Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes

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Abstract

Introduction: The aim of the study was to investigate predictors of mortality in patients hospitalized with hyperkalemia.
Material and methods: Data among hospitalized patients with hyperkalemia (serum potassium ≥ 5.1 mEq/l) were collected. Patients with end-stage renal disease on dialysis were excluded.
Results: Of 15,608 hospitalizations, 451 (2.9%) episodes of hyperkalemia occurred in 408 patients. In patients with hyperkalemia, chronic kidney disease, hypertension, diabetes, coronary artery disease and heart failure were common comorbidities. Acute kidney injury (AKI) and metabolic acidosis were common metabolic abnormalities, and 359 patients (88%) were on at least one drug associated with hyperkalemia. Mean duration to resolution of hyperkalemia was 12 ±9.9 h. Nonsteroidal anti-inflammatory drugs (HR = 1.59), highest potassium level (HR = 0.61), tissue necrosis (HR = 0.61), metabolic acidosis (HR = 0.77), and AKI (HR = 0.77) were significant independent determinants of duration prior to hyperkalemia resolution. Tissue necrosis (OR = 4.55), potassium supplementation (OR = 5.46), metabolic acidosis (OR = 4.84), use of calcium gluconate for treatment of hyperkalemia (OR = 4.62), AKI (OR = 3.89), and prolonged duration of hyperkalemia (OR = 1.06) were significant independent predictors of in-hospital mortality.
Conclusions: Tissue necrosis, potassium supplementation, metabolic acidosis, calcium gluconate for treatment of hyperkalemia, AKI and prolonged duration of hyperkalemia are independent predictors of in-hospital mortality.

Key words: potassium supplements, prolonged hyperkalemia, in-hospital mortality, drug-induced hyperkalemia.

Introduction

Hyperkalemia is potentially life-threatening and has been associated with increased all-cause and in-hospital mortality [1, 2]. The incidence of hyperkalemia has increased among hospitalized patients [3, 4]. The potential mechanisms resulting in hyperkalemia include

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increased potassium intake (potassium supplements), alteration in renal potassium handling (chronic kidney disease, hypoaldosteronism) and cation exchange at the cellular level (tissue necrosis, metabolic acidosis, and insulin deficiency) [5, 6]. Drugs are a major risk factor for hyperkalemia in up to 75% of hospitalized patients [3]. Polypharmacy and drug-drug interactions play a significant role in altering potassium homeostasis causing hyperkalemia [6, 7].

The Randomized Aldactone Evaluation Study (RALES) trial demonstrated improved outcomes in patients with severe congestive heart failure (New York Heart Association class III and IV) treated with spironolactone in combination with diuretics and angiotensin-converting enzyme (ACE) inhibitors [8]. Subsequently, Juurlink *et al.* reported an increase in the incidence of hyperkalemia and associated morbidity and mortality with the increased use of spironolactone in patients with heart failure [4]. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial reported a reduction in the risk of death from cardiovascular causes in patients with New York Heart Association class II heart failure treated with eplerenone, leading to the possibility of a higher incidence of hyperkalemia [9, 10].

Management of hyperkalemia includes treatment of precipitating risk factors, preventing life-threatening cardiac arrhythmias by administering calcium-based salts, shifting potassium into the cells, and enhancing elimination of potassium through cation exchange resins [6]. Various treatment options with variable onset and duration of action are currently used in clinical practice. However, there is a paucity of evidence limited by few randomized clinical trials regarding the most effective management of acute hyperkalemia [11, 12]. The recommendations regarding the frequency and duration of monitoring of patients with hyperkalemia also are based on opinion and usually depend on the clinician and/or the institutional practice guidelines [12]. This can lead to a wide variation of the duration the patient is exposed to the increased serum potassium level.

The primary objective of the present study was to determine the factors associated with all-cause and in-hospital mortality and to analyze the treatment and monitoring for hyperkalemia in hospitalized patients. The secondary objective of the study was to determine the clinical and drug-related risk factors associated with hyperkalemia among hospitalized patients. We analyzed the duration for which the patients had an elevated serum potassium level and evaluated possible risk factors associated with duration prior to hyperkalemia resolution.

Material and methods

All patients admitted to Westchester Medical Center (a 647-bed tertiary medical center) from January 1, 2010 to December 31, 2011 with a diagnosis of hyperkalemia based on the International Classification of Diseases, Ninth Revision (ICD-9) coding system either at the time of admission or during hospitalization were included in the analysis. Patients aged ≥ 18 years were included in the study. Hyperkalemia was defined as serum potassium ≥ 5.1 mEq/l as per the institutional laboratory guidelines. All patients with end-stage renal disease and on dialysis (ESRD on HD) were excluded from the study. For patients with multiple hospitalizations with hyperkalemia during the study period, only the first visit was analyzed and included. Records with missing values and outcomes were excluded.

