Factors Associated with Hypokalemia after Furosemide Treatment in Hospitalized Patients with Acute Decompensated Heart Failure

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Abstract

Background: Hypokalemia, defined as serum potassium <3.5 mmol/L, is commonly associated with the use of loop diuretics. Hypokalemia after furosemide treatment may lead to adverse outcomes in hospitalized patients with acute decompensated heart failure (ADHF). Risk factors associated with hypokalemia in this patient population are not well characterized. This retrospective case-control study aimed to identify risk factors and outcomes associated with hypokalemia after furosemide treatment in hospitalized patients with ADHF.

Methods: The data were retrieved from the medical records using ICD-10 coding. Factors associated with hypokalemia were analyzed using univariate and multivariate logistic regression analyses. Clinical outcomes associated with the hypokalemia were also examined.

Results: A total of 350 patients met the eligibility criteria, of whom 101 patients developed hypokalemia after receiving furosemide, while 249 patients did not. Furosemide dose >1.5 mg/kg, urine volume after furosemide treatment >2 ml/kg/hour, higher baseline serum albumin and body mass index, the presence of baseline hypomagnesemia and lower baseline serum potassium were independently associated with hypokalemia after furosemide treatment. Prior use of spironolactone was associated with a decreased risk of hypokalemia. Patients in the hypokalemia group had significantly higher incidence of cardiac arrhythmia and sepsis compared with the non-hypokalemia group.

Conclusion: Close monitoring of serum potassium among high risk patients may help reduce the incidence of hypokalemia and adverse clinical outcomes in hospitalized patients with ADHF who received furosemide.

Keywords: congestive heart failure; CHF; pulmonary edema; magnesium; diuresis

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ปัจจัยที่สัมพันธ์กับการเกิดภาวะโพแทสเซียมในเลือดต่ำหลังจากได้รับยาฟูโรซีไมด์ในผู้ป่วยที่นอนในโรงพยาบาลด้วยภาวะหัวใจล้มเหลวเฉียบพลัน

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บทคัดย่อ

บทนำ: ภาวะโพแทสเซียมในเลือดต่ำ (ซีรั่มโพแทสเซียม <3.5 มิลลิโมล/ลิตร) พบได้บ่อยจากการได้รับยาขับปัสสาวะในกลุ่ม loop diuretics สำหรับผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลด้วยภาวะหัวใจล้มเหลวเฉียบพลันและจำเป็นต้องได้รับยาฟูโรซีไมด์นั้น การเกิดภาวะโพแทสเซียมต่ำอาจส่งผลให้เกิดภาวะแทรกซ้อนที่ไม่พึงประสงค์ อย่างไรก็ตามปัจจัยเสี่ยงต่อการเกิดภาวะโพแทสเซียมต่ำในผู้ป่วยกลุ่มนี้ยังไม่ค่อยชัดเจน การศึกษาย้อนหลังนี้จึงมีวัตถุประสงค์เพื่อหาปัจจัยเสี่ยงต่อการเกิดภาวะโพแทสเซียมต่ำหลังจากได้รับยาฟูโรซีไมด์ และผลลัพธ์ทางคลินิก ในผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลด้วยภาวะหัวใจล้มเหลวเฉียบพลัน

ระเบียบวิธีวิจัย: การสืบค้นข้อมูลของผู้ป่วยอาศัยระบบเวชระเบียนอิเล็กทรอนิกส์โดยใช้รหัส ICD-10 ปัจจัยที่เกี่ยวข้องกับภาวะโพแทสเซียมต่ำถูกวิเคราะห์ด้วยวิธี univariate และ multivariate logistic regression นอกจากนี้ยังมีการวิเคราะห์ผลลัพธ์ทางคลินิกที่มีสัมพันธ์กับการเกิดภาวะโพแทสเซียมต่ำด้วย

