IS EMPAGLIFLOZIN A NEW DRUG IN THE MAKING FOR PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE?

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Abstract

Background and Objectives: Empagliflozin has dramatically enhanced outcomes in heart failure patients. The objective was to study the effect of Empagliflozin in acute setting as add-on treatment on cardiac hemodynamic by measuring pulmonary capillary wedge pressure (PCWP) and by Echocardio-graphy

Methods: It was a prospective observational study conducted on 75 patients presenting with acute heart failure at Chaudhary Muhammad Akram Teaching & Research Hospital Lahore,(CMAT & RH) with 4 days in-hospital echocardiographic follow up. After taking approval from IRB & written informed consent from patient, a questionnaire was used as data collection tool with information regarding basic demographic features prescribing empagliflozin as well as PCWP on day 0, day 1 & day 3 after fulfilling the inclusion criteria and results were calculated using Statistical Package for Social Sciences (SPSS) version v 20 32 bit.

Results: In our study, the mean age of participants was 57.5±7 years with 24% males (n=18) and 76% females (n=57). 93.3% of participants were known hypertensive, 57.3% were diabetic, 21.3% of cases were having significant family history of ischemic heart disease. Among all, 64% were having 2 or less risk factors and 36% were having more than 2 risk factors. In accordance to symptoms, 35% of participants were having NYHA class II to III symptoms and 65% were in NYHA class IV. 53% of participants were having chronic heart failure symptoms while 43% were having denovo symptoms. Among them, 42% were started with 25mg/day empagliflozin and 58% were started with 10mg/day according to their symptoms and requirements. Mean PCWP calculated at Day 0 was 22+7.5mmHg reduced to 14.3±5.2 mmHg at 1st day and10.6±3.3 mmHg at 2nd day after therapy which was statistically significant (p value=0.041).

Conclusion: This study concluded that addition of Empagliflozin to standard treatment significantly reduced PCWP in patients having acute decompensated heart failure.

Key Words: Pulmonary capillary wedge pressure(PCWP), Empagliflozin, Heart failure (HF).

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Heart failure is basically a complex clinical syndrome with functional or structural defect in ventricular filling or ejection of blood leading to reduced cardiac output and pulmonary or systemic congestion.[1] HF is a major burden on health and economy due to advancing ages of our populations, both globally as well as in United States[1,2] where for the first time, age-adjusted death rate per capita has increased significantly.[3] Recent data from US have found total deaths due to HF, increased from 275 000 in 2009 to 310 000 in 2014.3In 2017, the hospitalizations due to HF were 1.2 million HF in the United States among total 924 000 patients, showing 26% increase in HF hospitalizations.[4]

In 2014 the publication of PARADIGM HEART

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FAILURE trial was a major breakthrough and ARNI was considered to be the major discovery of the current era for Heart Failure patients.[5] However, with the most recent trials, data on Sodium Glucose transporter-2 inhibitors (SGLT2i), has opened another very important gateway for physicians because of their significant impact on morbidity & mortality on HF. Initially, Sodium-glucose cotransporter-2 (SGLT2) inhibitors were used to treat type 2 diabetes because of their glycosuria action leading to decreased Glucose levels in blood. These are major transport proteins that are responsible for renal reabsorption of glucose. However, many cardiovascular outcome trials in diabetic patients demonstrated an unexpected and significant decrease in hospitalization due to heart failure and mortality as well as morbidity with these agents.[6]

The first SGLT2 inhibitor was Empagliflozin which was used in trials to prevent the heart failure in high risk diabetic patients. In the EMPA-REG OUTCOME TRIAL, Diabetic patients at high cardiovascular risk of HF showed that empagliflozin, in comparison to placebo, markedly reduced all-cause death, the risk of major adverse cardiovascular events (MACE) that is myocardial infarction, stroke, and cardiovascular death and hospitalization for heart failure.[7] In DAPA-HF trial, 4744 heart failure patients having NYHA class II to IV and ejection fraction of 40% or less were randomly assigned in dapagliflozin 10 mg once daily or placebo in addition to standard therapy group. The risk of worsening heart failure or cardiovascular death was lower among dapagliflozin groups compared to placebo in both diabetics and non-diabetics. The secondary endpoints of heart failure hospitalization, CV death, and all-cause deaths also had significant reduction with dapagliflozin compared to placebo in both diabetic and non-diabetic groups.[8]

