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 – antplatelets, 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 was 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 Hospital of Xi’an Jiaotong University.
Hypokalemia and acute ischemic stroke outcome

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Total number of ischemic stroke patients between June 2015 and March 2016 in the Department of Neurology in the First Affiliated Hospital of Xi'an Jiaotong University
n=854

(1) The time from symptom onset to admission was over 7 days n=248
(2) Recurrent acute ischemic stroke n=213
(3) Patients received thrombolysis therapy or embolectomy n=23
(4) Serious comorbidities (cancer, renal dialysis, liver cirrhosis) n=6
(5) Hyperkalemic patients m=1
(6) Functional outcome at 3 months was not available n=2

First-ever acute ischemic stroke patients n=393
Acute ischemic stroke patients included in the study n=361

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

| Basic characteristics* | 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   |
| TC (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)        |         |

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

| Basic characteristics* | 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.
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...
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⁺, Mg²⁺, and H⁺ concentrations. Especially in patients with severe hypokalemia, replacement of Mg²⁺ might be required despite the serum Mg²⁺ being normal, since Mg²⁺ 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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