ORIGINAL ARTICLE

EFFECT OF SGLT2 INHIBITOR DAPAGLIFLOZIN ON SODIUM, POTASSIUM AND CREATININE LEVELS IN PATIENTS WITH ACUTE HEART FAILURE

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Background: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) is a new class of medication for the treatment of type 2 diabetes mellitus. Additionally, they have been found to have beneficial effects on heart failure outcomes, convincingly reducing the morbidity and mortality in heart failure. Although the medical data indicates SGLT2i to be safe and cardio-protective, very little attention has been given to the impact of these agents on electrolyte balance particularly in acute heart failure (AHF). We aimed to evaluate the effect of SGLT2i, and dapagliflozin on serum sodium, potassium and creatinine in AHF. **Methods:** Overall, 160 adult patients of either gender, admitted with AHF were selected for the study. Selected individuals were randomly assigned to receive dapagliflozin 10 mg orally added to standard medical treatment (n=80) or were in reception of standard medical therapy only (n=80). Serum electrolytes and serum creatinine were collected on admission and day 7 or on discharge whichever happened earlier. **Results:** The mean level of serum electrolytes displayed insignificant differences among both groups on admission. The mean level of serum potassium was higher in the dapagliflozin group compared with the control group (p<0.001) on day 7/discharge. Mean serum sodium level was comparable and showed significant differences between the two groups following treatment (p-value=0.021). Significant higher levels of serum creatinine were observed following treatment in both groups. However, on intergroup comparison, they were statistically insignificant. **Conclusion:** Dapagliflozin is an effective treatment of heart failure and is not associated with deterioration of serum electrolyte levels and renal functioning when used as add-on therapy in AHF.

Keywords: Dapagliflozin; Serum electrolytes; Acute heart failure; Serum creatinine

Citation: Gilani FF, Ali S, Noor M, Farhat K, Siddiqui MB, Fatima M. Effect of SGLT2 inhibitor dapagliflozin on sodium, potassium and creatinine levels in patients with acute heart failure. J Ayub Med Coll Abbottabad 2023;35(4 Suppl 1):715–20.

DOI: 10.55519/JAMC-S4-11906

INTRODUCTION

Globally, acute heart failure (AHF) is one of the foremost causes of hospital admissions. According to the latest estimations, approximately 25% of patients with AHF are re-hospitalized within 30 days of discharge, and 50% are readmitted within 6 months, attributed to fluid congestion and volume overload.[1] There is a limitation of effective medical therapy available that improves clinical outcomes in AHF. Loop diuretics, being the mainstay of treatment, are commonly used in the management of AHF. They work by increasing the excretion of salt and water from the body, which can reduce fluid overload and improve symptoms such as shortness of breath.[2] However, despite treatment with loop diuretics, the majority of patients are discharged with residual congestion, that may require the addition of some other diuretic like thiazide or mineralocorticoid.[3] The addition of these agents is not without risk as can lead to electrolyte imbalances like hyponatremia and hyperkalaemia. Moreover, the use of loop diuretics alone in AHF roots low levels of potassium, which can lead to arrhythmias and other complications. In addition, overuse of loop diuretics can lead to worsening kidney functions, increasing the risk of adverse outcomes.[4]

Sodium Glucose Co-transporter 2 inhibitors (SGLT2i), novel antidiabetic drugs, have exhibited favourable effects on clinical outcomes in chronic heart failure (CHF) with type 2 diabetes mellitus (T2DM).[5] Several large clinical trials have demonstrated that these medications can decrease the risk of hospitalization for heart failure (HF), cardiovascular death, and all-cause mortality in patients with and without diabetes, having established cardiovascular disease.[5] Recently, these agents emerged as an effective and well-tolerated treatment option for patients with AHF as well.[6] The beneficial effects of SGLT2 inhibitors on HF outcomes appear to be independent of their glucose-lowering effects and may be related to their ability to improve cardiac and renal function, reduce inflammation, and improve energy metabolism. SGLT2i blocks the reabsorption of glucose and sodium in the kidney, leading to increased urinary excretion of glucose.[7] Whether this mechanism, SGLT2 inhibition, can cause significant natriuresis is less clear, but is important in the context of

patients with AHF who are likely to be prescribed loop diuretics for quick relief of symptoms.

