ORIGINAL ARTICLE

Early initiation of Dapagliflozin and its effect on health related quality of life in acute heart failure: a randomised controlled trial

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Abstract

Objective: To determine the role of dapagliflozin in improving functional status and health-related quality of life in acute heart failure cases.

Method: The prospective, randomised controlled study was conducted from July 2022 to January 2023 at the Pharmacology Department of Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan, in collaboration with the Armed Forces Institute of Cardiology, Rawalpindi, and comprised hospitalised adult patients of either gender with acute heart failure. They were randomised into two equal groups, with intervention group A receiving oral dapagliflozin 10mg daily in addition to conventional therapy, and with control group B receiving conventional therapy alone. Health-related quality of life was assessed using Kansas City Cardiomyopathy Questionnaire. Improvement in functional status was assessed by New York Heart Association functional classification. Data was obtained at baseline and after 12-week follow-up. Data was compared using SPSS 26.

Results: Of the 150 patients, 75(50%) were group A; 62(82.66%) males and 13(17.3%) females with mean age 63.76±10.05 years. There were 75(50%) patients in group B; 60(80%) males and 15(20%) females with mean age 66.13±11.73 years ($p>0.05$). The study was completed by 73(97.3%) in group A and 69(92%) in group B. The Kansas City Cardiomyopathy Questionnaire scores improved post-intervention compared to baseline values ($p<0.001$) in both groups. Group A showed comparatively greater improvement in health status compared to group B ($p<0.05$).

Conclusions: Early initiation of dapagliflozin in patients admitted with acute heart failure was found to be associated with rapid and significant improvement in health and functional status.

Clinical Trial Link: https://www.irct.ir. RCT No. (IRCT20220529055013N).

Key Words: Heart failure, Dapagliflozin, HRQOL.

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Introduction

Heart failure (HF) is one of the prime health concerns affecting more than 64 million people worldwide[1]. Acute heart failure (AHF), categorised by sudden worsening of HF symptoms, such as dyspnoea and exertion, can cause a substantial decline in physical and social functioning. Additionally, it requires frequent medical appointments and hospitalisations, and that contributes to the detrimental impact on health-related quality of life (HRQOL)[1]. Individuals hospitalised with AHF experience a significant burden of HF-related symptoms and physical limitations[2,3]. Therefore, enhancing health status, including symptoms, functional status and QOL, is the main objective while managing AHF in admitted patients[3,4]. Despite advances in therapeutic treatment, there is still a considerable unmet need for therapies that may provide a compelling benefit in improving health status outcomes for individuals with AHF. The existing HF therapies have a varying effect on physical limitations and HRQOL. Despite their positive effect on ventricular remodelling, established therapies, like beta blockers, have not been extensively evaluated for their impact on physical limitation and QOL in the context of AHF. Although, beta blockers have been shown to improve heart function, morbidity and mortality, their effect on improving HRQOL appears to be limited[4,5].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, novel antidiabetic agents, have appeared as a promising therapeutic option for patients with chronic heart failure (CHF)[6]. Multiple clinical trials have shown that SGLT2 inhibitors can significantly improve symptoms and physical limitations in patients with CHF[7]. Additionally, clinical studies have demonstrated that these drugs can reduce hospitalisations and improve survival in CHF patients[6,7]. However, whether or not these drugs are

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equally effective in patients hospitalised with AHF is yet to be fully investigated.

The current study was planned to investigate the role of SGLT2 inhibitor dapagliflozin in improving functional status, physical limitations, symptom severity and QOL in hospitalised AHF patients.

Patients and Methods

The prospective, randomised controlled study was conducted from July 2022 to January 2023 at the Pharmacology Department of Army Medical College AMC), National University of Medical Sciences (NUMS), Rawalpindi, Pakistan, in collaboration with the Armed Forces Institute of Cardiology (AFIC), Rawalpindi.

