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Effect of Hypokalemia on Functional Outcome at 3 Months Post-Stroke Among First-Ever Acute Ischemic Stroke Patients

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Background: Hypokalemia has been confirmed to be a predictor of adverse cardiovascular and renal outcomes. There is a paucity of studies focusing on the potential connection between the serum K^+ level and the outcome after acute ischemic stroke (AIS). This study investigated whether hypokalemia in the acute stroke stage contributes to worse functional outcome in AIS patients.

Material/Methods: This retrospective cohort study included consecutive patients with first-ever AIS admitted between June 2015 and March 2016. Patients were divided into 2 groups: hypokalemia (K^+ <3.5 mmol/L) and normokalemia (3.5 mmol/L ≤K^+ ≤5.5 mmol/L). Primary outcome measure was poor outcome at 3 months (modified Rankin scale >2). Univariate and multivariate logistic regression analyses were used to assess the association between hypokalemia and poor outcome. Receiver operating curve (ROC) analysis was performed to determine the optimal cutoff point of serum K^+ level for predicting poor outcome.

Results: The percent of patients with poor outcome at 3 months was higher in the hypokalemic group (62.9%) than in the normokalemic group (45.5%). Hypokalemic patients tended to have lower fasting glucose at admission, lower Glasgow coma scale score, and longer time from symptom onset to treatment compared with normokalemic patients. Hypokalemia was associated with poor outcome at 3 months after adjusting for potential confounders (odds ratio=2.42, 95% confidence interval=1.21–4.86, P=0.013). ROC analysis showed that the optimal threshold for serum K^+ level was 3.7 mmol/L.

Conclusions: Hypokalemia at the initial admission is associated with poor prognosis at 3 months in first-ever AIS patients.

MeSH Keywords: Hypokalemia • Prognosis • Stroke

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Background

Acute ischemic stroke (AIS) is one of the most devastating diseases; it remains a significant health and social issue, with high disability and mortality rates. The World Health Organization (WHO) has reported that approximately 15 million people suffer a stroke every year, of which 5 million are fatal and 5 million result in permanent disability [1]. Currently, thrombolytic therapy with rtPA (recombinant tissue plasminogen activator) is the only approved and effective pharmacological treatment. However, rtPA increases the risk of hemorrhage, brain barrier, and activation of matrix metalloproteinases, and the therapeutic window is limited. Many patients miss the timing of rtPA treatment and still stay at risk of disability [2,3]. Therefore, it is vital to identify predictors of prognosis so that prompt medical intervention can be applied to improve outcomes of those patients who do not benefit from rtPA therapy. Several studies have already demonstrated that the status (e.g., sex, age, blood pressure, total cholesterol, plasma homocysteine, platelets, and serum Na^+) of AIS patients at admission influences their long-term functional prognosis [1,4–12].

Nonetheless, few studies have focused on the connection between hypokalemia and functional outcome in AIS patients after treatment. Hypokalemia is a common electrolyte disorder and complication of hospitalized patients. Serum K^+ has been confirmed to be a predictor of adverse cardiovascular and renal outcomes [12–15], but there has been only 1 previous report of hypokalemia being associated with high short-term mortality in acute stroke patients [16].

The objectives of the present study were to: (1) investigate relevant factors of hypokalemia at admission in first-ever AIS patients, and (2) determine the association between hypokalemia at admission and the functional prognosis at 3 months in these patients and detect whether this relationship is influenced by sex or age.