So far, several clinical trials have been carried out, endorsing the beneficial effect of SGLT2i, on cardiovascular risk factors including improvement in weight, blood pressure and lipid profile.[8] However, their impact on serum electrolytes has not been evaluated in particular. Our study aims to explore the plausible effect of SGLT2i, and dapagliflozin on serum electrolytes (sodium and potassium) and on serum creatinine in hospitalized patients with AHF.

MATERIAL AND METHODS

This randomized controlled study was conducted from July 2022 to November 2022 by the Department of Pharmacology, Army Medical College (AMC), National University of Medical Sciences (NUMS), Rawalpindi in collaboration with Armed Forces Institute of Cardiology, Rawalpindi. Prior permission was taken from the Ethical Review Committee of AMC, NUMS Rawalpindi (ERC/ID/205) and from the Institutional Ethical and Review Board of the hospital (S/017/2022) before the commencement of the study. The sample size of 64 was calculated based on the prevalence of HF[9], using Rao soft sample size calculator. Keeping the confidence interval (CI) 95% and power 80% the sample size was also confirmed based on mean serum potassium levels (post-treatment) of 3.83±0.5 for the control group and 4.11±0.4 for the dapagliflozin group.[10] All selected individuals were explained about the research protocol and informed written consent was taken before enrolment of the patients.

One hundred and sixty adult male and female patients hospitalized with AHF were enrolled via non-probability purposive sampling and were distributed equally in two groups on the basis of the medication they received. Dapagliflozin group (n=80) received Dapagliflozin 10 mg daily as add-on therapy to the standard medical therapy for AHF. While the control group (n=80) was in the reception of only standard medical therapy for AHF. The standard medical therapy includes initiation of intravenous (IV) furosemide in continuous infusion or in equally divided bolus doses. The minimum dose of furosemide initiated for all patients was 60 mg/24 hours. The dose of furosemide was adjusted at doses adequate to obtain optimum volume status and congestion relief. The suitable dose of furosemide was decided by the attending physician. Acute heart failure treatment is other than loop diuretics including beta-blockers, angiotensin-converting enzyme, angiotensin II receptor blockers or angiotensin receptor blockers-neprilysin inhibitor, was commenced in fixed doses, once patients got stabilized and was individualized according to patient's condition. For each patient, laboratory data, specifically serum sodium, serum potassium and serum creatinine were collected during hospital admission, particularly on admission, i.e., within 24 hours of hospitalization and on day 7 or on discharge whichever happened earlier. For patients who got discharged earlier data for a second assessment was collected on discharge and for those having longer hospital stay data was collected on day 7. Demographic details of all the participants were taken at the time of enrolment.

As per inclusion criteria, patients over 30 years of age both male and female hospitalized with AHF and requiring IV administration of furosemide were included. The diagnosis was made on the basis of presenting signs and symptoms described by the European Society of Cardiology (ESC)[11], which are breathlessness at rest or with minor physical exertion, orthopnoea, paroxysmal nocturnal dyspnoea, weariness, pulmonary congestion (crackles on chest auscultation), ankle oedema, rapid weight gain, raised jugular venous pressure, and ascites. Patients having ejection fraction (EF) less than 40% were selected for the study irrespective of their diabetic status. Patients requiring mechanical ventilation, IV inotropes or vasopressors or presenting with cardiogenic shock, diabetes mellitus type 1, and urinary tract infection were excluded from the study. Patients already taking SGLT2 inhibitors or having an allergy to SGLT2 inhibitors were not included. Patients having eGFR less than 30 ml/min/1.73m^2, a history of AHF primarily prompted by acute myocardial infarction.

The main outcome was the change in serum electrolytes (sodium and potassium) observed during hospital admission. Secondary outcomes included worsening of renal functions (WRF) described as an increase in serum creatinine level of 0.3 mg/dL or more within 48 hours according to KDIGO (kidney disease: Improving Global Outcomes) criteria.[12]

IBM-SPSS V.26.0 was used for statistical analysis. Student's t-test and Mann-Whitney test were employed for parametric and non-parametric distribution respectively. Pearson's Chi-Square test was applied to analyze categorical data. Normally distributed continuous variables are presented as mean values with standard deviation, and non-normally distributed variables as median and interquartile range. Shapiro Wilks test was applied to check the normality of data. To control the confounding in the analyses stratification of data was done and was found to have the least effect. CI 95% was used, and the level of significance was set at $p \leq 0.05$.

