up to quadruple-drug therapy.

Collected the data from the patients admitted into the general medicine and endocrine department who were diagnosed with T2DM. All the patients admitted during the study duration are followed from the day of prescribing of any antidiabetic with an SGLT-2 inhibitor up to not <1 year of the treatment or at least possible HbA1C done 3 times. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) are checked every month. Renal function test (serum creatinine, blood urea, and blood urea nitrogen) is checked every 4 months. HbA1C checked every 6 months.

Group 1: This group includes patients who were prescribed canagliflozin as an add-on therapy to their existing antidiabetic treatment. Patients in this group were on dual, triple, or quadruple-drug therapy, where canagliflozin was added as a third or fourth agent.

Group 2: This group consists of patients treated with dapagliflozin as an add-on therapy to their ongoing diabetes medication regimen. Similar to Group 1, these patients were also receiving dual to quadruple therapy, with dapagliflozin introduced as an adjunct.

Control

Patients in the control group were managed according to the ICMR-recommended standard treatment regimen, ranging from dual-drug therapy to quadruple-drug therapy, without the use of SGLT-2 inhibitors [29]. The treatment protocols followed in this group were in line with Indian national guidelines for diabetes management, incorporating commonly prescribed medications such as metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and insulin.

All groups of canagliflozin and dapagliflozin are compared to control therapy as per their number of antihypoglycemias, respectively [30-32].

Study site

Anu Group of Hospitals, Main Branch, located in Suryaraopet, Vijayawada, Andhra Pradesh, India. This site provides a suitable setting with a high volume of diabetes patients and specialized care in endocrinology and internal medicine, ensuring a reliable and diverse patient population.

Study duration

The study was conducted over a span of 1 year. Patient enrollment and initial data collection were completed over the first 3 months. All enrolled patients were then followed for a period of 12 months from the date of inclusion to monitor treatment response and outcomes.

Study criteria

The study was carried out by cogitating about the ensuing norms:

Inclusion criteria

The study will include patients who are admitted to the general medicine or endocrine departments of a hospital. These departments often treat individuals with chronic conditions such as diabetes mellitus, making them ideal settings for recruitment [33]. Only patients who have been diagnosed with diabetes mellitus (either Type 2 or other forms) are eligible for inclusion in the study. This includes individuals whose diabetes is being actively managed in a clinical setting. Participants must be within the age range of 35–65 years at the time of enrolment. This age range captures adults who are typically managing chronic diseases such as diabetes, but excludes elderly individuals who may have additional comorbidities that could affect treatment responses.

Both male and female patients will be included, ensuring gender diversity in the study. Eligible patients must be prescribed SGLT-2 inhibitors as add-on therapy in combination with other antihyperglycemic agents. Includes patients who are being treated with oral medications, insulin therapy, or a combination of both.

Exclusion criteria

Patients with Type 1 diabetes, gestational diabetes, or those under 18 years of age will be excluded from the study. Patients who have been discharged against medical advice will be excluded from the study. Patients who are unwilling or unable to participate due to various reasons (e.g., personal, logistical, or psychological barriers) will not be enrolled. Any patient who does not meet the specific inclusion criteria (such as age, diagnosis, or treatment regimen) will be excluded from the study. The study was approved with ethical numbers IEC Reg. No.: ECR/1049/INST/AP/2018/RR-21 and IEC. Ref. No.: IEC/2021/042GM/SAH.

Statistical analysis

Descriptive statistics such as mean, standard deviation (SD), and percentages were used to summarize demographic characteristics, treatment regimens, and incidence of adverse drug reactions (ADRs). Continuous variables such as HbA1C, FBS, PPBS, and renal function parameters were expressed as mean±SD and compared using one-way analysis of variance for group-wise comparisons. Categorical variables, including the frequency of ADRs and the number of patients on different drug regimens, were expressed as counts and percentages. The Chi-square (χ^2) test was used to determine the statistical significance of differences in categorical outcomes such as the incidence of ADRs among the canagliflozin, dapagliflozin, and control groups. A $p<0.05$ was considered statistically significant. The severity and probability of ADRs were assessed using Naranjo's ADR probability scale. All statistical tests were two-tailed and performed at a 95% confidence level.