ผลการศึกษา: มีผู้ป่วยที่เข้าเกณฑ์การศึกษาทั้งหมด 350 คน โดยเป็นผู้ป่วยที่พบภาวะโพแทสเซียมต่ำจำนวน 101 คน และไม่พบภาวะโพแทสเซียมต่ำจำนวน 249 คน ปัจจัยที่พบว่ามีความสัมพันธ์อย่างอิสระต่อภาวะโพแทสเซียมต่ำหลังจากที่ได้รับยาฟูโรซีไมด์ ได้แก่ ขนาดยาฟูโรซีไมด์ >1.5 มิลลิกรัม/กิโลกรัมของน้ำหนักตัว ปริมาณปัสสาวะหลังจากได้รับยาฟูโรซีไมด์ >2 มิลลิลิตร/กิโลกรัม/ชั่วโมง ระดับอัลบูมินแรกรับ และ ค่าดัชนีมวลกายที่สูง ระดับโพแทสเซียมแรกรับที่ต่ำ และการมีซีรั่มแมกนีเซียมในเลือดต่ำตั้งแต่ก่อนได้รับยา ส่วนประวัติของการได้รับยาสไปโรโนแลคโตนตั้งแต่ก่อนเข้ารับการรักษาในโรงพยาบาลพบว่าสามารถลดความเสี่ยงต่อการเกิดภาวะโพแทสเซียมต่ำได้ กลุ่มผู้ป่วยที่มีภาวะโพแทสเซียมต่ำมีอุบัติการณ์ของหัวใจเต้นผิดจังหวะ และการติดเชื้อ สูงกว่ากลุ่มผู้ป่วยที่ไม่เกิดภาวะโพแทสเซียมต่ำอย่างมีนัยสำคัญทางสถิติ

สรุป: การติดตามซีรั่มโพแทสเซียมอย่างใกล้ชิดในผู้ป่วยที่มีความเสี่ยงสูง อาจช่วยลดการเกิดภาวะโพแทสเซียมต่ำ ซึ่งอาจช่วยภาวะแทรกซ้อนทางคลินิกของผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลด้วยภาวะหัวใจล้มเหลวเฉียบพลันและจำเป็นต้องได้รับยาฟูโรซีไมด์

คำสำคัญ: หัวใจวาย; น้ำท่วมปอด; โปตัสเซียม; โปแตสเซียม; เกลือแร่ต่ำ

Introduction

Congestive heart failure (CHF) impairs the quality of life, increases mortality and requires substantial amount of treatment resources. Diuretics are often used to reduce fluid retention and alleviates the symptoms of HF.[1,2] Furosemide is a loop diuretic that works by inhibiting the reabsorption of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle.[3,4] According to the previous study, administering furosemide to patients with HF was associated with a 30% incidence of hypokalemia (serum potassium <3.5 mmol/L). However, combining potassium supplements with

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furosemide reduced the risk of hypokalemia by 12%.[5] Intravenous administration of furosemide at dose >1 mg/kg within a 24-hour period has been shown to increase the risk of hypokalemia, with an odds ratio of 1.21 compared with no treatment.[6]

A previous study identified several risk factors contributing to hypokalemia in patients with HF who were on long-term furosemide treatment in an outpatient setting. These risk factors included advanced age, chronic kidney disease, diabetes mellitus, and female sex. Patients with acute myocardial infarction and HF appeared to be more susceptible to hyperkalemia. Other types of diuretics including thiazide, acetazolamide, chlorthalidone, bumetanide, and metolazone can also augment urinary potassium excretion leading to hypokalemia.[7] A recent study revealed that thiazide diuretics might have the greatest impact in lowering serum potassium.[8] The presence of hypokalemia is associated with increased mortality, cardiac arrhythmia, and longer hospital stay among patients with HF.[9,10] The concurrent use of potassium supplements and trying to maintain serum potassium within the normal range have been shown to reduce mortality risk in these patients.[11-13]

Despite its clinical significance, factors associated with hypokalemia in hospitalized patients with acute decompensated heart failure (ADHF) requiring furosemide treatment are not well characterized. Understanding these risk factors could help reduce adverse clinical outcomes. Therefore, the aim of the present study was to identify risk factors and clinical outcomes associated with hypokalemia after furosemide treatment in hospitalized patients with ADHF.

Methods

This is a retrospective case-control study of hospitalized patients with ADHF who received furosemide therapy between 1 January 2017 and 31 December 2021. The patient records were retrieved from the hospital database using ICD-10 codes. The study protocol was approved by the ethics committee of Police General Hospital and informed consent was not required.

Outcomes

The primary outcome was risk factors associated with hypokalemia after furosemide treatment in hospitalized patients with ADHF. The secondary outcomes included adverse clinical outcomes associated with hypokalemia including death, cardiac arrhythmia, acute kidney injury and sepsis within 7 days of hospitalization and the length of hospital stay. The differences in the clinical outcomes between the two groups of patients with >15% decline in serum potassium and <15% decline in serum potassium from baseline were also investigated. The cut-off of 15% was chosen because the previous study has demonstrated an increased risk of cardiac arrythmia and mortality as well as prolonged hospital stay among patients with >15% decline in serum potassium.