Patients with chronic heart failure with decreased ejection fraction (HFrEF) were enrolled in the DAPA-HF and EMPEROR-decreased trials.[6,9] whereas patients with chronic heart failure with preserved ejection fraction (HFpEF) were evaluated in the EMPEROR-Preserved trial.[10] Compared to a placebo, SGLT2 inhibitors demonstrated a relative decrease in hospitalizations for heart failure or cardiovascular deaths of 20% to 25% across all three of these trials. The impact of SGLT2 inhibitors on hemodynamics, as determined by PA pressures or PCWP in cases of acute heart failure, has not, however, been thoroughly examined in any randomized double-blind trials before. The effects of empagliflozin on pulmonary artery pressure (PAP) in patients with advanced heart failure (HFrEF and HFpEF), regardless of the presence of diabetes, were examined in the EMBRACE-HF trial (Empagliflozin Evaluation by Measuring the Impact on Hemodynamics in Patients with Heart Failure) using a previously implanted Cardio MEMS remote PA pressure sensor in those who showed indications of implantation.[11] As a result, a small number of additional trials revealed that the advantages of SGLT2i are unlikely to be accounted for by improvements in traditional secondary cardiovascular risk factors such blood pressure, cholesterol, or HbA1c levels.[14-16]

In our study, we specifically aimed to measure the acute effect of empagliflozin on PCWP in addition to standard HF therapy, using Nagueh formula[17] in patients admitted with acute heart failure during index hospita-lization, as most of the previous studies have focused on long term and intermediate effects of SGLT2i on cardiovascular health and there is no previous work done in our continent as per best my knowledge so our study will bridge this gap and will help understand the effect in our population.

METHODS

It was a Prospective observational study conducted on 75 patients calculated with 95% confidence level & 4% margin of error, collected via non-probability purposive sampling, presenting with acute heart failure at Chaudhary Muhammad Akram Teaching & Research Hospital Lahore,(CMAT & RH) with 4 days in-hospital echo-cardiographic follow up. After taking approval from IRB & written informed consent from patients fulfilling the inclusion criteria of all patients diagnosed clinically and confirmed on ECHO as having acute heart failure with a high calculated PCWP irrespective of underlying cause a

questionnaire was filled. Patients with normal PCWP, those having Mitral Stenosis, Atrial Fibrillation, advanced CKD, restrictive cardiomyopathy, those already having SGLT2 inhibitors or having contraindication to SGLT2 inhibitor were excluded from the study. Patients were given empagliflozin according to their symptoms and presence of co-morbid contition (dosage: 25mg & 10mg). The questionnaire was used as data collection tool with information regarding basic demographic features as well as PCWP on day 0, day 1 & day 3 and results were calculated in Statistical Package for Social Sciences (SPSS) version v 20 32 bit. For quantitative studies, descriptive and frequency distribution were utilized, while percentages and graphs were utilized to display categorical data. A P-value of less than 0.05 was deemed significant.

Cost of medication & investigations was the sole responsibility of the researcher & patient had to bear no financial burden.

RESULTS

In our study, the mean age of participants was 57.5±7 years with 24% males (n=18) and 76% females (n=57). 93.3% of participants were known hypertensive, 57.3% were diabetic, and 21.3% of cases were having family history of ischemic heart disease.

Among all 64% were having 2 or less risk factors and 36% were having more than 2 risk factors. (Table 1) In accor-dance to symptoms, 35% of participants were having dyspnea of NYHA class II to III symptoms and 65% were in NYHA class IV. (Figure 1) 53% of participants were having chronic heart failure symptoms while 43% were having denovo symptoms. (Figure 2) Among them, 42% were started with 25mg/day empagliflozin and 58% were started with 10mg/day according to their symptoms and requirements. (Figure 3)

Table 1: Baseline Characteristics

Age (mean ± S.D) in years	57.5±7.04
Gender n (%)	
Males	18 (24%)
Females	57 (76%)
Risk Profile n (%)	
Hypertensive	75 (93.3%)
Diabetic	43 (57.3%)
Family History	16 (21.3%)
Patient with 2 risk factors	48 (64%)
Patient with > 2 risk factors	27 (36%)