Material and Methods

Patients

All patients involved in this retrospective study were recruited consecutively from the Department of Neurology, the First Affiliated Hospital of Xi'an Jiaotong University between June 2015 and March 2016. Only patients with ischemic stroke were enrolled in the study. All of the patients had a clinical diagnosis of ischemic stroke commensurate with the WHO criteria, further confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI) in the hospital. Patients were excluded based on the following criteria: (1) recurrent ischemic stroke; (2) <18 years old; (3) a duration from symptom onset to treatment of >7 days; (4) having received thrombolysis therapy or embolectomy; (5) presence of a serious comorbidity such as cancer, liver disease, chronic renal disease, pulmonary, or endocrine disease; (6) presence of hyperkalemia (K^+ >5.5 mmol/L); or (7) nonavailability of the functional outcome at 3 months. Written informed consent was obtained from all subjects and the protocol for this study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Data collection

The following baseline data were collected and used in the analyses: (1) basic characteristics – age, sex, dates of being admitted to and discharged from hospital, and systolic and diastolic blood pressures on arrival at hospital; (2) vascular risk factors – current smoking, alcohol intake, hypertension, and diabetes mellitus (DM); (3) other diseases – myocardial infarction and atrial fibrillation; (4) previous medications – antiplatelets, antihypertensives, and hypoglycemics; (5) levels in laboratory tests – fasting serum glucose, hemoglobin A1c, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, urea nitrogen, serum K^+, and homocysteine; (6) neurological assessment – initial stroke severity on the National Institute of Health Stroke Scale (NIHSS), the Glasgow coma scale (GCS); (7) occlusion site and stroke subtype; and (8) length of symptom onset to treatment time (OTT).

Hypokalemia and normokalemia were defined as serum K^+ concentrations of <3.5 mmol/L and 3.5–5.5 mmol/L, respectively [17]. DM was defined as a previous diagnosis and treatment of DM, a fasting plasma glucose of ≥7.0 mmol/L (126 mg/dL), a value of 2 h in the oral glucose tolerance test, or a random plasma glucose concentration of ≥11.1 mmol/L (200 mg/dL) in the presence of the classic symptoms of hyperglycemia or a hyperglycemic crisis [8]. Hypertension was defined as the current use of antihypertensive medications, a systolic blood pressure of ≥140 mmHg, and/or a diastolic blood pressure of ≥90 mmHg [18]. Myocardial infarction was defined based on the self-report history [4]. Atrial fibrillation was defined based on the self-report history or diagnosed when present on a standard 12-lead electrocardiogram [8]. The occlusion site was detected by brain MRI, which included diffusion-weighted imaging and was performed using an echo planar instrument operating at 3.0 T or 1.5 T. The stroke subtype was ascertained according to the TOAST classification [19].

All blood samples were collected from patients within 24 h of hospital admission after at least 8 h of fasting. If a patient's blood sample is tested more than 1 time within 24 h, the data for the first time was collected. All plasma and serum samples were tested in the Clinical Laboratory of the First Affiliated

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Hospital of Xi'an Jiaotong University. All laboratory values were measured using a Hitachi BJ-G188 Automatic Biochemistry Analyzer (Hitachi, Tokyo, Japan).

The functional status after 3 months was assessed using the modified Rankin scale (mRS), with favorable and unfavorable outcomes defined as mRS scores of 0–2 and 3–6, respectively [6,7]. Outcome data were collected by a neurological clinician via telephone at 3 months after AIS.

Statistical analyses

Data were analyzed using SPSS Statistics for Windows software, version 19 (IBM, Chicago, IL, USA). Hypokalemic and normokalemic patients were compared using the Pearson χ^2 test, modified by Fisher's exact test for categorical variables, the *t* test for parametric analysis, and the Mann-Whitney *U* test for nonparametric analysis [17].

The associations between hypokalemia and other baseline variables were analyzed by nonconditional logistic regression. These variables with $P<0.05$ in univariate logistic regression were entered into a stepwise multivariate logistic regression model. Univariate and multivariate nonconditional logistic regression models were used to assess the relationship between hypokalemia and poor outcome (mRS score=3–6) at 3 months in AIS patients. Significant factors in univariate logistic regression analysis ($P<0.05$) were entered into the multivariate logistic regression model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. A prespecified subgroup analysis was undertaken stratified by sex and age (<65 or ≥65 years) in multivariate adjusted logistic regression models. Forest plots with overall-effect lines and interaction terms added to the logistic regression model were utilized to assess the effects of subgroups [20,21]. Receiver operating curve (ROC) analysis was performed to identify the optimal cutoff value for the K^+ to predict poor outcome at 3 months after stroke. The optimal cutoff point was determined based on the Youden Index when it is maximized [7]. A 2-sided *P* value of <0.05 was considered significant.