Operational definitions

Hypokalemia was defined as serum potassium <3.5 mmol/L. Hypomagnesemia was defined as serum magnesium <1.8 mg/dL. Cardiac arrhythmia was characterized by abnormal heart rhythm manifesting as tachycardia (heart rate >120 beats per minute) or bradycardia (heart rate <60 beats per minute). ADHF was defined as the presence of signs and symptoms of structural or functional cardiac failure including decreased physical activity, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, jugular vein distension, and the presence of S3 gallop. Heart failure with reduced ejection fraction (HFrEF) required the presence of left ventricular ejection fraction <40%. Sepsis was a systemic inflammatory response syndrome (SIRS) in response to an infectious process. SIRS required the presence of two or more of the following criteria: abnormal body temperature (<36 °C or >38 °C), heart rate (>90 BPM), respiratory rate or blood gas (>20/min or $PaCO_2$<32 mmHg), and white blood cell count (<4000 cell/mm^3, or >12,000 cell/mm^3, or ≥10% bands).

Participants

To be included in the study, patients had to fulfill the following criteria: (1) age ≥18 years; (2) estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2; (3) received ≥40 mg of furosemide within 24 hours; (4) baseline serum potassium 3.5 - 4.5 mmol/L; and (5)

availability of serum potassium within 24 hours after the first dose of furosemide. The exclusion criteria were as follow: (1) severe acute kidney injury stage 3 as determined by the KDIGO criteria.[14]; (2) concomitant use of other types of diuretics; (3) pregnancy; (4) kidney transplant recipient; (5) presence of medical conditions that could affect renal handling of potassium.

Sample size calculation

The calculation of the sample size was performed by using the commonly mentioned "rule of thumb" that suggested a minimum of 10 events per predictor.[15] Since there were almost 10 possible predictors in the model, therefore, 100 (10*10) events of hypokalemia were required. These possible predictors included eGFR, receiving angiotensin converting enzyme Inhibitor (ACEI), angiotensin II receptor blockers (ARBs), or angiotensin receptor neprilysin inhibitor (ARNI), receiving insulin, urine output >2 ml/kg/hr, furosemide dose >1.5 mg/kg/day, increasing age, female sex, diabetes mellitus, hypomagnesemia, and the use of digoxin. Since the previous study reported a 30% incidence of hypokalemia in patients with HF receiving furosemide, therefore, the appropriate sample size was 334 cases (calculated from 100/30*100).[5]

Statistical analysis

Continuous data were presented as mean ± standard deviation or median (interquartile range). Number and frequency were used for categorical data. To compare continuous or categorical variables between two groups, Chi-square test, Fisher's exact test, Wilcoxon Rank Sum test or independent t-test were applied. To determine factors associated with hypokalemia, univariable and multivariable logistic regression analyses were performed. After assessing for multicollinearity, variables with p <0.20 were entered into the multivariable model using forward stepwise selection. Statistical significance was defined as p-value of <0.05. All statistical analyses were performed using SPSS version 26.

Results

The Study Flow Chart is shown in Figure 1. A total 450 patients were screened. One hundred patients were excluded resulting a total of 350 patients in the final analysis. Among these 350 patients, 101 patients were in the hypokalemia group and 249 patients were in the non-hypokalemia group.