RESULTS

A prospective interventional comparative study was conducted in the general medicine and endocrine department, Anu Group of Hospitals, Main Branch, Suryaraopet, Vijayawada for 12 months in 3456 patients (N) out of which 1854 (n_1) patients using canagliflozin and 1602 (n_2) patients using dapagliflozin from January 2022 to January 2023. In this study, the Control group population was 800. Table 1 represents the number of patients prescribed canagliflozin and dapagliflozin, and the number of patients with dual therapy, triple therapy, and quadruple

Table 1: Number of patients prescribed with canagliflozin and dapagliflozin

No. of patients prescribed with canagliflozin (n_1)			No. of patients prescribed with dapagliflozin (n_2)			Total (n)
1854			1602			3456
Dual therapy	Triple therapy	Quadruple therapy	Dual therapy	Triple therapy	Quadruple therapy	
636	616	602	582	526	494	

Table 2: Patients with ADR's after using canagliflozin and dapagliflozin

ADR's	Canagliflozin		Dapagliflozin	
	No. of patients	Percentage	No. of patients	Percentage
Vaginal candidiasis	112	7	86	9
Hypotension	432	29	224	23
Ketoacidosis	40	3	16	2
Weight loss	222	15	186	19
Polyuria	180	12	120	12
Dehydration	392	26	254	26
Urinary tract infection	50	3	40	4
Hypoglycemia	76	5	48	5
Total	1504	1504/1854*100=81.12	974	974/1602*100=60.8

ADRs: Adverse drug reactions, * (symbolizing multiplication)

therapy. Table 2 represents the patients with ADRs after using canagliflozin and dapagliflozin. Table 3 represents the patients who presented with more than one ADR. Table 4 shows the mean HbA1C levels among control subjects, canagliflozin-treated subjects, and dapagliflozin-treated subjects. Table 5 shows that the mean FBS and PPBS of control, canagliflozin, and dapagliflozin were similar; hence, efficacy was similar for control and canagliflozin, as well as it is similar for control and dapagliflozin.

Where 9.12529 is the calculated Chi-square value at 5° of freedom and 5% level of significance (p<0.1042 – not significant). This shows that there was a slight difference but similar effects using canagliflozin versus dapagliflozin.

Where the values are expressed as mean±SD (n=1854 for canagliflozin and n=1602 for dapagliflozin).

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DISCUSSION

Hypotension was more common after using canagliflozin, whereas dehydration was more common after using dapagliflozin as an ADR. We performed a Chi-square test for patients with ADR's after using canagliflozin versus dapagliflozin used to treat type-2 diabetes. 9.12529 is the calculated Chi-square value at 5° of freedom and 5% level of significance (p<0.1042-not significant). This shows that there was a slight difference but similar effects using canagliflozin versus dapagliflozin. The number of patients prescribed dual, triple, and quadruple therapies were 203,192 and 181 patients in Canagliflozin prescribed group and 208, 195 and 173 patients in Dapagliflozin prescribed group respectively. The number of patients prescribed with dual, triple, and quadruple therapies was 212, 425, and 163, respectively, in the control group of patients.

Patients with ADR's after using canagliflozin where hypotension (29%) was more common ADR followed by dehydration (26%), weight loss (15%), polyuria (12%), vaginal candidiasis (7%), urinary tract infection (UTI) (3%), hypoglycemia (5%) and ketoacidosis (3%). Percentage of patients with ADR's after using canagliflozin, in which hypotension had the highest percentage (25%) of occurrence in canagliflozin-prescribed patients.

Patients with ADR's after using dapagliflozin where dehydration (26%) was more common ADR followed by hypotension (23%), weight loss (19%), polyuria (12%), vaginal candidiasis (9%), UTI (4%), hypoglycemia (5%) and ketoacidosis (2%). Percentage of patients with ADR's after using dapagliflozin, in which dehydration had the highest percentage (14.69%) of occurrence in dapagliflozin-prescribed patients.

The positive effect after using canagliflozin and dapagliflozin to treat type-2 diabetes was weight loss, which was greater in canagliflozin

Table 3: Patients presented with more than one ADR

ADR's	Canagliflozin	Dapagliflozin
Hypotension, dehydration, and polyuria	135	108
Dehydration and hypotension	207	196
Polyuria and dehydration	162	117
UTI and vaginal candidiasis	45	35
Weight loss, ketoacidosis, vaginal candidiasis	13	6

ADR: Adverse drug reaction, UTI: Urinary tract infection

Table 4: Control versus canagliflozin versus dapagliflozin mean HbA1C levels

Days	Mean HbA1C levels±SD		
	Control group	Canagliflozin	Dapagliflozin
Day 0	9±1.21	9±1.45	9±1.45
Day 90	7.5±1.08	6.5±1.36	6.5±1.32
Day 180	6.5±1.02	5.5±1.45	5.5±1.46
Day 270	6.5±1.16	5.5±1.56	5.5±1.50
Day 360	6±1.03	5±1.62	5±1.59