Results

There were 854 AIS patients admitted to the hospital between June 2015 and March 2016, of which 493 were excluded for the following reasons (Figure 1): 213 had a previous history of stroke, 248 presented more than 7 days after the onset of stroke symptoms, 23 received thrombolysis therapy or embolectomy, 6 had serious comorbidities (cancer, renal dialysis, or liver cirrhosis), 1 was hyperkalemic, and 2 had inadequate follow-up information. Therefore, 361 AIS patients were finally included in the study, of which 175 (48.5%) had a poor outcome at 3 months.

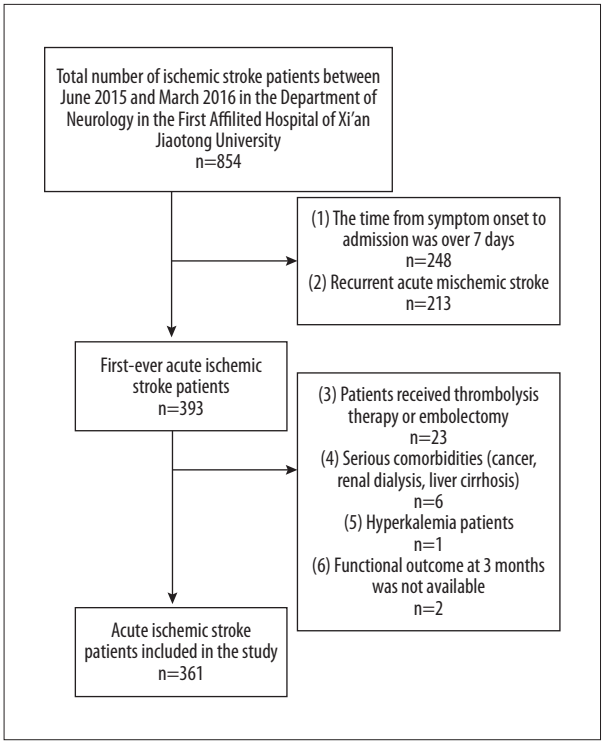

Figure 1. Reasons for exclusion from 854 cases of consecutively admitted acute ischemic stroke. Functional outcome means the modified Rankin scale (mRS).

The patient characteristics are grouped according to serum K^+ levels in Table 1. Sixty-two patients (17.2%) were hypokalemic. The fasting glucose, LDL-C, and creatinine levels were significantly lower in hypokalemic patients. The impairment of consciousness at admission was more evident in hypokalemic patients compared with normal patients, as reflected by GCS. A poor prognosis (mRS score=3–6) at 3 months after AIS was significantly more common in hypokalemic patients than in patients with a normal serum K^+ at admission ($P=0.013$). The length of stay in an acute stroke hospital did not differ significantly between the 2 serum K^+ groups. The other basic characteristics at admission did not differ significantly between normokalemic and hypokalemic patients.

Univariate logistic regression analysis revealed that fasting glucose, baseline GCS score, and OTT were associated with hypokalemia. The stepwise multivariate logistic regression model (Table 2) showed that lower fasting glucose, lower baseline GCS score, and longer OTT might be the determinants of hypokalemia.

The results of multivariate logistic regression analyses of the relationship between selected variables and a poor outcome at 3 months are listed in Table 3. Univariate logistic regression analysis indicated that age, myocardial infarction, hypokalemia, LDL-C, NIHSS score, GCS score, and occlusion site were

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Table 1. Demographic and clinical characteristics of acute ischemic stroke patients with hypokalemia and normokalemia.