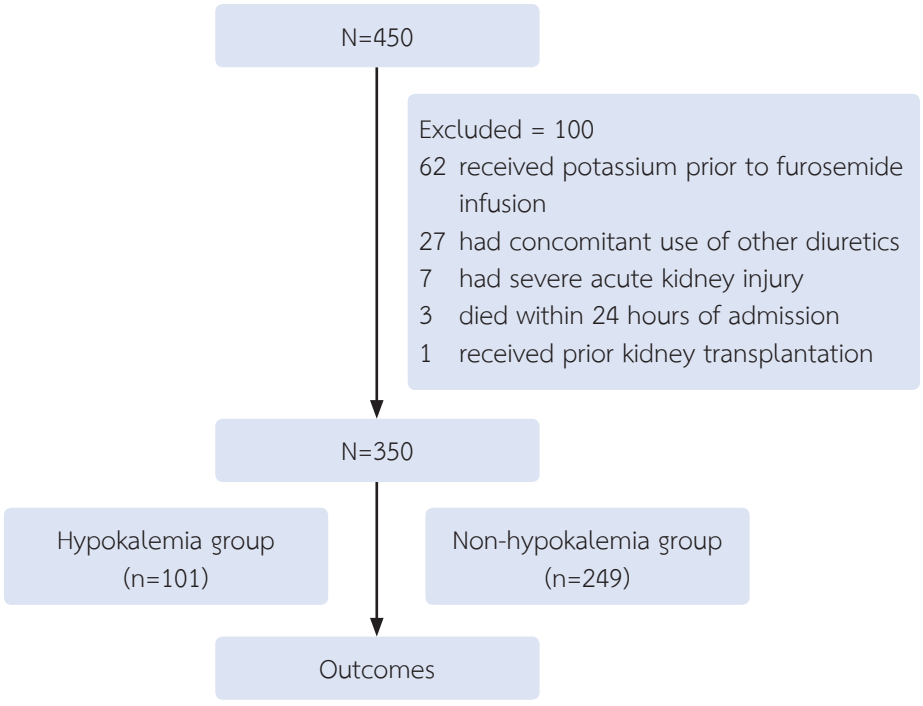

Figure 1 Study Flow Chart

Baseline characteristics and laboratory data of all patients and according to the presence or the absence of hypokalemia are shown in **Table 2**. In the hypokalemia group, most patients were female with lower body weight. There were no differences in the coexisting conditions between the two groups. Patients in the hypokalemia group received higher dose of furosemide prior to admission. They also had lower serum potassium and magnesium, higher serum albumin and were more likely to have hypomagnesemia at baseline.

Table 2 Baseline characteristics and laboratory data of all patients

Parameters	All	Hypokalemia	Non-hypokalemia	P
	N=350	N=101	N=249	
Clinical characteristics				
Age (years)	59±16	60±16	59±16	0.597
Male, n (%)	186 (53.1)	40 (39.6)	146 (58.6)	0.001
Body mass index (kg/m^2)	25.2±4.2	24.6±4.9	25.4±3.9	0.108
Body weight (kg)	67.5±15.5	63.6±16.3	69.1±14.9	0.002
Systolic blood pressure (mmHg)	143±25	142±24	143±25	0.938
Diastolic blood pressure (mmHg)	75±16	75±15	74±17	0.936
Heart rate (beats per minute)	80±17	79±17	80±17	0.575
LVEF (%)	52±16	51±16	52±16	0.687
Coexisting conditions, n (%)	331 (94.6)	95 (94.1)	236 (94.8)	0.788
Hypertension	188 (53.7)	53 (52.5)	135 (54.2)	0.767
Diabetic mellitus	76 (21.7)	23 (22.8)	53 (21.3)	0.760
Cardiovascular diseases	51 (14.6)	16 (15.8)	35 (14.1)	0.668
HFrEF	122 (34.9)	41 (40.6)	81 (32.5)	0.151
Coronary arterial disease	132 (37.7)	40 (39.6)	92 (36.9)	0.642
Atrial fibrillation	58 (16.6)	18 (17.8)	40 (16.1)	0.689
Chronic kidney disease stage 3	159 (45.4)	47 (46.5)	112 (45.0)	0.719
Peripheral arterial disease	33 (9.4)	8 (7.9)	25 (10.2)	0.539
Home Medications				
Oral furosemide, n (%)	135 (38.6)	45 (44.6)	90 (36.1)	0.143
Daily dose of oral furosemide	40 (20-40)	40 (20-70)	20 (20-40)	0.017
Spironolactone, n (%)	56 (16.0)	12 (11.9)	44 (17.7)	0.181

Table 2 Baseline characteristics and laboratory data of all patients (ต่อ)