RESULTS

The participants in both groups were analyzed and compared based on demographic and clinical characteristics. The results were statistically insignificant among both groups as shown in Table-1. The majority of participants were males 130 (81.25%). Out of a total of 160 individuals, 88 (55%) presented with Class III of

New York Heart Association (NYHA) and 72 (45%) with Class IV of NYHA. The presence of co-morbidities and medical therapy was analyzed and was found statistically nonsignificant between the two groups.

Regarding serum electrolytes, the two groups demonstrated insignificant differences in mean potassium and sodium levels on admission. However, following treatment mean level of serum potassium was found to be greater in the dapagliflozin group (4.28±0.46 mEq/L), in comparison to the control group (4.05±0.41 mEq/L) (p<0.001). Likewise, the mean level of serum sodium was greater in the dapagliflozin group (137.05±3.19 mEq/L), in comparison to the control group (135.75±3.81 mEq/L) (p=0.021). The percentage of patients who developed deterioration of serum electrolyte levels following treatment in both groups is presented in Table-3. Overall, a decreased trend towards electrolyte imbalance was observed in patients subjected to dapagliflozin treatment. Logistic regression also revealed an association between the administration of dapagliflozin and serum electrolyte levels. Initiation of dapagliflozin was associated with a decreased frequency of detrimental effects on potassium levels even after adjusting for possible confounders like age, gender, and baseline serum potassium. Odds ratio (OR) 0.36 (95% CI 0.16, 0.86) p=0.017. The same attribute was observed with serum sodium levels, OR 0.39 (95% CI 0.18, 0.86) p=0.02. An insignificant difference regarding the mean level of serum creatinine was observed among both groups on admission. Regarding serum creatinine levels, a statistically significant increase was depicted by both groups during admission as shown in Table-2. However, on comparison among groups, this difference couldn't reach a statistically significant level. Administration of dapagliflozin did not cause any noteworthy deterioration of renal function. The incidence of deterioration of renal function in both groups, observed following treatment was statistically insignificant. OR 0.68 (95% CI 0.32, 1.4) p>0.05.

Table-1: Baseline characteristics

Study Variables	Control Group (n=80)	Dapagliflozin Group (n=80)	*p*-value
Age (years)	66.03±11.44	64.22±10.39	0.299
Male Female	65 (81.25) 15 (18.75)	65 (81.25) 15 (18.75)	0.742
BMI (kg/m^2)	24.32±2.95	24.03±3.18	0.550
Hypertension	44 (55)	33 (41.25)	0.082
Dilated cardiomyopathy	32 (40)	34 (42.5)	0.748
Ischemic Heart Disease	37(46.25)	39 (48.75)	0.752
Atrial Fibrillation	14 (17.50)	11 (13.75)	0.514
Diabetes Mellitus	40 (50)	42 (52.5)	NS
NYHA Class III	29 (36.25)	37(46.25)	0.199
NYHA Class IV	51 (63.75)	43 (53.75)	0.199
Systolic BP (mm Hg)	124.24±10.09	123.19±9.45	0.498
Diastolic BP (mm Hg)	76.69±6.56	76.58±7.48	0.920
HR beats /min	80.24±5.14	79.47±5.82	0.381
Haemoglobin mg/dL	11.94±1.70	12.10±1.76	0.540
Platelets Count	220.27±60.64	227.81±75.75	0.488
Random Blood glucose mg/dL	167 (114.5 - 232)	160.5 (115.75 - 224.75)	0.551
LVEF%	30 (25 - 35)	30 (25 - 30)	0.333
Medical Therapy			
Loop Diuretics	80 (100)	80 (100)	NS
Beta Blockers	65 (81.25)	61 (76.25)	0.440
ACEI/ARNI/ARB	51 (63.75)	55 (68.75)	0.504

Values are presented as n (%), mean ± SD, or median IQR. BMI: Body mass index, BP: Blood Pressure, HR: Heart Rate, LVEF: Left ventricular ejection fraction, IQR: Interquartile range

Table-2: Comparison of variation in serum sodium, potassium and creatinine levels in the study groups over the period of time