Basic charateristics*	Normokalemia n=299		Hypokalemia n=62		*P* value
Demographic data					
Male	182	(60.9)	33	(53.2)	0.264
Age (years)	62±12.9		63.2±13.1		0.511
Risk factors					
Current smoking	105	(35.1)	15	(24.2)	0.097
Current alcohol drinking	54	(18.1)	11	(17.7)	0.953
Hypertension	194	(64.9)	48	(77.4)	0.056
Diabetes mellitus	76	(25.4)	15	(24.2)	0.840
Myocardial infarction	10	(3.3)	0	(0)	0.301
Atrial fibrillation	29	(9.7)	6	(9.7)	0.996
Parameters on admission					
Systolic BP (mmHg)	144	(127–161)	150	(133–165)	0.207
Diastolic BP (mmHg)	82	(77–92)	83.5	(76–93)	0.577
Baseline NIHSS score	5	(2–7)	5	(3–8)	0.467
Baseline GCS score	15	(14–15)	15	(15–15)	0.035
OTT (h)	48	(24–72)	48	(24–120)	0.145
Laboratory test					
Fasting glucose (mmol/L)	5.1	(4.5–6.7)	4.7	(4–6)	0.011
Hemoglobin A1c (%)	5.7	(5.4–6.6)	5.8	(5.3–6)	0.330
Creatinine (umol/l)	64	(57–73)	58	(48–72)	0.013
TC (mmol/L)	4.2	(3.6–4.8)	4	(3.5–4.6)	0.189
HDL-C (mmol/L)	1	(0.9–1.2)	1.1	(0.9–1.2)	0.282
LDL-C (mmol/L)	2.6	(2.1–3.1)	2.3	(1.8–2.7)	0.035
TG (mmol/L)	1.4	(1–2.1)	1.4	(1–1.9)	0.789
Blood usea nitrogen (mmol/L)	4.9	(4.1–6)	4.8	(4–5.8)	0.306
Homocysteine (umol/L)	16.8	(12.7–25.5)	16.7	(13.5–23)	0.875
Previous medications					
Antiplatelets	14	(4.7)	1	(1.6)	0.483
Antihypertensives	126	(42.1)	30	(48.4)	0.366
Hypoglycemics	44	(14.7)	10	(16.1)	0.776
TOAST subtype					0.931
Large artery atherosclerosis	82	(27.4)	17	(27.4)	
Cardioembolism	22	(7.4)	5	(8.1)	
Small artery occlusion	172	(57.5)	34	(54.8)	

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Table 1 continued. Demographic and clinical characteristics of acute ischemic stroke patients with hypokalemia and normokalemia.

Basic charateristics*	Normokalemia n=299		Hypokalemia n=62		*P* value
Other determined	10	(3.3)	3	(4.8)	
Undetermined	13	(4.3)	3	(4.8)	
Occlusion site					0.354
Internal carotid	13	(4.3)	5	(8.1)	
Middle cerebral artery	170	(56.9)	37	(59.7)	
Others	116	(38.8)	20	(32.3)	
Outcome					
mRS3-6 at 3 months	136	(45.5)	39	(62.9)	0.013
Duration of hospitalization (days)	11	(8–13)	12	(9–15)	0.051

BP – blood pressure; NIHSS – the National Institute of Health Stroke Scale; GCS – Glasgow Coma Scale; OTT – onset to treatment time; TC – total cholesterol; HDL – C-high-density lipoprotein cholesterol; LDL – C-low-density lipoprotein cholesterol; TG – triglycerides; mRS – modified Rankin Scale. * Categorical variables are expressed as frequency (percent); Continuous variables are expressed as mean ± standard deviation, or as median (interquartile range).

Table 2. Related factors with hypokalemia in patients with first-ever ischemic stroke in stepwise multivariate logistic regression model.

Factors	OR	95% CI	*P* value
Fasting glucose	0.85	0.73–0.97	0.021
Baseline GCS score	0.85	0.76–0.96	0.006
OTT	1.01	1.00–1.01	0.046

OR – odds ratio; CI – confidence interval; GCS – Glasgow Coma Scale; OTT – onset to treatment time.

Table 3. The association between hypokalemia and poor outcome at 3 months by multivariate logistic regression analysis.