Parameters	All	Hypokalemia	Non-hypokalemia	P
Daily dose of spironolactone	12.5 (12.5-25.0)	12.5 (12.5-12.5)	25.0 (12.5-25.0)	0.061
ACEI/ARB/ARNI, n (%)	152 (43.4)	44 (43.6)	108 (43.4)	0.974
Beta-blockers, n (%)	155 (44.3)	47 (46.5)	108 (43.4)	0.590
Insulin, n (%)	24 (6.9)	6 (5.9)	18 (7.2)	0.666
Daily dose of insulin	20 (17-40)	20 (20-94)	21 (16-40)	0.484
Beta-agonist, n (%)	13 (3.7)	4 (4.0)	9 (3.6)	0.877
Digoxin, n (%)	16 (4.6)	6 (5.9)	10 (4.0)	0.435
SGLT2 inhibitors, n (%)	29 (8.3)	10 (9.9)	19 (7.6)	0.485
Hydrochlorothiazide, n (%)	1 (0.3)	1 (1.0)	-	0.116
Baseline laboratory data				
Sodium (mmol/L)	135±6	135±5	135±7	0.376
Potassium (mmol/L)	3.90±0.24	3.81±0.21	3.93±0.24	<0.001
HCO_3 (mmol/L)	22.9±3.6	22.6±3.8	23.1±3.6	0.256
Magnesium (mg/dL)	1.90±0.32	1.70±0.28	1.98±0.29	<0.001
Hypomagnesemia, n (%)	103 (29.4)	60 (59.4)	43 (17.3)	<0.001
Calcium (mg/dL)	8.88±0.60	8.83±0.60	8.89±0.60	0.347
Phosphorus (mg/dL)	3.29±0.92	3.34±0.90	3.28±0.92	0.584
Albumin (g/dL)	3.42±0.44	3.53±0.41	3.38±0.45	0.003
eGFR (mL/min/1.73 m^2)	62±21	63±22	62±20	0.724
Creatinine (mg/dL)	1.19±0.33	1.21±0.34	1.19±0.33	0.629
Hemoglobin (g/dL)	11.7±1.8	11.7±1.9	11.8±1.7	0.829

LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; ACEI/ARB/ARNI; angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitor; SGLT2, sodium-glucose cotransporter 2

Table 3 shows the dose of furosemide used for treatment of ADHF, the amount of urine output, the change in systolic blood pressure and laboratory data after furosemide treatment. Substantially higher dose of furosemide and urine output were observed in the hypokalemia group. The hypokalemia group also showed a more substantial decline in systolic blood pressure.

Table 3 Furosemide dose and biochemical parameters after furosemide treatment

Parameters	All patients	Hypokalemia	Non-hypokalemia	P
	N=350	N=101	N=249	
Furosemide dose				
Dose (mg/day)	80 (40-120)	120 (80-160)	80 (40-80)	<0.001
Dose/BW (mg/kg/day)	1.2 (0.7-1.7)	1.8 (1.4-2.4)	1.0 (0.7-1.4)	<0.001
Dose/BW >1.5 mg/kg/day, n (%)	106 (30.3)	64 (63.4)	42 (16.9)	<0.001
Urine output after furosemide treatment				
24-hour urine output (ml)	2,764±754	3,315±850	2,542±580	<0.001
Urine output >2ml/kg/hr, n (%)	121 (34.6)	69 (68.3)	52 (20.9)	<0.001
Change in blood pressure after furosemide treatment				
Decrease in SBP from baseline (mmHg)	-7.85±13.84	-11.19±15.06	-6.49±13.10	0.004
Laboratory data after furosemide treatment				
Sodium (mmol/L)	137±5	137±4	137±5	0.960
Potassium (mmol/L)	3.62±0.33	3.22±0.22	3.79±0.20	<0.001
>15% decrease in serum potassium from baseline, n (%)	75 (21.4)	60 (59.4)	15 (6.0)	<0.001
HCO_3 (mmol/L)	24.2±3.6	23.7±3.8	24.3±3.5	0.134
Creatinine (mg/dL)	1.21±0.32	1.22±0.34	1.20±0.32	0.569
eGFR (ml/min/1.73 m^2)	61±19	61±21	61±19	0.822

BW, body weight; SBP, systolic blood pressure; HCO_3, bicarbonate; eGFR, estimated glomerular filtration rate

Univariate and multivariable logistic regression analyses of factors predicting hypokalemia are shown in **Table 4**. Urine output after furosemide treatment >2ml/kg/hr, the dose furosemide >1.5 mg/kg/day, higher body mass index, the presence of baseline hypomagnesemia and higher baseline serum albumin were independently associated with hypokalemia after furosemide treatment. On the other hand, prior use of spironolactone and higher baseline serum potassium were protective against hypokalemia.

Table 4 Logistic regression analyses of factors associated with the development of hypokalemia

Biochemical parameters	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Clinical characteristics						
Male (%)	0.46	0.29-0.74	0.001			
Body mass index (kg/m^2)	0.96	0.90-1.01	0.108	1.10	1.00-1.21	0.045
Coexisting condition						
HFrEF (%)	1.42	0.88-2.29	0.152			
Prior medications						
Furosemide (%)	1.42	0.89-2.27	0.144			
Spironolactone (%)	0.63	0.32-1.25	0.183	0.12	0.04-0.36	<0.001
Baseline laboratory data						
Potassium (mmol/L)	0.11	0.04-0.33	<0.001	0.02	0.00-0.14	<0.001
Hypomagnesemia (%)	7.01	4.19-11.74	<0.001	8.55	4.06-18.04	<0.001
Albumin (g/dL)	2.27	1.31-3.93	0.004	4.50	1.85-10.93	0.001
Furosemide dose in the hospital						
Furosemide dose >1.5 mg/kg/day (%)	8.53	5.05-14.39	<0.001	4.96	2.22-11.10	<0.001
Urine output after furosemide treatment						
Urine output >2ml/kg/hr (%)	8.17	4.86-13.72	<0.001	17.86	7.30-43.70	<0.001

