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Research Article

A STUDY ON THE PREVALENCE OF ADVERSE EFFECTS ASSOCIATED WITH SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR DAPAGLIFLOZIN IN A TERTIARY CARE CENTRE

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ABSTRACT

Objectives: The objective of this study was to assess the prevalence of adverse effects associated with sodium-glucose cotransporter 2 inhibitors (SGLT2i) dapagliflozin in a real-world setting.

Methods: This observational study was conducted prospectively over 3 months in a tertiary care center in India. It focused on in-patients aged over 18 who were diagnosed with heart failure, Type 2 diabetes mellitus, or chronic kidney disease, and undergoing treatment with SGLT2i, specifically dapagliflozin, at doses of 5 or 10 mg. Patients with a glomerular filtration rate of <25 mL/min/1.73 m^2, pregnant or lactating women, and individuals with end-stage renal disease or undergoing dialysis were excluded from this study. Patient demographics, clinical history, and medication usage were collected using a structured pro forma.

Results: Among 60 patients, 15 (25%) experienced adverse effects. Women and those over 50 years had a significantly higher prevalence of adverse effects. The common adverse effects were urinary tract infection 5 (8.3%), urinary-like symptoms 4 (6.6%), gastrointestinal upset 3 (5%), weakness 2 (3%), and hyponatremia 1 (1.6%). The dosage (5 mg and 10 mg) was significantly associated with side effects ($p<0.002$). Management strategies varied, including discontinuation, temporary halting, or no change in treatment.

Conclusion: The observed higher prevalence of adverse effects in older individuals, particularly women, and with higher drug doses further emphasizes the necessity for close clinical monitoring during the initial phases of treatment.

Keywords: Sodium-glucose cotransporter 2 inhibitors; Dapagliflozin; Diabetes; Adverse effects; Urinary tract infection.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by insulin resistance and impaired glucose tolerance. It is associated with elevated blood glucose levels and a 2–4 times higher risk of cardiovascular disease (CVD). It is one of the leading causes of chronic kidney disease (CKD) and is associated with a 9–58% increased risk of heart failure (HF) and 75% increase in all-cause mortality rate [1,2]. Typical treatment options for T2DM include metformin, sulfonylurea (SU), sitagliptin, glucose-like peptide-1 receptor agonist, and insulin. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are recent therapeutic agents for treating T2DM and are rapidly gaining traction [3]. These SGLT2i are used for treating diabetes with a novel mechanism of action that distinguishes them from other oral antihyperglycemic agents. SGLT2 protein is responsible for the reabsorption of glucose and sodium in the proximal tubule of nephrons in kidneys. By inhibiting this SGLT2 protein, SGLT2i allows excess glucose to be excreted in the urine, along with glycosuria; they also stimulate osmotic diuresis and natriuresis and achieve the desired effect of decreasing plasma glucose levels [4,5]. Dapagliflozin, canagliflozin, and empagliflozin are three SGLT2i currently available for clinical use in India. They are recommended for treating patients with T2DM as monotherapy or combination therapy with other antidiabetic drugs [6]. These medications have shown excellent tolerance and safety, with no risk of causing blood sugar levels to drop below the optimal threshold. SGLT2i has been proven effective in decreasing and maintaining blood glucose levels, lipid profiles, blood pressure, body weight, and glycosylated hemoglobin A1C (HbA1C). Another remarkable aspect of this medication class is that it is cardioprotective since it improves endothelial tissue function [7]. Hence, these agents have an important role, especially in the management of T2DM patients with established atherosclerotic CVD, HF, or CKD, as per the recent guidelines of the American Diabetes Association and the American Association of Clinical Endocrinologists [8,9].

The glucose-lowering effect of SGLT2i depends on glomerular filtration and is progressively attenuated as kidney function declines. Due to this, and considering that the balance of benefits and risks may vary for those with kidney disease, initiation of SGLT2i dapagliflozin is not recommended in individuals who have kidney disease with an estimated glomerular filtration rate (eGFR) below 25 mL/min/1.73 m^2 [10].