Predictors	OR*	95% CI	*P* value
Age	1.02	1.00–1.04	0.045
Myocardial infarction	10.32	1.07–99.68	0.044
Hypokalemia	2.42	1.21–4.86	0.013
LDL-C	1.74	1.25–2.41	0.001
Baseline NIHSS score	1.42	1.29–1.56	<0.001
Baseline GCS score	0.82	0.67–0.99	0.040
Occlusion site			
Internal carotid	2.43	0.59–9.89	0.459
Middle cerebral artery	2.10	1.21–3.62	0.457
Others	–	–	

OR – odds ratio; CI – confidence interval; LDL-C – low-density lipoprotein cholesterol; NIHSS – the National Institute of Health Stroke Scale; GCS – Glasgow Coma Scale. * Adjusted by age, myocardial infarction, LDL-C, baseline NIHSS score, baseline GCS score, occlusion site.

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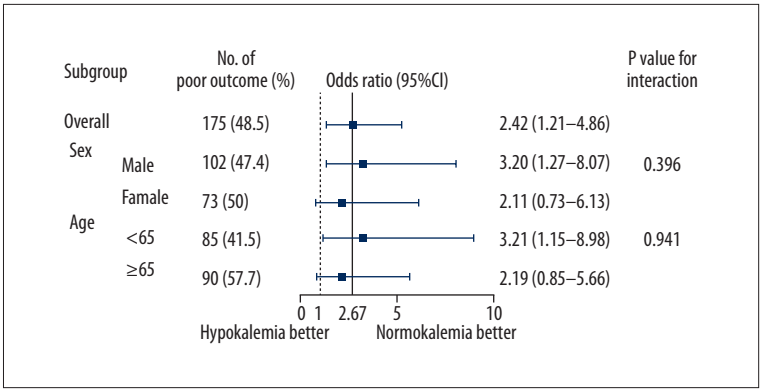

Figure 2. Subgroup analysis of OR (95%CI) of poor outcome in acute ischemic stroke patients at 3 months according to hypokalemia. The squares and horizontal lines represent odds ratio and the 95% confidence interval. Dotted line shows no-effect point, and bold line shows overall-effect point.

variables (P<0.05) likely to be associated with poor outcome at 3 months in patients with acute, first-ever ischemic stroke. The multivariate logistic regression model demonstrated that hypokalemia was a significant risk factor for a poor outcome at 3 months in these patients after adjusting for related variables (OR=2.42, 95% CI=1.21–4.86, P=0.013).

The results of subgroup analyses are shown in Figure 2. There were similar effect estimations for hypokalemia in the male and female subgroups, while the male group showed significance (OR=3.20, 95% CI=1.27–8.07) and female group crossed the no-effect point (OR=2.11, 95% CI=0.73–6.13). The association between hypokalemia and poor outcome appeared to be more pronounced in patients who were younger than 65 years (OR=3.21, 95% CI=1.15–8.98) than those aged at least 65 years (OR=2.19, 95% CI=0.85–5.66). Replacing the effect line (OR=1) by the overall-effect line (OR=2.42) resulted in the CI in all of the subgroups crossing the overall-effect line, suggesting a homogeneous impact of hypokalemia among the subgroups. This putative implication was confirmed in the interaction test. Subgroup analyses did not reveal any differences in the effect of hypokalemia on poor outcome (P>0.05 for all interactions). The ROC analysis indicated that K^+ concentration lower than 3.7 mmol/L could be used for predicting poor outcome at 3 months after AIS, with a sensitivity of 78.5% and a specificity of 32.6%.

Discussion

The results of this retrospective study involving a cohort of patients with AIS indicate that hypokalemia at admission is associated with a worse prognosis with respect to the mRS score (3–6) following first-ever AIS. The results were suitably adjusted for significant factors in univariate logistic regression analysis, including age, myocardial infarction, LDL-C, NIHSS score, GCS score and occlusion site. Subgroup analyses further revealed that the association between hypokalemia and a poor outcome at 3 months did not differ with sex and age (<65 or ≥65 years). The study also found potential factors associated with hypokalemia at admission. Lower fasting glucose, lower baseline GCS score and longer OTT seem to be related with hypokalemia.