OR, odds ratio; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction

The most common complications within 7 days of admission were sepsis, cardiac arrhythmia, and acute kidney injury **(Table 5)**. In the group with hypokalemia, substantially higher incidence of cardiac arrhythmias and sepsis and longer hospital stay were observed. The three most common causes of sepsis were pneumonia, urinary tract infection and thrombophlebitis. After categorizing patients into two groups according to the degree of the reduction in serum potassium (>15% or <15%) from baseline, the group with >15% decline in serum potassium showed a significant increase in the risk of cardiac arrhythmias and sepsis. The etiologies of sepsis for both groups of patients are also illustrated in **Figure 2**.

Table 5 Clinical outcomes associated hypokalemia

Outcomes (n/%)	All (N=350)	HypoK (N=101)	Non-hypoK (N=249)	P	↓Serum K >15% (N=75)	↓Serum K <15% (N=275)	P
Death	10 (2.9)	5 (5.0)	5 (2.0)	0.134	3 (4.0)	7 (2.5)	0.503
Arrhythmia	29 (8.3)	20 (19.8)	9 (3.6)	<0.001	16 (21.3)	13 (4.7)	<0.001
Acute kidney injury	21 (6.0)	6 (5.9)	15 (6.0)	0.976	3 (4.0)	18 (6.5)	0.411
Sepsis	38 (10.9)	21 (20.8)	17 (6.8)	<0.001	14 (18.7)	24 (8.7)	0.014
•UTI	15 (41.7)	6 (30.0)	9 (56.3)	0.129	3 (23.1)	12 (52.2)	
•Pneumonia	18 (50.0)	11 (55.0)	7 (43.8)		9 (69.2)	9 (39.1)	
•Thrombophlebitis	3 (8.3)	3 (15.0)	-		1 (7.7)	2 (8.7)	
Length of hospital stay (days)	9 (6,13)	10 (7,14)	8 (6,12)	0.009	9 (6,14)	9 (6,13)	0.281

HypoK, hypokalemia; Non-hypoK, non-hypokalemia; K, potassium; UTI, urinary tract infection

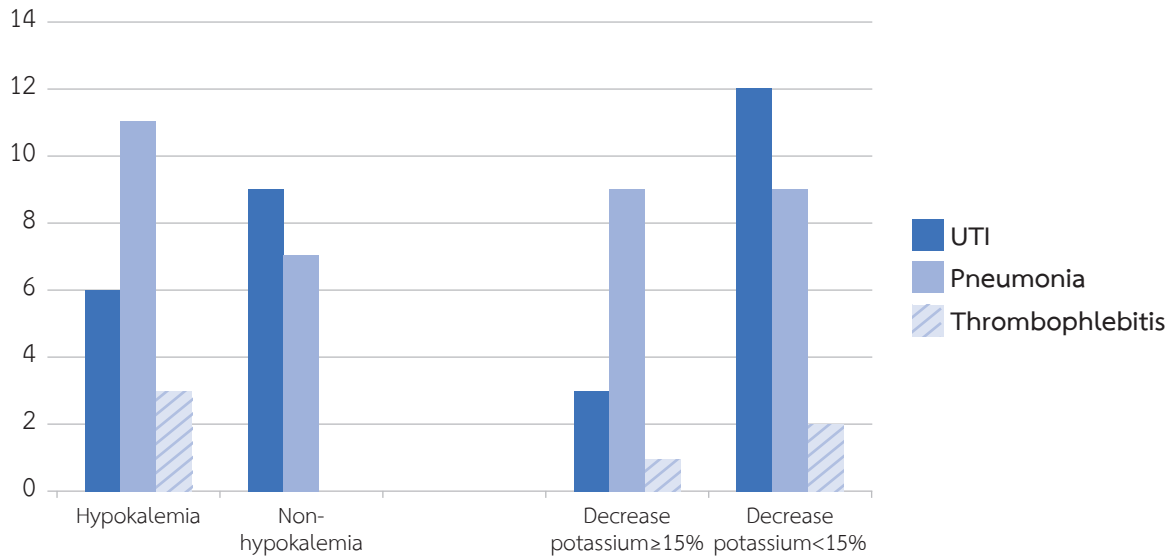

Figure 2 *Etiology of sepsis according to the presence and the degree of hypokalemia*