HbA1C: Hemoglobin A1c, SD: Standard deviation

than in dapagliflozin. Negative effects after using canagliflozin and dapagliflozin to treat type-2 diabetes were hypotension, dehydration, vaginal candidiasis, polyuria, UTI, ketoacidosis which were greater in canagliflozin than dapagliflozin. Female patients were more prone to UTI and vaginal candidiasis, and it is seen in 16 patients at an age group of 35–44 years. Naranjo's severity score was 9 for all the patients who were presented with ADRs, as the probability is definite. Patients after using canagliflozin and dapagliflozin for treating type 2 diabetes were presented with more than one ADR mentioned in Table 3. Patients presented with more than one ADR, in which dehydration along with hypotension was more common when compared to others in both canagliflozin and dapagliflozin prescribed patients. Control group of medicines steady state was obtained after 6 months, but using canagliflozin and dapagliflozin within <3 months' steady state was obtained. Mean FBS and PPBS of control, canagliflozin, and dapagliflozin were similar; hence, efficacy was similar for control and canagliflozin, as well as it is similar for control and dapagliflozin. In the control group, hypoglycemia occurred in 566 patients out of 800 patients at any point of time in 1 year. Efficacy was similar for control, canagliflozin, and dapagliflozin, but because of additive effects such as weight loss, hypotension, and hypoglycemia. Opting for a new drug was helpful, but it may be a cost-related burden. Serum creatinine levels in canagliflozin and dapagliflozin prescribed patients which is similar to controls, but with a slight difference, and with no pathological evidence (no symptoms of kidney injury or kidney disease). Patients who are having kidney injuries such as CKD, acute kidney injury, renal calculi, UTI, or any kidney-related disorders should not be prescribed canagliflozin or dapagliflozin. The control group had no effect on BP. According to the

Table 5: Control versus canagliflozin versus dapagliflozin mean FBS, PPBS levels

Values	Mean FBS (mg/dl)±SD	Mean PPBS (mg/dL)±SD	Mean FBS (mg/dL)±SD	Mean PPBS (mg/dL)±SD	Mean FBS (mg/dL)±SD	Mean PPBS (mg/dL)±SD
	Control group		Canagliflozin		Dapagliflozin	
Day of prescribing SGLT-2 inhibitor	250±25.21	320±28.05	230±23.06	300±17.95	230±22.50	306±19.56
After 1 month	150±26.40	225±27.69	142±24.08	232±17.62	140±22.63	230±19.07
After 2 months	156±26.62	238±27.90	145±19.06	225±16.95	145±21.98	225±18.64
After 3 months	160±26.59	255±28.32	159±23.54	254±17.98	155±22.34	252±19.39
After 4 months	150±25.48	240±28.52	155±24.06	246±16.99	155±22.56	246±19.62
After 5 months	165±24.6	250±28.93	160±23.65	250±17.59	163±22.63	251±19.52
After 6 months	148±25.98	236±26.79	147±25.02	235±17.64	148±22.72	235±18.96
After 7 months	157±26.25	245±27.95	155±23.87	242±16.43	152±23.09	244±18.42
After 8 months	161±26.06	252±28.63	156±23.54	244±15.98	159±23.15	246±19.03
After 9 months	154±25.76	248±27.98	151±23.61	245±16.54	151±22.45	245±18.99
After 10 months	149±20.19	245±28.06	154±23.51	242±17.09	148±22.94	242±17.95
After 11 months	163±27.01	254±28.68	161±23.13	253±17.83	161±21.75	255±20.03
After 12 months	157±26.62	244±28.58	152±23.18	240±17.25	152±23.64	243±19.65

FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, SD: Standard deviation, SGLT-2: Sodium-glucose cotransporter-2

drug discovery, SGLT-2 in an incident to be prescribed in patients with hypertension, showing some effect over patients without hypertension as an ADR, but in patients with hypertension, it shows an additive effect. Only in dual therapy, there is no incidence of hypoglycemia, but in triple and quadruple therapies, there is an incidence of hypoglycemia, which indicates the safety of canagliflozin and dapagliflozin than control. We performed a Chi-square test for patients in the control and canagliflozin groups for ADRs.

31.868 is the calculated Chi-square value at 3° of freedom and 5% level of significance (p=0.0000 and 0.05 – significant). This shows that canagliflozin and the control groups were equally efficient, with the evidence of the Chi-square and p-value.