Medical records and laboratory data of the 408 patients with hyperkalemia were reviewed for the entire hospitalization. Prior to initiating the study, we reviewed the available literature to establish a list of drugs and non-drug-related risk factors known to be associated with hyperkalemia [6, 13–17]. Data were collected on demographics and clinical characteristics, treatment of hyperkalemia, duration to resolution of hyperkalemia, exposure to drugs that could potentially cause hyperkalemia, and in-hospital mortality. In patients who died, the duration of hyperkalemia was determined to be the time from the onset of hyperkalemia to the documented time of death. The duration to resolution of hyperkalemia was determined by observing serum potassium levels obtained in all patients at intervals of every 4 h according to the hospital protocol. The baseline glomerular filtration rate (GFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.

Statistical analysis

Stepwise logistic regression analyses were conducted to identify significant independent risk factors for in-hospital mortality. Stepwise Cox regression analyses were done to identify significant independent risk factors associated with the duration to hyperkalemia resolution. Statistical significance was defined as a *p*-value < 0.05. All analyses were performed with SAS software version 9.3 (SAS Institute, Cary, North Carolina).

Results

There were a total of 16,420 in-patient hospitalizations during the study period out of which 812 hospitalizations were excluded secondary to the diagnosis of ESRD on HD. Of the remaining 15,608 hospitalizations, 451 (2.9%) had hyperka-

lemia either at admission or during the hospitalization. These 451 hospitalizations included 408 patients who constituted our study population after elimination of the repeat hospitalizations with hyperkalemia. No patient was excluded because of missing values or missing outcomes.

Table I shows the baseline characteristics of the 408 patients hospitalized with hyperkalemia. Table II shows the prevalence of the medications associated with hyperkalemia in the 408 patients hospitalized with hyperkalemia. Of the 408 patients, 357 (88%) were on at least one drug known to be associated with hyperkalemia.

In the present study, 285 patients (70%) had hyperkalemia at the time of admission, and 123 pa-

tients (30%) developed hyperkalemia during their hospitalization. The mean serum potassium value was 5.7 ±0.59 mEq/l. Hyperkalemia was treated with sodium polystyrene sulfonate in 318 patients (78%), with intravenous insulin and dextrose in 253 patients (62%), with calcium gluconate in 147 patients (36%), and with hemodialysis in 50 patients (12%). Fifty-one patients (13%) were not treated with any of the above and were monitored for spontaneous correction of elevated serum potassium. The mean duration for resolution of hyperkalemia was 12 ±9.9 h. Thirty-three patients (8%) died with hyperkalemia.

Stepwise Cox regression analysis showed that patients who had hyperkalemia induced by nonsteroidal anti-inflammatory drugs (NSAIDs) had a 59% higher chance of early hyperkalemia resolution (HR = 1.59, 95% CI: 1.03–2.45, $p < 0.01$). All other medications listed in Table II were not significantly associated with duration of hyperkalemia. Patients with tissue necrosis (HR = 0.61, 95% CI: 0.14–0.92, $p = 0.02$), metabolic acidosis (HR = 0.77, 95% CI: 0.62–0.96, $p = 0.02$), and acute kidney injury (HR = 0.77, 95% CI: 0.50–0.75, $p = 0.02$) had a higher chance of prolonged duration of hyperkalemia. Patients had a 39% lower chance of early hyperkalemia resolution for a 1-unit increment of the highest potassium level after adjusting for confounding factors such as NSAIDs, tissue necrosis, metabolic acidosis, and acute kidney injury (Table III).

Table I. Baseline characteristics of 408 patients hospitalized with hyperkalemia

Variable	Results
Age, mean ± standard deviation [years]	64 ±17
Men, n (%)	232 (57)
Women, n (%)	176 (43)
GFR ≥ 60 with no CKD, n (%)	95 (48)
GFR ≥ 60 with CKD, n (%)	17 (4)
GFR 30–59, n (%)	83 (20)
GFR 15–29, n (%)	83 (20)
GFR < 15, n (%)	30 (7)
Acute kidney injury, n (%)	251 (62)
Diabetes mellitus, n (%)	172 (42)
Blood transfusion, n (%)	6 (4.58)
Tissue necrosis, n (%)	8 (6.11)
Metabolic acidosis, n (%)	48 (36.64)
Adrenal insufficiency, n (%)	9 (6.87)
Coronary artery disease, n (%)	110 (27)
Congestive heart failure, n (%)	93 (23)
Hypertension, n (%)	230 (57)
Atrial fibrillation, n (%)	60 (15)
Liver cirrhosis, n (%)	60 (15)
End-stage renal disease post renal transplant, n (%)	32 (8)
End-stage liver disease post liver transplant, n (%)	11 (3)
Bone marrow transplant, n (%)	11 (3)
Solid tumors, n (%)	56 (14)
Lymphoma/leukemia, n (%)	47 (12)