Discussion

The findings of the present study included urine output after furosemide treatment >2 ml/kg/hr, the dose furosemide >1.5 mg/kg/day, higher body mass index, the presence of baseline hypomagnesemia and higher baseline serum albumin were independently associated with the development of hypokalemia after furosemide treatment. Prior use of spironolactone and higher baseline serum potassium were protective against hypokalemia. Patients who developed hypokalemia were more likely to experience worse clinical outcomes including cardiac arrhythmia, sepsis, and longer hospital stay.

Furosemide works by inhibiting the Na^+-K^+-$2Cl^-$ co-transporter in the apical membrane of the thick ascending limb, leading to the loss of water, sodium, and potassium. Reyes et al. conducted a study to compare the effect of furosemide 80 mg with placebo on urinary potassium excretion and found substantially higher

urinary potassium concentration (7.9±0.6 mmol/L vs. 4.0±0.3 mmol/L) and urine volume (2.9±0.7 L/day vs. 1.2±0.8 L/day) in the furosemide group.[16] The incidence of hypokalemia was also 11% higher in the furosemide group. Similarly, the present study also showed that higher urine output after furosemide was associated with hypokalemia. In accordance with the European guideline for heart failure in 2021, loop diuretics are recommended for the treatment of pulmonary congestion in HF, with the goal of increasing urine output to 100-150 ml/hr within the first 6 hours.[17] The use of furosemide in the present study also achieved the target urine output of 2 ml/kg/hr.

The 2021 European guideline for heart failure recommends the use of mineralocorticoid receptor antagonists such as spironolactone or eplerenone in patients with hypokalemia.[17] The RALES study reported that the use of spironolactone reduced the risk of cardiovascular event-related death by up to 30% in patients with HF and reduced the incidence of hypokalemia by 10%.[18] In the EMPHASIS-HF study, eplerenone was found to be effective in preventing hypokalemia, with 38.8% of patients in the eplerenone group having serum potassium levels below 4.0 mmol/L compared with 48.4% in the placebo group. Furthermore, serum potassium levels <3.5 mmol/L were reported in only 7.5% of the eplerenone group compared with 11% of the placebo group.[19] In the present study, prior use of spironolactone was also associated with a decreased risk of hypokalemia. Although spironolactone has a half-life of only 1.4 hours, but the drug can remain effective for up to 12 hours.[20] In addition, patients who were on spironolactone prior to admission tended to have higher baseline serum potassium compared with patients who were not on the drug.

Hypomagnesemia and reduced intracellular magnesium level can interfere with the function of ROMK channels, resulting in an increase in renal potassium excretion.[21] Whang et al discovered a strong association between hypomagnesemia and hypokalemia. Approximately 56% of the patients who had hypomagnesemia also demonstrated hypokalemia.[22] Similarly, the association between baseline hypomagnesemia and the development of hypokalemia after furosemide treatment was also observed in the present study.

Higher body mass index has been found to predict hypokalemia in the present study. It is possible that the activation of the renin-angiotensin system (RAS) in adipose tissue is enhanced in obesity. The previous study also showed an increase in the risk of hypokalemia among obese patients due to RAS activation.[23] Another factor associated with hypokalemia after furosemide treatment is higher baseline serum albumin. Because furosemide is >90% protein bound, therefore, higher serum albumin likely enhances the action of furosemide.[24] A randomized cross-over study in patients with chronic kidney disease and hypalbuminemia by Phakdeekitcharoen et al revealed an increase in urine output and sodium excretion in the group of patients that received furosemide with intravenous albumin compared with furosemide alone.[25]

The relationship between high dose of furosemide and hypokalemia has been reported by Lowe et al.[26]. Furosemide <40 mg/day resulted in hypokalemia in only 1.3%, whereas furosemide 40-80 mg/day and >80 mg/day were associated with hypokalemia in up to 6.5% of the patients. The present study also observed the relationship between the higher dose of furosemide and hypokalemia.

The risk of hypokalemia in patients receiving loop diuretics has been examined previously by Kieneker et al. [27] Patients with a baseline serum potassium between 3.5-3.9 mmol/L had a significantly higher risk of developing hypokalemia compared with those with a baseline potassium between 4.0- 4.4 mmol/L. The present study also demonstrated the relationship between higher baseline serum potassium and lower incidence of hypokalemia.