Time	Control group	Dapagliflozin group	*p*-value*
Serum sodium (mEq/L) (Mean ±SD)			
Admission	136.96±2.51	136.80±3.41	0.732
Day7/Discharge	135.75±3.81	137.05±3.19	0.021
p*-value*	0.002	0.496	
Serum potassium (mEq/L) (Mean ±SD)			
Admission	4.25±0.39	4.32±0.39	0.263
Day7/Discharge	4.05±0.41	4.28±0.46	0.001
p*-value*	<0.001	0.508	
Serum creatinine (mg/dL) (Mean ±SD)			
Admission	1.22±0.28	1.17±0.24	0.161
Day7/Discharge	1.39±0.28	1.32±0.29	0.110
p*-value*	<0.001	<0.001	

p-value* = Independent sample t-test employed for intergroup comparison. *p*-value** = paired sample t-test employed for intragroup comparison

Table-3: Occurrence of deterioration in renal function and serum electrolytes during hospitalization

Variable	Control group n (%)	Dapagliflozin group n (%)	*p*-value
Worsening of renal function	21 (26.2)	16 (20)	0.348*
Deterioration in Potassium levels	25 (31.25)	12 (15)	0.015*
Deterioration in Sodium levels	17 (21.25)	6 (7.5)	0.02*

p-value*= chi-square test applied

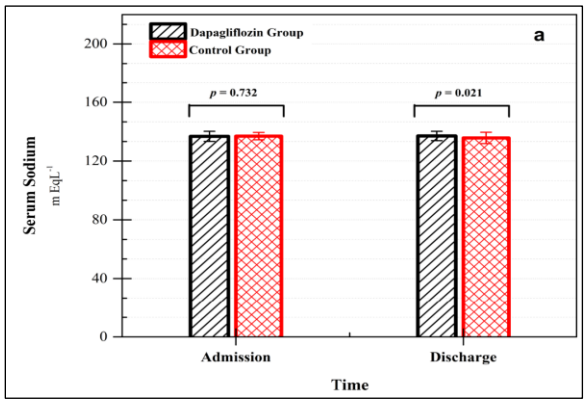
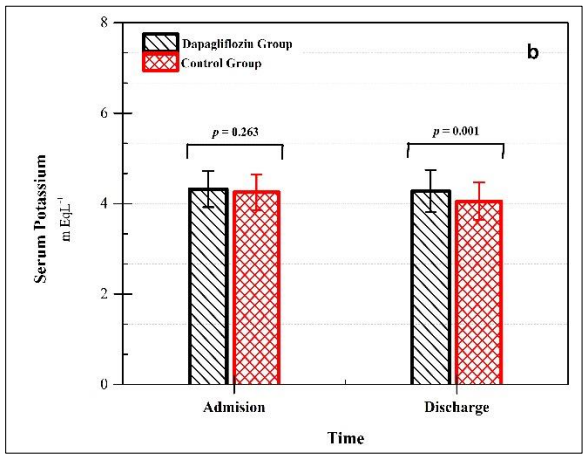
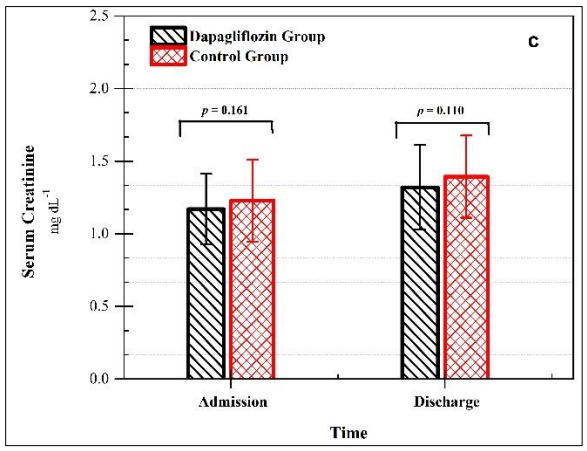


Figure-1: Comparison of Serum Sodium (a), Serum Potassium (b) and Serum Creatinine (c) between two groups



Serum Potassium



Serum Creatinine

DISCUSSION

AHF is one of the leading causes of morbidity in the elderly and requires repeated hospitalizations due to congestion and volume overload[1]. Loop diuretics, being the cornerstone for the treatment, are administered to almost all patients. They provide immediate relief, when used in high doses, however, sustain risks like diuretic resistance, electrolyte imbalance and increased incidence of acute kidney injury (AKI).[13] Multiple pharmacological therapies have been evaluated to minimize the risks and improve clinical outcomes, and the addition of thiazide and mineralocorticoids has been suggested.[14] These agents do not come without cons and can cause electrolyte disorders as hyponatremia, hypokalaemia and hyperkalaemia, which can lead to other complications like arrhythmia.[14] Hence, the development of effective and new approaches is essential to manage patients with AHF.