After approval form the institutional ethics review committee, the sample size was calculated using Raosoft[8] sample size calculator based on HF prevalence reported in literature[8] while keeping 95% confidence level and 5% margin of error. The prevalence of HF has been reported to be 1-2% but it significantly increased within older age, amounting to 4.3% in population aged >65 years[9]. The sample was raised using non-probability purposive sampling technique. Those included were hospitalised AHF patients aged >30 years having New York Heart Association (NYHA) class II-IV. The diagnosis was established on the basis of presenting signs and symptoms described by the European Society of Cardiology (ESC)[10]. Patients having ejection fraction (EF) <40% were selected irrespective of their diabetic status.

Patients requiring mechanical ventilation (MV) or intravenous (IV) inotropes, and those presenting with cardiogenic shock, or having type 1 diabetes mellitus were excluded. Also excluded were patients having history of urinary tract infection (UTI), already taking SGLT2 inhibitors or having allergy to SGLT2 inhibitors, having estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2, and so were pregnant and lactating women.

After taking written informed consent, the patients were randomised into two equal groups using the envelope method within 24 hours of hospital admission. Intervention group A received oral dapagliflozin 10mg daily in addition to conventional therapy, and control group B received conventional therapy alone. The conventional therapy included medical treatment in accordance with recommended clinical guidelines[10], including the initiation of primarily loop diuretics[10]. Medical therapy for AHF, other than dapagliflozin, was left to the decision of the attending physician.

Dapagliflozin was initiated within 24 hours of hospital admission, and was continued till follow-up. During hospital admission, demographic details and baseline laboratory investigations were recorded. HRQOL was assessed using Kansas City Cardiomyopathy Questionnaire (KCCQ-23)[11], while improvement in functional status was assessed using the NYHA functional classification[10]. Data was obtained at baseline and after 12-week follow-up.

The main outcome was the difference in change from baseline in pre-specified KCCQ-23 domains, including physical limitation score (PLS), total symptom score (TSS) and overall summary score (OSS). The secondary outcome was any improvement in NYHA functional class.

KCCQ-23 is a patient-reported outcome measure used to assess HRQOL in people with HF. It is a reliable, valid and disease-specific 23-item tool that computes physical function, symptom severity, QOL, and social function associated with HF over the preceding 2 weeks[11]. KCCQ-OSS originates from the combination of all domains. The total score ranges 0-100, with higher scores indicating better HRQOL. A change in score of at least 5 points is considered clinically significant, indicating a meaningful improvement in HRQOL[11].

Data was analysed using SPSS 26. Data normality was assessed using Shapiro Wilk's test. Student's t-test was employed to analyse normally distributed data, and Mann Whitney U test to analyse non-normally distributed data. Pearson's chi-square test was applied to analyse categorical data. Parametric continuous variables were presented as mean ± standard deviation, while non-parametric continuous variables were presented as median with interquartile range (IQR). Confidence interval (CI) 95% was used, and $p<0.05$ was considered significant.

Results

Of the 150 patients, 75(50%) were group A; 62(82.66%) males and 13(17.3%) females with mean age 63.76±10.05 years. There were 75(50%) patients in group B; 60(80%) males and 15(20%) females with mean age 66.13±11.73 years ($p>0.05$). The study was completed by 73(97.3%) in group A and 69(92%) in group B (Figure 1). N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) data was available for 119(79.3%) patients; 61(51.3%) in group A and 58(48.7%) in group B. Demographic, clinical, echocardiographic and laboratory parameters were not significantly different at baseline (Table 1).

The KCCQ scores improved post-intervention compared to baseline values ($p<0.001$) in both groups (Figure 2). Group A showed comparatively greater improvement in NYHA health status compared to group B (Table 2).

Discussion

Patients admitted with AHF experience a great deal of incapacitating symptoms, physical limitations and declining functional status that make life difficult for the patients even after discharge[12]. Although various pharmacological therapies have been studied in this context, definite treatment is still lacking. SGLT2 inhibitors have shown to improve symptoms in CHF patients[7], but their impact on HRQOL in the population hospitalised with AHF requires exploration.