In various clinical trials, genital tract infection (GTI) is the most common adverse effect associated with SGLT2i. Diabetic patients are generally considered to be at an increased risk of GTI, and the utilization of SGLT2i may significantly contribute to this issue. In addition, other adverse effects have emerged with notable frequency, including nasopharyngitis, hypotension, and hypokalemia. More severe adverse effects, though less common, encompass an elevated risk of amputations, bone fractures, and euglycemic diabetic ketoacidosis [6,11]. There is a scarcity of real-world data on the use of SGLT2i, with the existing focus primarily on their effectiveness. It is crucial to gather real-world data to determine whether the safety and efficacy outcomes observed in clinical trials for SGLT2i can be applied to practical clinical settings.

Therefore, this study aims to systematically assess the prevalence of adverse effects associated with SGLT2i in a tertiary care center, providing crucial real-world evidence to enlighten on the safety profile of these medications and guide their use in routine clinical practice.

METHODS

This observational study was conducted prospectively at a tertiary care center over 3 months in India. The study included in-patients aged over 18 diagnosed with HF, T2DM, and CKD, and receiving treatment with SGLT2i, specifically dapagliflozin in doses of 5 or 10 mg, and those patients with eGFR <25 mL/min/1.73 m^2, pregnant or lactating women, and individuals with end-stage renal disease or undergoing dialysis were excluded from the study. A standardized data collection form was utilized for collecting patient details such as demographics, medical history, and clinical and laboratory data. The prevalence of adverse effects associated with the use of dapagliflozin was calculated, and the associations between categorical variables, including age, gender, comorbidities, dapagliflozin dosage, and side effects, were assessed using the Chi-square test. The demography and clinical characteristics of the study population were presented using descriptive statistics. Statistical analysis was conducted using Statistical Packages for the Social Sciences version 23, and a $p<0.05$ was considered statistically significant at a 5% level of significance corresponding to a confidence interval of 95%. The entire study was conducted in compliance with ethical guidelines and received approval from the Institutional Ethics Committee. Informed consent was obtained from all participants.

RESULTS

The study population predominantly consisted of individuals aged over 50, with a higher proportion of males 41 (68%) than females 19 (32%). The common comorbid conditions include T2DM, hypertension, and CVD. Along with dapagliflozin, SU, beta-blockers, and diuretics were the most commonly prescribed drugs. The most commonly prescribed combination drug was found to be SU and Metformin. Out of 60 patients, 40 (67%) were prescribed a 10 mg dose of dapagliflozin, while the remaining 20 (33%) received a 5 mg dose. The demographic details and baseline characteristics are shown in (Table 1).

Clinical parameters at baseline, including blood pressure, random blood sugar, fasting blood sugar, postprandial blood sugar, HbA1C, electrolytes, eGFR, blood urea nitrogen, serum creatinine, uric acid, and left ventricular ejection fraction in echocardiogram, were measured and are presented in (Table 2).

The prevalence of adverse effects was examined over 3 months in 60 patients. Approximately 15 (25%) patients experienced adverse effects. Urinary tract infection (UTI) was the most common adverse effect seen. About 5 (8.3%) patients suffered at least one episode of UTI out of 60 patients. These were much higher in females 3 (60%) than males 2 (40%). *Escherichia coli* was the common organism isolated. The prevalence of other adverse effects is illustrated in (Fig. 1).

Patients more than 50 years of age had a significantly higher prevalence of adverse effects than patients aged <50 years ($p<0.001$). Notably, women experienced a significantly higher number of adverse effects compared to men ($p<0.000$). The dosage of the drug (5 mg and 10 mg dapagliflozin) was significantly associated with adverse effects ($p<0.002$). Detailed results for other variables associated with adverse effects are presented in (Table 3).

Fig. 2 illustrates the management strategies implemented for the fifteen patients who experienced adverse effects. The drug was discontinued due to the onset of drug-induced hyponatremia for one patient. Six patients had their medication temporarily halted during their admission, but it was reinstated upon discharge once their adverse effects had resolved. For the remaining eight patients, there was no change in treatment, and they continued the prescribed drug.