As for clinical outcomes, the present study revealed the association between hypokalemia with cardiac arrythmia, sepsis and longer hospital stay. In a prospective cohort study of 754 hospitalized patients with ADHF, Salah et al. reported that lower serum potassium and a decline in serum potassium >15% from baseline were independent predictors of 180-day all-cause mortality.[28]

The present study is a retrospective study that could be influenced by selection bias and confounders. The study was conducted in a single center, which limited the generalizability of the findings. The effects of the concomitant use of other types of diuretics were not explored. There was no data on urinary potassium concentration, therefore, the loss of potassium in the urine could not be confirmed.

Conclusion

In conclusion, the present study identified several risk factors and worse clinical outcomes associated with hypokalemia after furosemide treatment in hospitalized patients with ADHF. These findings should emphasize the need for close monitoring of serum potassium especially among high risk patients.

References

1. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016:10;375(19):1868-77.
2. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003; 348(20):2007-18.
3. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line?. Ann Pharmacother. 2009;43(11):1836-47.
4. Wu MY, Chang NC, Su CL, Hsu YH, Chen TW, Lin YF, et al. Loop diuretic strategies in patients with acute decompensated heart failure: a meta-analysis of randomized controlled trials. J Crit Care. 2014;29(1):2-9
5. Hussain M, Walton K, Davidson C, Morgan DB. A study of two diuretic/potassium combinations in heart failure. Postgrad Med J. 1985;61(711):29-33.
6. Cote JM, Bouchard J, Murray PT, Beaubien-Souligny W. Diuretic strategies in patients with resistance to loop-diuretics in the intensive care unit: A retrospective study from the MIMIC-III database. J Crit Care. 2021;65:282-91.
7. Tamargo J, Segura J, Ruilope LM. Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents. Expert Opin Pharmacother. 2014;15(5):605-21.
8. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46(3): 213-21.
9. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. Circ Heart Fail. 2010;3(2): 253-60.
10. Ikram HW, Chan W, Espiner EA, Nicholls MG. Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. Clin Sci (Lond). 1980;59(6): 443-9.
11. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. Arch Intern Med. 2000;160(16):2429-36.
12. Leonard CE, Razzaghi H, Freeman CP, Roy JA, Newcomb CW, Hennessy S. Empiric potassium supplementation and increased survival in users of loop diuretics. PloS one. 2014;9(7):e102279.
13. Kaplan NM, Carnegie A, Raskin P, Heller JA, Simmons M. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. N Engl J Med. 1985;312(12): 746-9.
14. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. Kidney Int Suppl. 2012;2(1):1-38.
15. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48(12):1503-10.
16. Reyes AJ. Effects of diuretics on outputs and flows of urine and urinary solutes in healthy subjects. Drugs. 1991;41 Suppl 3:35-59.
17. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
18. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341(10):709-17.

19. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.
20. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. Heart Fail Rev. 2005;10:23-9.
21. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol. 2007;18(10):2649-52.
22. Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia: requested vs routine. JAMA. 1990;263(22): 3063-4.
23. Mariosa LS, Ribeiro-Filho FF, Batista MC, Hirota AH, Borges RL, Ribeiro AB, et al. Abdominal obesity is associated with potassium depletion and changes in glucose homeostasis during diuretic therapy. J Clin Hypertens (Greenwich). 2008;10(6):443-9.
24. Duffy M, Jain S, Harrell N, Kothari N, Reddi AS. Albumin and furosemide combination for management of edema in nephrotic syndrome: a review of clinical studies. Cells. 2015;4(4):622-30.
25. Phakdeekitcharoen B, Boonyawat K. The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. BMC Nephrol. 2012;13:92.
26. Lowe J, Gray J, Henry DA, Lawson DH. Adverse reactions to frusemide in hospital inpatients. Br Med J. 1979;2(6186): 360-2.
27. Kieneker LM, Eisenga MF, Joosten MM, de Boer RA, Gansevoort RT, Kootstra-Ros JE, et al. Plasma potassium, diuretic use and risk of developing chronic kidney disease in a predominantly White population. PloS one. 2017;12(3):e0174686.
28. Salah K, Pinto YM, Eurlings LW, Metra M, Stienen S, Lombardi C, et al. Serum potassium decline during hospitalization for acute decompensated heart failure is a predictor of 6-month mortality, independent of N-terminal pro–B-type natriuretic peptide levels: An individual patient data analysis. Am Heart J. 2015;170(3):531-42.