SGLT2i in recent trials, have been advocated for its promising results in HF and in the current study we have evaluated and equated the impact of SGLT2i, dapagliflozin in admitted patients with AHF, particularly focusing on serum electrolytes and serum creatinine. Dapagliflozin was found to have little impact on electrolyte imbalance as no marked hypokalaemia or hyponatremia was detected in the patients subjected to dapagliflozin treatment. Whereas, the control group demonstrated statistically significant decreased levels of potassium and sodium following treatment when compared to the study group. This observation might be due to the consumption of larger doses of loop diuretic by the control group. In the present study, we did not observe any significant detrimental effects of dapagliflozin on serum electrolytes. The effect of dapagliflozin on renal functioning ascribed by any change in serum creatinine was also explored. Both groups showed increased levels of creatinine during admission. However, on intergroup comparison, the change was statistically insignificant. The addition of dapagliflozin to the standard medical therapy was not associated with any deterioration of renal function. Validating our results, Wilcox *et al.*[15] reported the same findings in 2018 and showed clinically insignificant changes in serum sodium and creatinine levels when dapagliflozin 10 mg per oral was given alone and in combination with bumetanide to the study participants. The follow-up period was 1 week. He

included 42 healthy volunteers for the study whereas our study was conducted on patients admitted with AHF. Parallel findings were stated by Ibrahim and associates[10] in 2020 when oral dapagliflozin 10 mg/day was given to 50 diabetic patients admitted with AHF and was compared with control. The initiation of dapagliflozin significantly improved dyspnoea in hospitalized patients and produced adequate decongestion without causing any hypokalaemia. A comparison of mean levels of serum creatinine and serum electrolytes (sodium and potassium) was also done between the two groups that demonstrated statistically significant and better results with dapagliflozin, thus supporting our findings. In addition to this, a study was conducted by Nakagaito M *et al*.[16] in 2019. They enrolled 81 patients hospitalized with AHF and T2DM. A comparative analysis was done equating the efficacy of dapagliflozin, canagliflozin and empagliflozin. They analyzed serum creatinine, potassium and sodium levels obtained at baseline, after 1 and 7 days. The study showed no significant deterioration in the levels of serum creatinine and no electrolyte disturbances were observed by the addition of any of the three SGLT2 inhibitors. Our study proved the same effects of SGLT2i, but we used only dapagliflozin for AHF, in our project. Moreover, our study population included both diabetic and non-diabetic patients. Recently, a study conducted by Voors *et al*.[17] in 2022 also demonstrated similar findings endorsing negligible effect SGLTi on electrolytes. They evaluated the effect of empagliflozin 10 mg in AHF, on renal functions and serum electrolytes and came up with statistically insignificant findings. Empagliflozin did not demonstrate any electrolyte imbalance, signifying the findings in our study.

The least effect of SGLT2i on electrolyte balance might be due to the fact that they augment the excretion of plasma glucose via kidneys, coupled with sodium and appear to reduce interstitial volume via osmotic diuresis. Unlike traditional diuretics, their action is least likely to activate the neurohormonal system[7] thus, the reason for insignificant variations in the electrolyte profile of patients. Hence, the findings in our study prove the negligible effect of dapagliflozin on serum sodium and potassium, accompanied by an insignificant impact on renal functions as well. Multiple references from the literature support the findings of our study. Hence, SGLT2i should be considered and added to the treatment regime for AHF.

Study limitations:

The study had its limitations as for loop diuretics, only furosemide was given in our study. Further research, to determine synergetic effects with other loop diuretics should also be planned. Moreover, a comparison between dapagliflozin with thiazide diuretics as add-on therapy should also be considered in future studies.

CONCLUSION

Dapagliflozin despite being an anti-diabetic drug, is an effective treatment for HF. Initiation of dapagliflozin is not associated with deterioration of serum potassium and sodium levels and does not cause any deterioration of renal function when used as add-on therapy in AHF.

AUTHORS' CONTRIBUTION

SFFG: Conceived, and designed, statistical analysis with interpretation, and write-up. SA: Project supervision, evaluated manuscript for important intellectual content. MN, KF: Review and final approval of the manuscript. MBS, MF: Supervision, revision.

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Submitted: March 19, 2023	*Revised: July 23, 2023*	*Accepted: August 8, 2023*

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