GFR – glomerular filtration rate (ml/1.73 m²); CKD – chronic kidney disease as defined by ICD-9 diagnosis codes

Table II. Prevalence of medications associated with hyperkalemia in patients with hyperkalemia

Medications	Results
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, n (%)	131 (32)
Amiloride/triamterene, n (%)	4 (1)
Azole antifungals, n (%)	42 (10)
β-Blockers, n (%)	248 (61)
Cyclosporine, n (%)	11 (3)
Digoxin, n (%)	25 (6)
Eplerenone/spironolactone, n (%)	70 (17)
Heparin, n (%)	62 (15)
Hypertonic saline, n (%)	1 (0.2)
Nonsteroidal anti-inflammatory drugs, n (%)	25 (6)
Penicillin G, n (%)	1 (0.2)
Pentamidine, n (%)	1 (0.2)
Potassium supplements, n (%)	45 (11)
Tacrolimus, n (%)	32 (8)
Trimethoprim, n (%)	32 (8)

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Table III. Stepwise Cox regression analysis for the time to hyperkalemia resolution

Risk factors	Hazard ratio	95% Confidence intervals	Value of p
Tissue necrosis	0.61	0.14–0.92	0.02
Nonsteroidal anti-inflammatory drugs	1.59	1.03–2.45	0.03
Metabolic acidosis	0.77	0.62–0.96	0.02
Acute kidney injury	0.77	0.62–0.96	0.02
Serum potassium per 1 unit increase	0.61	0.50–0.75	< 0.001

Table IV. Stepwise logistic regression analysis to determine the predictors of mortality in patients with hyperkalemia

Risk factors	Odds ratio	95% Confidence intervals	Value of p
Tissue necrosis	4.55	1.74–11.90	0.002
Potassium supplements	5.46	1.56–19.20	0.008
Metabolic acidosis	4.84	1.48–15.82	0.009
Calcium gluconate	4.62	1.60–13.35	0.005
Acute kidney injury	3.89	1.14–13.26	0.03
Duration prior to resolution of hyperkalemia	1.06	1.02–1.09	< 0.001

Stepwise logistic regression analyses (Table IV) showed that duration prior to hyperkalemia resolution was associated with a higher chance of in-hospital mortality (OR = 1.06, p < 0.01). Patients who had acute kidney injury (OR = 3.88; p = 0.03), metabolic acidosis (OR = 4.84; p < 0.01), and tissue necrosis (OR = 4.55; p < 0.01) had higher in-hospital mortality. Patients who received calcium gluconate as part of their treatment of hyperkalemia had higher in-patient mortality (OR = 4.62; p < 0.01). Hyperkalemia associated with use of potassium supplements was associated with a higher chance of in-hospital mortality (OR = 5.46; p < 0.01).

All variables listed in Tables I and II were used in the multivariate analyses for Tables III and IV.

Discussion

The incidence of hyperkalemia in our hospitalized patients not on dialysis was 2.9% (1.45% per year), which is comparable to the incidence reported in previous studies [3]. The comorbidities chronic kidney disease [18], hypertension [18, 19], diabetes mellitus [18, 20], congestive heart failure, and coronary artery disease [19–26] and the acute conditions acute kidney injury, metabolic acidosis, recent blood transfusions, and tissue necrosis are important clinical risk factors associated with hyperkalemia. The prevalence of these comorbidities was higher in our patient population compared to previous studies [3, 27, 28]. This can be explained by the case mix index of the patient population admitted to our hospital being one of the highest in the nation.

Drugs are a major risk factor for hyperkalemia [11], and of the 408 patients in our study, 88% of patients were on at least one drug known to cause hyperkalemia, in contrast to 35% to 75% of patients in other studies [3]. One of the reasons for the higher prevalence of drug-induced hyperkalemia in our study is the increased use of medications such as β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists, heparin, and potassium supplements in patients with hypertension, heart failure, or myocardial infarction because of clinical trial data. The drugs associated with hyperkalemia in our study were similar to those in studies with a high use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aldosterone antagonists, heparin, and potassium supplements [3, 5, 7, 27–30].

