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Frequency of Hyperkalaemia in Patients with Heart Failure with Reduced Ejection Fraction at Tertiary Care Hospital

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Abstract:

Background: *Hyperkalaemia in Patients with Heart Failure with Reduced Ejection Fraction. The present study, the rationale was to show the frequency of hyperkalemia & related factors in the HF outpatient clinic with real life facts.*

Methods: *573 patients monitored in the HF outpatient clinic with left ventricular ejection fraction ≤42% and potassium level ≥3.5 mmol/L were included.*

Results: *The potassium value of the patients was median 4.6 mmol/L [IQR, 3.2-4]. It was reviewed in three groups as 3.5-5 mmol/L (normokalemia), 5.1-5.5 mmol/L (mild hyperkalemia) and ≥ 5.5 mmol/L (moderate to severe hyperkalemia), according to baseline potassium levels. Mild hyperkalemia was present in 14.5% and moderate to severe hyperkalemia was present in 7.1%. The potassium value was >5 mmol/L in 21.6% of the patients. The likely glomerular filtration rate (eGFR) (OR: 0.969, 95% CI: 0.631-0.643, p<0.001), angiotensin alterinh enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) (OR: 1.697, 95% CI: 1.124-2.562, p=0.012), and mineralocorticoid receptor antagonists (MRA) (OR: 0.200, 95% CI: 0.033-2.142, p=0.02) were considered as independent factors for hyperkalemia.*

Conclusion: *eGFR level, ACE-I/ARB, and MRA were associated with hyperkalemia in chronic heart failure in real-life facts.*

Keywords: Renin-Angiotensin System, Hyperkalemia; Potassium, Heart Failure.

INTRODUCTION

Hyperkalemia is a condition characterized by a blood potassium level of > 5.0 mmol/L (mEq/L). This is a critical and problematic situation that is often seen in the clinical followup of heart failure (HF) patients [1,2]. The severity of hyperkalemia is defined as mild, with potassium levels >5.0 to <5.5 mmol/L, moderate, between 5.5 and 6.0 mmol/L and severe, > 6.0 mmol/L [1]. Renin angiotensin aldosterone system modulators (RAAS-

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M), known to reduce mortality and recommended by guidelines, are the cornerstone of HF treatment.

However, the widespread use of these agents has resulted in an increased incidence of life threatening hyperkalemia.[1,3] The frequency of hyperkalemia varies according to the reference value. In acute HF, the proportion of potassium levels > 5 mmol/L has been reported to be 35% [4]. In one study, the rate of patients with > 5 mmol/L in the angiotensin-converting enzyme inhibitor (ACE-I) group was reported at 13.5%, and 12.3% in the angiotensin receptor/neprilysin inhibitor (ARNI) group, with the frequency of hyperkalemia at >5.5 mmol/ L reported as 2.5% vs. 2.2%, respectively [5]. When mineral corticoid receptor antagonists (MRAs) were added in addition to ACE-I, the incidence of hyperkalemia (> 5.5 mmol/L) has been reported at 11.8% with eplerenone and 13% with spironolactone [6,7].

Many studies have observed the association of potassium levels with mortality in chronic HF [8-10]. Reducing the dose or completely discontinuing RAAS-M due to increased potassium may result in symptoms of withdrawal from this therapy, which has been shown to improve clinical outcomes [11,12].

The purpose of our study to show the frequency of Hyperkalaemia in patients with Heart failure with reduced ejection fraction at tertiary care hospital.

MATERIALS AND METHODS

573 patients with left ventricular ejection fraction (LVEF) ≤ 40%, followed in a tertiary hospital HF clinic between 2022 to 2023, were retrospectively analyzed. 573 patients, who were followed up for at least one year and whose potassium level was known at admission, were evaluated for the study. The patients were evaluated according to the basal potassium level at the first HF outpatient clinic admission. Since hyperkalemic and normokalemic patients were to be compared, 10 patients were excluded because their potassium level was < 3.5 mmol/L. Thus, 563 patients diagnosed with HF according to the HF Guidelines[2], with LVEF ≤40%, potassium level ≥ 3.5 mmol/L and ≥18 years of age, were included in the study.