Table 1: Baseline characteristics of the study population (n=60)

Characteristics	No of patients (%)
Age	
<50 years	5 (8)
>50 years	55 (92)
Gender	
Male	35 (58)
Female	25 (42)
Co-morbidities	
T2DM	49 (81)
Hypertension	43 (71)
Dyslipidemia	2 (3)
Hypothyroidism	8 (13)
CVD	18 (30)
CKD	3 (5)
Medications	
SU	11 (18)
Insulin	7 (12)
DPP-4 inhibitors	6 (10)
Metformin	4 (7)
Thiazolidinediones	1 (2)
Diuretics	8 (13)
Nitrate	1 (2)
Beta blockers	12 (20)
ARB	6 (10)
CCB	6 (10)
ACEi	3 (5)
Statins	6 (10)
Antithyroid drugs	5 (8)
Antiplatelet drugs	3 (5)
Sulfonylureas+metformin	11 (18)
DPP-4 inhibitors+metformin	7 (12)
Statins+antiplatelet drugs	10 (17)
ARB+CCB	1 (2)
Dapagliflozin 5 mg	20 (33)
Dapagliflozin 10 mg	40 (67)

T2DM: Type 2 diabetes mellitus, CVD: Cardiovascular disease, CKD: Chronic kidney disease, SU: Sulfonylurea, DPP-4 inhibitors: Dipeptidyl peptidase 4 inhibitors, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, ACEi: Angiotensin-converting enzyme inhibitor

Table 2: Baseline clinical parameters of the study population

Parameters	Mean (±SD)
Body weight	71.70 (16.04)
Blood pressure	
Systolic blood pressure	136.64 (28.44)
Diastolic blood pressure	79.64 (14.91)
Blood sugar level	
Random	203.41 (94.85)
Fasting	142.3 (50.4)
Postprandial	202.2 (72.8)
HbA1C	8.72 (2.05)
Electrolytes	
Sodium	130.48 (21.31)
Potassium	4.25 (0.44)
Renal function test	
eGFR	76.49 (25.11)
BUN	15.82 (13.97)
Uric acid	5.28 (2.82)
Serum creatinine	1.29 (1.69)
ECHO	
LVEF	55.35 (14.92)

Note: SD: Standard deviation, HbA1C: Glycosylated hemoglobin, eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, ECHO: Echocardiography, LVEF: Left ventricle ejection fraction

DISCUSSION

This study mainly focused on the adverse effects among patients taking SGLT2i dapagliflozin. Out of 60 patients, 15 (25%) patients developed adverse effects. The glycosuric effect of dapagliflozin can predispose patients to the risk of GTI, mainly UTI, by providing a good flourishing environment for the bacteria, mycotic balanitis, and vulvovaginitis, which are the most frequently reported adverse events of SGLT2i [6]. The reported prevalence of UTIs in clinical trials ranged from 4% to

Table 3: Association of different variables with occurrence of side effects

Variable	Adverse effects		p-value
	Yes	No	
Age			
<50 years	5	0	0.001*
>50 years	10	45	
Gender			
Male	6	35	0.000*
Female	9	10	
Co-morbidities			
Diabetic	15	34	0.003*
Non-diabetic	0	11	
Hypertensive	28	15	0.006
Non-hypertensive	17	0	
Dapagliflozin dose			
5 mg	0	20	0.002*
10 mg	15	25	

mg: Milligram; p-value was found using Chi-square test; *statistically significant difference was found

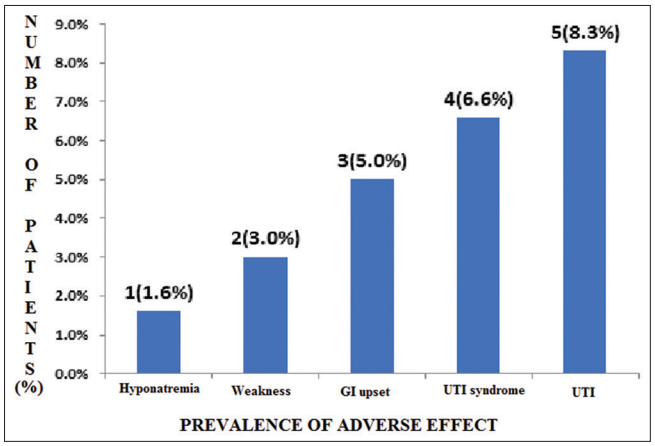

Fig. 1: Prevalence of adverse effects associated with the drug dapagliflozin. Note: UTI: Urinary tract infection, GI: Gastrointestinal