Mean PCWP calculated at Day 0 was 22+7.5mmHg

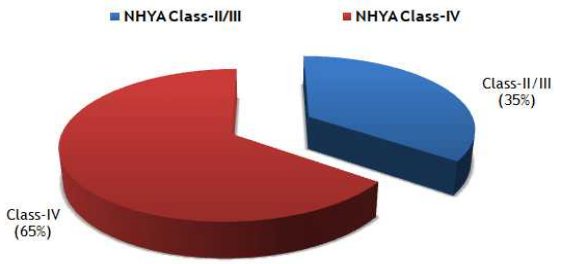

Figure 1: NYHA Classification

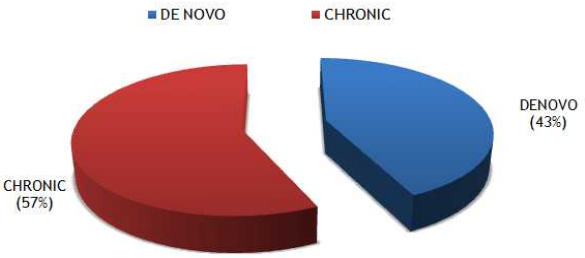

Figure 2: Types of Heart Failure

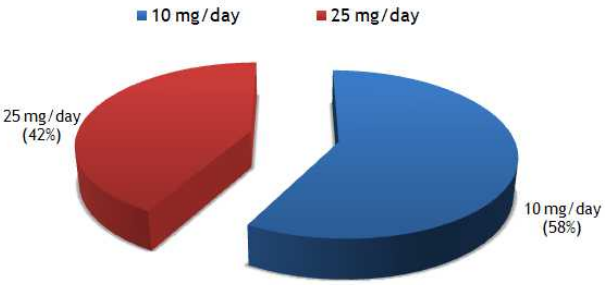

Figure 3: *Dose of Empagliflozinin*

reduced to 14.3±5.2 mmHg at 1st day and 10.6±3.3 mmHg at 2nd day after therapy which was statistically significant (p value=0.041)=Reduction in mean PCWP was similar with dosage of 25mg &

Table 2: Reduction In Pulmonary Catheter Wedge Pressure (pcwp) After Therapy

Day 0	Day 1	Day 2	P-value
22±7.5mmHg	14.3±5.2mmHg	10.6±3.3mmHg	.041
p- value < 0.05 = Significant			

10mg.(Table 2).

DISCUSSION

The studies done on SGLT2 inhibitors has opened a major gateway to knowledge and improved the QoL as well as reduced morbidity and mortality in heart failure patients by decreasing the PCWP even at short index hospitalization in both diabetics and non-diabetics. In patients with heart failure, the addition of a SGLT2i to ARNI, betablocker, and aldosterone-anta-gonist significantly decreased PA-pressures after three weeks, regardless of Diabetes Mellitus, and increased up to 3 mmHg after ten weeks, according to a non-randomized, small, single-centered observational study.[18] For the diastolic, systolic, and mean PA pressures, the findings were consistent. Since pulmonary hyperten-sion, which is more common in patients with HFrEF (40–75%) and HFpEF (18–80%) and is linked to inc-reased hospitalization rates and mortality rates, the inclusion of PA pressures as a treatment target decreased the hospitalization rate in both HFrEF and HFpEF.[19,20] After a 12-week course of medication, a smaller clinical trial shown that empagliflozin significantly decreased the PCWP in patients with HFrEF.[21]

Our study also concluded more or less the same results, mean PCWP calculated at Day 0 was 22+7.5 mmHg reduced to 14.3±5.2 mmHg at 1st day and 10.6 ±3.3 mmHg at 2nd day after therapy with Empagliflozin for heart Failure patients regardless of their diagnosis of T2DM, which was statistically significant. EMBRACE HF trial also backed up our results as it was observed that Empagliflozin reduced PA pressures by 1.7–mm Hg in comparison to placebo at 12 weeks (that increased to 1.9–mm Hg at 13 weeks).[11]

Due to its small size, one centre design, non-randomized research, and use of a restricted sample in a single hospital context, our study is also subject to several limitations. Nonetheless, it builds upon and expands upon earlier findings and investigations, and the regular evaluation of PA pressures in this study made it possible to produce important and trustworthy data for the future.

CONCLUSION

This study concluded that addition of Empagliflozin in addition to standard HF treatment had significant effect on reducing PCWP in patients presenting with acutely decompensated HF. This also translated into functional improvement of the patients in short term in terms of improvement in their in-hospital NYHA class. Randomized Controled trials are warranted to confirm the efficacy and safety of this approach.

Ethical Approval:

The ethical Approval was obtained from Azra Naheed Medical College. (Reference No. IRB/ANMC/2022/016)

Conflict of Interest: *None*

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