Demographic and biochemical parameters and drugs used by patients were collected from hospital records. In our hospital, potassium levels are measured from serum and other biochemical measurements are standard. The patients were compared in three groups according to their baseline serum potassium levels as 3.5-5 mmol/L, 5.1-< 5.5 mmol/L, and ≥ 5.5 mmol/L [1]. Approval was obtained for the study by the local ethics committee.

Statistical analyses were evaluated with the Statistical Package for the Social Sciences software v. 22.0. Using the Kolmogorov-Smirnov test, data with normal distribution was presented as standard deviation, and mean and non-normally distributed data was presented as interquartile ranges [25-75] as the median. Groups were compared according to normality using the Kruskal-Wallis test or Student's t-test. Categorical variables were provided as numbers and percentages and compared with the Chi-square test. Parameters associated with hyperkalemia were presented as 95% confidence intervals and odds ratios by logistic regression analysis. A statistically significant P value was accepted at 0.05.

RESULTS

563 suitable heart failure patients (411 males, 152 females) were included in our study. The median age of the patients was 64 [IQR, 54-73]. 55.8% had an ischemic etiology and an LVEF of 30% [IQR,25-35%]. 53.6% had hypertension and 40.1% had diabetes. 43% of patients were NYHA II and 24% were NYHA III or IV. The median potassium value was 4.6 mmol/L [IQR, 4.3-5]. The potassium level of the majority of patients (78.4%) was normal (3.5-5 mmol/L), while those with mild hyperkalemia (5.1-<5.5 mmol/L) made up 14.5% and moderate to severe hyperkalemia (≥ 5.5 mmol/L) was 7.1%. Only 1% of patients had potassium > 6 mmol/L.

When the cut off value of potassium was evaluated as > 5 mmol/L, the frequency of hyperkalemia was 21.6%. The comparison of variables according to the patient's potassium levels is shown in Table 1. Patients with hyperkalemia were significantly older than patients with normal potassium levels (p<0.001). Most of those with potassium ≥ 5.5 mmol/L were men (p=0.03). In this group, 51.9% of the patients had diabetes (p=0.03) and other comorbidities were similar. Among the laboratory findings, hemoglobin A1c, creatinine, and N-terminal pro-brain natriuretic peptide were higher in the hyperkalemia group (p<0.001, p<0.001, p=0.03, respectively) while estimated glomerular filtration rate (eGFR) and sodium were lower (p<0.001, p<0.001, respectively).

The eGFR was < 60 mL/min/1.73m² in 41.5% of all patients. The rate of GFR < 60 mL/min/1.73m² was higher in patients with moderate to severe hyperkalemia and mild hyperkalemia, than in those with normokalemia (69.1% vs. 54.8% vs 36.6%, p<0.001).

When medical treatments were evaluated, 80.9% of the patients were using ACE-I/ARB, 71.1% were taking ACE-I and only 9.8% were taking ARB. Additionally, only 29 of patients were using ARNI with, 70% using MRA and 92.8% using beta-blockers. While the rate of using any RAAS-M was 89.3%, the rate of using MRA together with ACE-I/ARB was 62%.

Hyperkalemia (potassium > 5mmol/L), 82.2% were using ACE-I/ARB, while 64.8% were taking both ACE-I/ARB and MRA.

The comparison of medical treatments and groups according to potassium levels is given in Table 2. Those who received ACE-I/ARB, MRA and those who take 50% or more of the target dose, were similar between the normokalemia and hyperkalemia groups. In addition, all groups had similar rates of using beta-blockers, ARNI, any RAAS-M and dual RAAS-M (ACE-I/ARB and MRA).

Factors associated with hyperkalemia were examined by logistic regression analysis, which included eGFR, diabetes, hypertension, ACE-I/ ARB, MRA and beta-blockers use (Table 3). (eGFR) (OR: 0.969, 95% CI: 0.631-0.643, p<0.001), angiotensin alterinh enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) (OR: 1.697, 95% CI: 1.124-2.562, p=0.012), and mineralocorticoid receptor antagonists (MRA) (OR:0.200, 95% CI: 0.033-2.142, p=0.02) were considered as independent factors for hyperkalemia.