CLINICAL PRESENTATION OF ADRs

ADRs manifest through various clinical presentations. Hypotension is characterized by low BP. Dehydration symptoms include headache, delirium, confusion, tiredness, dizziness, weakness, light-headedness, dry mouth, dry cough, high heart rate with low BP, loss of appetite, sugar cravings, flushed skin, and swollen feet. Hypoglycemia presents with pallor, shakiness, dizziness, sweating, hunger, nausea, irregular heartbeat, difficulty concentrating, fatigue, irritability, anxiety, tingling or numbness in the lips, tongue, or cheek, and headache. Polyuria is marked by increased thirst, the urge to urinate, and subjective evidence. Vaginal candidiasis symptoms include vaginal itching and irritation, thick white discharge resembling cottage cheese, burning micturition, and increased total count. UTIs manifest as frequency, urgency, dysuria, and suprapubic pain for lower UTI; upper UTI may include costovertebral angle pain/tenderness, fever, and chills. Complete urine examination reveals increased pus cells, epithelial cells, burning micturition, and total count. Diabetic ketoacidosis symptoms encompass fast, deep breathing, dry skin and mouth, flushed face, fruity-smelling breath, headache, muscle stiffness or aches, fatigue, nausea, vomiting, and stomach pain. Weight loss is evidenced both subjectively and objectively.

CONCLUSION

Our study focused on evaluating the prevalence of UTIs and vaginal candidiasis among female patients with type 2 diabetes, as well as the comparative effects of two commonly prescribed SGLT-2 inhibitors-canagliflozin and dapagliflozin-on the management of type 2 diabetes. Based on our findings, several significant observations emerged, which offer both clinical insights and future directions for treatment. A notable trend in our study was the higher incidence of UTIs and vaginal candidiasis among female patients. These conditions were found to be particularly predominant within the age group of 35–45 years, suggesting a potential vulnerability in this demographic. The higher incidence could be attributed to a variety of factors, including the hormonal changes typical of this age range, as well as potential underlying comorbidities commonly associated with type 2 diabetes. The study highlights the need for heightened vigilance and preventive strategies for infections in this particular group of patients. Both canagliflozin and dapagliflozin belong to the class of SGLT-2 inhibitors. They are widely used in the management of type 2 diabetes due to their ability to reduce blood glucose levels through increased urinary glucose excretion. However, our study revealed that the efficacy of these two drugs was similar, with both demonstrating comparable effects in terms of glycemic control, which aligns with previous literature. Despite this similarity in efficacy, there were notable differences in side effects observed between the two drugs. Canagliflozin was associated with more pronounced positive and negative effects, such as weight loss, hypotension, and a higher incidence of hypoglycemia, when compared to dapagliflozin. These additive effects might contribute to greater clinical considerations in managing patients on canagliflozin, including more frequent monitoring and potential dose adjustments. While the side effects were generally manageable, they might be considered burdensome in some patients, particularly those at risk of dehydration or cardiovascular events. While canagliflozin and dapagliflozin offer similar efficacy in managing type-2 diabetes, the differential side effect profile, with canagliflozin showing more pronounced adverse reactions, requires careful patient selection and management. The higher prevalence of UTI and vaginal candidiasis in the female cohort, particularly those aged 35–45 years, underscores the need for personalized care strategies to mitigate these risks. In addition, while newer drug options may offer promise, their cost-effectiveness remains a significant concern, potentially hindering their widespread use. As a result, the decision to switch or combine therapies should be carefully considered both clinical outcomes and economic implications. Our findings suggest that continued research into safer, and more effective treatments for type 2 diabetes – along with comprehensive cost-benefit evaluations – will be essential in shaping the future landscape of diabetes management.

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AUTHOR CONTRIBUTION STATEMENT

Dhanush Bellapu conceptualized the study, designed the methodology, and conducted data analysis on the efficacy of SGLT2 inhibitors in diabetes treatment. Dr. Ronald Darwin contributed to the literature

review, interpretation of results, and manuscript drafting. All authors reviewed, edited, and approved the final manuscript for publication.

DECLARATION OF INTEREST STATEMENT

We, Dhanush Bellapu and Ronald Darwin, declare that there were no conflicts of interest.

FUNDING STATEMENT

There is no funding for this study.

DATA ACCESS STATEMENT

Both authors have complete access to the study data.

DATA AVAILABILITY STATEMENT

The data will be shared on reasonable request to the corresponding author.

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