The stepwise Cox regression analysis in our study demonstrated an early recovery to the normokalemic state in patients with NSAIDs-induced hyperkalemia. Nonsteroidal anti-inflammatory drugs cause impaired potassium homeostasis principally by causing relative hyporeninemic hypoaldosteronism by inhibiting renal prostaglandin synthesis [3, 31]. Prerenal azotemia impairs delivery of salt and water to the distal nephron, further reducing potassium excretion and leading to hyperkalemia. The probable explanation for early hyperkalemia resolution was prompt therapeutic

interventions with intravenous fluids and stopping NSAIDs. The lower use of NSAIDs causing hyperkalemia in our study (6%) was due to the high prevalence of chronic kidney disease and coronary artery disease in our patients who were less likely to receive NSAIDs [32, 33]. Data to study medication use were recorded in such a way as to reflect the medications the patient was taking immediately prior to the episode of hyperkalemia (36 h). This method of data collection to measure drug exposure is often controversial as it has the potential to miss out on use of over-the-counter medications. The quality of such data also depends on the drug class and remains acceptable for drugs regularly used in the treatment of chronic disorders. Among the drugs we studied for association with hyperkalemia, NSAIDs are the likely medications which could have been underestimated.

Tissue necrosis, metabolic acidosis, and acute kidney injury were found to be independent predictors of a prolonged duration before recovery to the normokalemic state. These acute metabolic derangements take longer to correct.

Hyperkalemia has been associated with adverse clinical outcomes and increased in-hospital mortality [2, 34–37]. Mortality from hyperkalemia increases with increase in the severity of hyperkalemia [1, 37, 38], but the progression from benign to lethal arrhythmias in hyperkalemia is unpredictable [2]. Severe acute untreated hyperkalemia can result in fatal cardiac arrhythmias [35], which are secondary to a rapid rise in the serum potassium level [29].

Hyperkalemia reduces the resting membrane potential of the myocardium, leading to a decreased myocardial cell conduction rate and increased rate of repolarization [39]. This may contribute to hyperkalemia-induced arrhythmic death.

We demonstrated that tissue necrosis, potassium supplementation, metabolic acidosis, use of calcium gluconate in the treatment of hyperkalemia, acute kidney injury, and duration prior to hyperkalemia resolution were significantly associated with in-hospital mortality. Tissue necrosis, acute kidney injury, and metabolic acidosis contribute to prolonging the duration of hyperkalemia, contributing to its association with mortality. However, each one of these conditions is also independently associated with increased mortality. Our findings are similar to those reported in other studies [37, 38].

The association between hyperkalemia (> 5.1 mEq/l) secondary to potassium supplementation and higher in-hospital mortality is an important result of our study. Previous studies have shown conflicting results [2, 29]. McMahon *et al.* found that in patients with serum potassium > 5.5 mEq/l, potassium supplementation was associated with increased mortality [2]. However, An *et al.* observed no association between potassium supplementation and mortality [37]. Both these studies investigated only critically ill patients, a population different from our study cohort.

Our study showed that use of calcium gluconate in treating hyperkalemia increased mortality. This increased mortality can be explained by guidelines recommending use of calcium salts in patients with electrocardiographic changes suggestive of severe hyperkalemia [12], a subset of patients at higher risk of mortality.

Our study demonstrated that duration prior to hyperkalemia resolution was associated with higher in-hospital mortality. McMahon *et al.* also demonstrated that decrease in serum potassium by ≥ 1 mEq/l within 48 h of treatment eliminated hyperkalemia-associated mortality in critically ill patients [2].

Systematic reviews have highlighted the paucity of evidence to determine the most effective therapy for acute management of hyperkalemia [11]. Elliott *et al.* reviewed multiple studies about management of hyperkalemia and found that none of them addressed the adequate frequency and duration of monitoring of patients with hyperkalemia [12]. Guidelines suggest that after initial treatment of hyperkalemia, the serum potassium should be rechecked within 1 to 2 h, following which the frequency of monitoring could be reduced [12]. Subsequent monitoring depends on the serum potassium level and the potential reversibility of the underlying cause. However, previous studies have shown that adherence to these guidelines is low [11]. Because of our findings that prolonged duration of hyperkalemia is independently associated with adverse outcomes, we suggest that protocol-based aggressive management of hyperkalemia in hospitalized patients is essential. Further studies are needed to assess and quantify the benefit of intensive monitoring of serum potassium value after initiation of treatment of hyperkalemia in improving outcomes, especially with regard to in-hospital mortality.

A major limitation of our study is its retrospective observational design. Another limitation is that electrocardiograms were not obtained during all episodes of hyperkalemia. We identified patients using the ICD-9 diagnosis code for hyperkalemia, enabling us to identify all true hyperkalemia cases that occurred during the study period, minimizing any selection bias [40]. Since chronic kidney disease is a major risk factor, quantifying the prevalence of chronic kidney disease stage based on calculated glomerular filtration rate is a major strength of our data collection Bielecka-Dąbrowa *et al.* extensively discuss the risk of hyperkalemia in heart failure [41].

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In conclusion, tissue necrosis, potassium supplementation, metabolic acidosis, calcium gluconate for treatment of hyperkalemia, acute kidney injury, and prolonged duration of hyperkalemia are independent predictors of in-hospital mortality in patients hospitalized for hyperkalemia. Therefore, aggressive management of hyperkalemia is warranted in these patients.

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