DISCUSSION

We analyzed real-life data of patients followed in the HF outpatient clinic. We showed the following: (i) hyperkalemia affected 21.6% of the patients, mild hyperkalemia

frequency was at 14.5%, with moderate to severe hyperkalemia frequency at 7.1%; (ii) factors associated with hyperkalemia were eGFR level, ACE-I/ARB and MRA use.

The rate of hyperkalemia (>5.5 mmol/L) in patients taking eplerenone was 11.8%, while the rate of severe hyperkalemia (>6 mmol/L) was 2.5% [6]. In the RALES study, in which ACE-I was used in combination with spironolactone, 13% of patients had hyperkalemia (>5.5 mmol/L) and only 2% had severe hyperkalemia (>6 mmol/L) [7]. Hyperkalemia is not exceptionally rare in the general population, but its true incidence is unknown; it is estimated to occur in the range of 2 to 3% [13]. The reason for the variation in frequency is that different potassium thresholds are used to define hyperkalemia. In the SOLVD study, hyperkalemia (≥ 5.5 mmol/L) was 6% and severe hyperkalemia (≥ 6.0 mmol/L) was 1.1% during the 2.7-year follow-up [14]. In the PARADIGM-HF study, the ARNI group comprised 16.1% of patients with potassium > 5.5 mmol/L and 4.3% of patients with potassium > 6 mmol/L [15].

Mild hyperkalemia was found at 14.5%, moderate to severe hyperkalemia was found at 7.1% and only 1% of patients had potassium >6 mmol/L in our study. Current procedure maintain patients with low ejection fraction HF receiving triple therapy, ACE-I/ARB or ARNI, beta-blocker, and MRA. All these drugs are known to be at their greatest effectiveness in recommended target doses tested in clinical trials or tolerated by the patients [2]. RAAS-M used in the treatment of HF are common, with causes of hyperkalemia, and patients with hyperkalemia are more probable to be taking these drugs. However, it has been shown that the mortality benefits of these drugs continue, even in hyperkalemia [11,12,16-18].

Heart Failure guidelines recommend discontinuing RAAS-M as needed, albeit briefly, and carefully restarting it as soon as possible by monitoring potassium levels [2]. However, because of these concerns, most clinicians choose to cut or reduce dose ACE-I/ARB or MRA when potassium is > 5.5 mmol/L [19]. One of the main reasons for reducing or discontinuing RAAS-M titration is hyperkalemia. Discontinuation or dose reduction of these life-saving drugs due to hyperkalemia may play a role in increasing long term mortality in high-risk HF patients [20-22].

Independent predictors of hyperkalemia were reported as baseline serum creatinine, serum potassium, atrial fibrillation, history of diabetes and NYHA class III or IV [14]. In the CHARM program, male gender, advanced age, baseline hyperkalemia (≥ 5.0 mmol/L), diabetes, creatinine ≥ 2.0 mg/dl and use of ACE-I or spironolactone were defined as risk factors for hyperkalemia [23].

In our study, we found eGFR, ACE-I/ARB and MRA to be strong independent predictors for hyperkalemia. Although the diabetes rate and hemoglobin A1c level were higher in those with hyperkalemia, it was not related to diabetes in the regression model. However, we think that it may be indirectly related to low eGFR caused by uncontrolled diabetes.

The affect of RAAS-M was common in the PROTECT study, with 75.6% of patients using ACE-I and 45.7% using MRA. Hyperkalemia (potassium >5 mmol/L) was present in 35% and there was no increase in mortality with hyperkalemia at day 180. However, in this study, reduction and discontinuation of RAAS-M, especially MRAs, were reported as a leading cause of increased mortality [4]. In present study, ACE-I/ARB use was 80.9%, MRA use was 70%, and ACE-I/ARB use together with MRA was 62%. Although the number of patients with potassium > 5 mmol/L was lower (21.6%), the rate of MRA use was higher than in the PROTECT study. In addition, in present study, we did not find a significant increase in

hyperkalemia in those using ACE-I/ARB, MRA, and those taking at least 50% of the target dose.

CONCLUSION

Hyperkalemia is frequently seen in patients receiving RAAS-M in chronic HF with the recommendation of current guidelines. We found that low eGFR, ACE-I/ARB and MRA were more closely associated with hyperkalemia. Close monitoring and awareness in terms of hyperkalemia in these patients may be important in increasing adherence to treatment.

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