The current randomised-controlled study carried out among hospitalised AHF patients demonstrated that initiation of 10mg oral dapagliflozin convincingly improved symptomatology and physical limitations in AHF. After 12 weeks of treatment, the findings demonstrated a significant and consistent improvement in patient-reported outcomes across PLS, TSS and OSS domains of KCCQ-23 in both diabetic and non-diabetic patients. To our knowledge, the current study is the first clinical research to demonstrate the benefits of dapagliflozin on patient-reported outcomes in AHF individuals in South Asian population, and the results support early initiation of dapagliflozin to improve physical limitations in such patients.

Although the current is the first local effort to establish the effect of dapagliflozin on HRQOL in hospitalised patients with AHF, the data is comparable to the results of previously conducted studies on SGLT2 inhibitors. For instance, a clinical trial[13] found that sotagliflozin, a mixed SGLT1/2 inhibitor, improved KCCQ-12 mean score by 4.1 points compared to placebo after 4 months in diabetic patients with AHF. Similarly, a recent study[14] found that empagliflozin was superior to placebo in improving HRQOL, assessed using KCCQ, in patients with AHF during the immediate post-discharge period.

The assessment of functional class is crucial in the management of HF. In addition to KCCQ-23, the current study also evaluated NYHA functional classification of patients in both groups. The distribution of patients in both groups according their functional class was comparable and statistically non-significant at the baseline. However, after 12 weeks, the patients treated with dapagliflozin demonstrated a clear upgradation in the NYHA functional class compared to the controls. These findings are consistent with a study[15] which evaluated the effect of dapagliflozin in HF with mildly reduced EF. Similar effects of dapagliflzoin were stated by another study[16] which observed a significant improvement in NYHA class with the addition of 10mg dapagliflozin to standard therapy for refractory HF patients.

Although the exact mechanism of cardiovascular benefits by SGLT2 inhibitors is not known, various plausible mechanisms have been described. Augmented renal excretion of glucose leading to osmotic diuresis, antihypertensive effect on both systolic and diastolic blood pressure, weight-loss, improved myocardial energetics and reduction in arterial stiffness are probable reasons for the clinical benefits of SGLT2 inhibitors[17].

Table-1: Baseline clinical characteristics.

Variables	Dapagliflozin (n=75)	Control (n=75)	p Value
Age (years)	63.76 ± 10.05	66.13 ± 11.73	0.185
Male	62 (82.66)	60 (80)	0.675
Female	13 (17.3)	15 (20)	
Systolic BP, mm Hg	123.68±9.47	124.41±10.10	0.647
Diastolic BP, mm Hg	77.05±7.36	76.71±6.53	0.761
Heart Rate beats/min	79.44±5.65	80.48±5.15	0.241
Body mass Index Kg/m2	24.01±3.24	24.37±2.93	0.476
Serum Creatinine, mg/dL	1.17 ±0.24	1.21±0.28	0.388
NT-pro-BNP, pg/mL	10536 (4981.35-16114.15)	10785.90 (4889.10-16832.25)	0.989
Fasting Blood Glucose mg/dL	127.48±43.79	130.70±45.60	0.659
Haematocrit %	36.86±4.92	37.03±4.63	0.826
LVEF %	30 (25-30)	30 (25-35)	0.274
Medical History			
Hypertension	32 (42.6)	41 (54.6)	0.142
Type 2 Diabetes Mellitus	36 (48)	37 (49.3)	0.870
Ischaemic Heart Disease	36 (48)	36 (48)	1.00
Atrial Fibrillation	10 (13.3)	12 (16)	0.644
Dilated Cardiomyopathy	33(44)	30(40)	0.620
Guideline Directed Medical Therapy			
Loop Diuretics	75 (100)	75 (100)	NS
Beta blockers	59 (78.6)	60 (80)	0.840
ACEi/ARB	51 (68)	49 (65.3)	0.729

Values are presented as Mean ± standard deviation (SD), n (%) or median (interquartile range [IQR]). BP: Blood pressure, LVEF: Left ventricular ejection fraction, ACEi: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, NT-pro-BNP: N-terminal prohormone of brain natriuretic peptide.

Table-2: NYHA classification in the study groups.