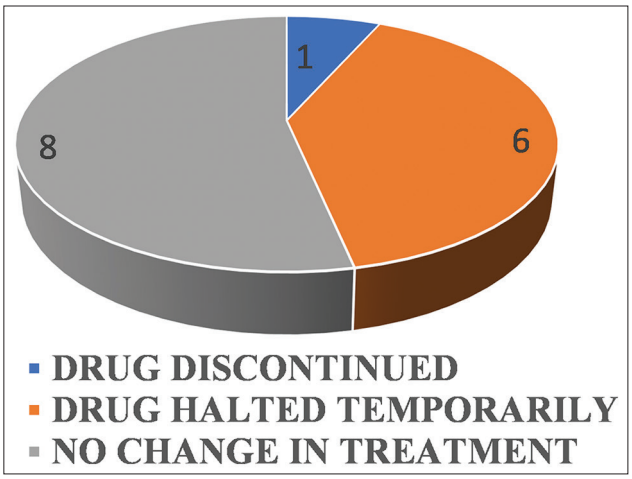

Fig. 2: Management strategies for adverse effects

9% [12]. In our study, 60% of females and 40% of males suffered from UTI and urinary-like symptoms. These UTIs were significantly more common in females older than 50 years; this observation is consistent with previous reports [13-16] and might be due to postmenopausal changes in the female urogenital system [17].

The next common complaint we noticed was a feeling of weakness and lethargy, particularly in the absence of hypotension and hypoglycemia, which is also reported by the study conducted by Khan *et al.* [3]. These symptoms were more likely due to osmotic diuresis. Patients also reported nausea and vomiting initially after starting treatment, which is in accordance with the study conducted by Burke *et al.* [18].

Dapagliflozin-induced hyponatremia was reported in one patient and the drug was discontinued, this is supported by the study conducted by Yeoh *et al.* [19] where 4.6% had hyponatremia on dapagliflozin. This is due to the osmotic effect that causes more water along with sodium to get excreted in urine leading to hypovolemia and hyponatremia.

The higher dose of dapagliflozin increases the urinary excretion of glucose and would theoretically increase the risk of UTI, hypovolemia, hyponatremia, and weakness [3,6]. We did observe this in our study, as adverse effects were statistically associated with the dose strength of dapagliflozin (p=0.002).

Factors such as weakened immune system, impaired blood supply, bladder dysfunction, and glycosuria can cause UTI in T2DM than non-diabetic persons [20]. Our study also found an association between diabetes and adverse effects (p=0.003) with UTI being the most common infection.

Limitations

The 3-month observation period may not capture long-term adverse effects or complications and our study mainly focused on patients with HF, T2DM, and CKD. The interactions of these comorbidities with SGLT2i may vary, and further research should be undertaken.

CONCLUSION

This study provides valuable information into the prevalence and nature of adverse effects associated with SGLT2i, specifically dapagliflozin, in a tertiary care setting. The higher prevalence of adverse effects such as UTI, weakness, nausea, and vomiting observed in older individuals, particularly women, and with higher drug doses emphasizes the necessity for close clinical monitoring during the initial phases of treatment. The strategies employed, including drug discontinuation and temporary cessation, further stress the need to quickly address adverse events. Despite these adverse reactions, it is essential to recognize that the advantages of SGLT2i in the treatment of HF, T2DM, and CKD are still significant. Individualized risk assessment and patient education are essential to optimizing the therapeutic benefit and minimizing the potential harm.

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AUTHOR'S CONTRIBUTION

All the authors contributed equally to study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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