The concentration gradient of K^+ across the cell membrane plays a key role in maintaining the membrane potential, and so an abnormal serum K^+ level will affect this potential in cardiac, vascular, and neuronal tissues. The study from Cheng et al. suggested that hypokalemia reduced conductance hyperpolarization in potassium channel of skeletal muscle cells. Even slight deviations in the serum K^+ level from the normal range may result in severe muscle dysfunction, palpitations, cardiac dysrhythmias, and deterioration of neurological function [12,16,22]. Several meta-analyses have reported that potassium intake can decrease stroke risk, and the potential mechanism could be that K^+ suppress the formation of free radicals and preclude endothelial dysfunction [23–25]. Also, other groups found that K^+ can inhibit vascular smooth muscle cell proliferation [25,26]. Nevertheless, there are few studies focusing on the relationship between serum K^+ level and the prognosis of stroke. Gariballa et al. reported that a lower plasma K^+ at admission was associated with the 3-month mortality rate of AIS (hazard ratio=1.73, 95% CI=1.03–2.90) [16], while Fofi et al. found no significant association between mortality and the serum K^+ level [11]. This discrepancy might be due to differences in the population characteristics between the 2 studies. The study by Gariballa et al. included patients with different types of stroke, while that of Fofi et al. was limited to AIS patients with an OTT of less than 6 h. Most of the patients in the present study were admitted to hospital 6 h later after symptom onset, so they missed the timing for thrombolysis and instead received conventional treatment. Longer OTT means that AIS patients were not admitted to hospital in a timely manner. Oropharyngeal dysphagia may occur in these patients, which could lead to inadequate dietary intake of K^+ and hypokalemia because of the delayed admission [27]. This may explain why OTT was positively correlated with hypokalemia in this study.

To the best of our knowledge, this is the first study to identify the cutoff value of serum K^+ for predicting the 3-month

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outcome after AIS. According to the ROC analysis of the present study, a serum K^+ level lower than 3.7 mmol/L on admission could be used for prediction of poor outcome at 3 months post-stroke following AIS, which confirmed that hypokalemia was a marker of unfavorable clinical outcome. This could be valuable for physicians in screening and targeting AIS patients who are at a high risk of a poor prognosis due to the serum K^+ level at admission. This study did not investigate if K^+ supplementation for hypokalemic patients could improve the prognosis following AIS. Our results provide useful information for clinical teams who frequently monitor serum K^+ with AIS and maintain its concentration above 3.7 mmol/L. It is usually necessary to check if there is any abnormality in the serum Na^+, Mg^{2+}, and H^+ concentrations. Especially in patients with severe hypokalemia, replacement of Mg^{2+} might be required despite the serum Mg^{2+} being normal, since Mg^{2+} can result in activation of the Na^+/K^+ pump [17,28,29].

This study was subject to several limitations that should be taken into account when interpreting the results. First, the type of information available for collection could not be controlled by the investigators due to the retrospective design of this study. It would therefore be of interest to implement a prospective study to examine the association between the dynamic alteration of serum K^+ during hospitalization and the prognosis of AIS over a longer observation period. Second, despite applying statistical adjustments to factors that were significant in univariate logistic regression analysis, other pre-existing clinical confounders may have also affected the prognosis of AIS patients, such as life style and different medications being administered to the patients before admission [30]. Third, the relatively small sample might have resulted in imprecise estimations of the CI values in subgroup analyses. Further studies with larger samples might yield more stable estimations in such analyses.

Conclusions

This is the first study to demonstrate that hypokalemia at admission is an independent predictor of poor outcome at 3 months (mRS score=3–6) in patients with first-ever AIS. Moreover, hypokalemic patients tend to have lower fasting glucose at admission, lower baseline GCS score, and longer OTT compared with normokalemic patients. Further studies in larger study populations should attempt to replicate these findings and determine if correcting serum K^+ improves the clinical outcome of AIS patients.

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Competing interests

None declared.

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