	DAPAGLIFLOZIN	Control	p Value
NYHA CLASS BASELINE			
CLASS III	35 (46.66%)	28 (37.33%)	0.247
CLASS IV	40 (53.33%)	47 (62.66%)	0.247
NYHA CLASS AFTER 12 WEEKS			
CLASS II	44 (60.27%)	17 (24.63%)	< 0.001
CLASS III	29 (39.72%)	44 (63.76%)	0.014
CLASS IV	2 (2.73%)	14 (20.28%)	0.002

NYHA: New York Heart Association.

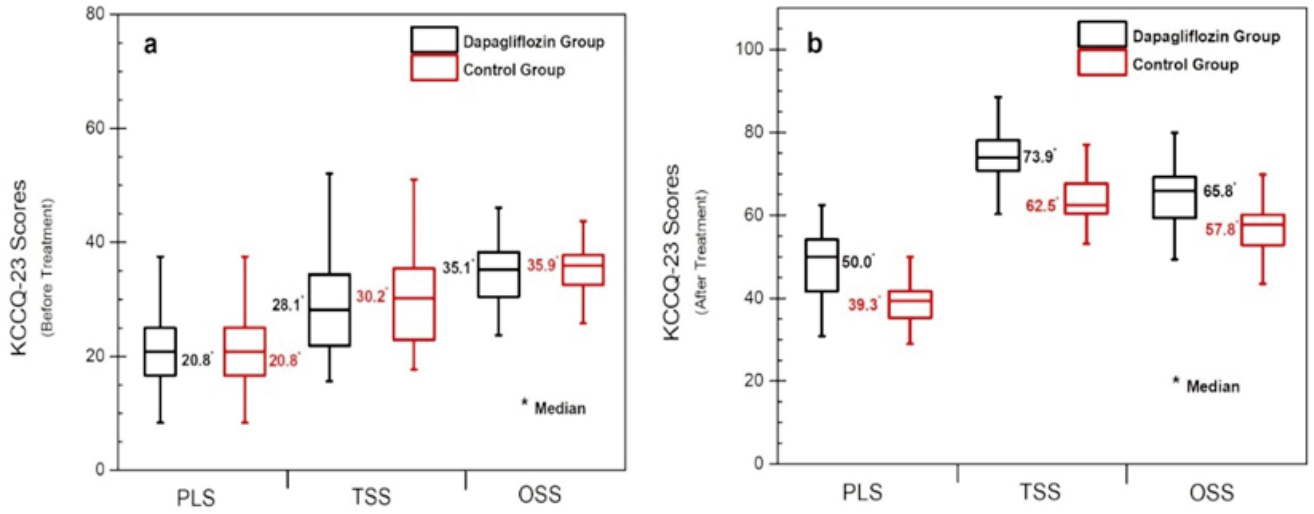

Figure-2: Comparison of Kansas City Cardiomyopathy Questionnaire (KCCQ-23) scores between the study groups a) before treatment and b) after 12 weeks of intervention.
PLS: Physical limitation score, TSS: Total symptom score, OSS: Overall summary score

The outcomes pertaining to HRQOL in the current study are of clinical importance and contribute to the previously reported beneficial effects of SGLT2 inhibitors in various ways. There are only a few therapies that have shown an improvement in symptoms and functional status in the early post-discharge period in population hospitalised with AHF[11]. The current study evidently proved the beneficial effect of SGLT2 inhibitor dapagliflozin in early post-discharge period.

The current study has its limitations as it was done at a single centre, with a relatively small sample size. A multicentre study with larger sample size and longer follow-up is recommended.

Conclusion

Evidence supported the early initiation SGLT2 inhibitor, specifically dapagliflozin, in hospitalised patients with AHF. Patients subjected to dapagliflozin demonstrated a greater improvement in physical limitation, functional status and HRQOL.

Disclaimer: None.

Conflict of Interest: None.

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Authors' Contributions

SFFG: Conceived idea, study designed, collected data, statistical analysis and interpretation, writing.
SA: Project Supervision and evaluation.
MNKF: Review and Final approval.
MBS and **FW**: Project Supervision at the hospital, helped with data collection.