

The Relation of Hypokalemia to Hypertensive and Non-Hypertensive Ischemic Stroke

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Abstract

Background Several clinical and laboratory observations are consistent with the hypothesis that hypokalemia might be a risk factor for the development of ischemic stroke in humans.

Objectives To evaluate the level of serum potassium in ischemic stroke patients and its relation to non-stroke patients and those with hypertension.

Methods Serum potassium was estimated from one hundred newly discovered first-life ischemic event of acute ischemic stroke patients and one hundred control patients with an attempt to evaluate the its level in ischemic stroke and the relation to hypertension. Normal value of serum potassium in both sexes was considered as 3.5-.5.5 mmol/L.

Results Mean serum potassium level of stroke patients was significantly lower than that of control group (3.89±0.67 versus 4.19±0.56, p=0.0001). Hypokalemia was found in 23 (23%) patients with stroke compared to 7 (7%) of the control group. The Mean serum potassium in hypertensive patients was significantly lower than those without hypertension (3.91 ±0.65 versus 4.2 ±0.54). The mean serum potassium for hypertensive stroke patients was significantly lower than non-hypertensive stroke patients (3.79±0.78 versus 4.26±0.72), while there was no significant difference among the control hypertensive and non-hypertensive subjects (4.05±0.57 versus 4.43±.40).

Conclusions Serum potassium should be taken in consideration as low levels are significantly associated with ischemic stroke with hypertension.

Keywords Serum Potassium, ischemic stroke

List of Abbreviation: K⁺ = Potassium, IS = ischemic stroke, HT = hypertension, BP = blood pressure, CVD = cardiovascular disease.

Introduction

Stroke is defined by the WHO as the clinical syndrome of rapid onset (usually seconds or minutes) of focal (or global, as in subarachnoid hemorrhage) cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one⁽¹⁾.

Pathologic process is given an inclusive meaning, namely, occlusion of the lumen by embolus or thrombus, rupture of a vessel, an altered

permeability of the vessel wall, or increased viscosity or other change in the quality of the blood flowing through the cerebral vessels⁽²⁾.

Stroke is the first leading cause of disability in developed and developing countries⁽³⁾. Stroke is the third most common cause of death in most western populations, after coronary heart disease and cancer⁽⁴⁾. Information on incidence, prevalence, and mortality of stroke is extremely important in the assessment of priorities for dealing with this disease, in the recognition of its occurrence, and hence the design of programs for prevention and control. Such information is

limited in the developing world ⁽⁴⁾. Humans evolved ingesting a potassium-rich, sodium-poor diet, and mechanisms developed to retain sodium and excrete potassium (K^+). The sodium-rich diet of modern humans produces sodium overload and K^+ depletion ⁽²⁾. There are no specific interventional studies on whether stroke incidence could be affected by K^+ supplementation. Since serum K^+ is kept within a narrow range, it may be clinically difficult to monitor whether K^+ supplement is adequate for an individual ⁽⁵⁾. Hypokalemia contributes to the pathogenesis of cardiovascular disease (CVD), and many CVD and drugs aggravate hypokalemia. Hypokalemia is therefore a common, reversible factor in the natural history of CVD ⁽⁶⁾.

Numerous studies have found that low K^+ intake and low serum K^+ are associated with increased stroke mortality, but data regarding stroke incidence have been limited. A lower stroke mortality rate has been found with higher K^+ intake, and higher stroke rate with low K^+ intake ⁽⁵⁾.

In two population-based studies, individuals on a low K^+ diet had a 40 to 50 percent increase in the risk of stroke, independent of other risk factors such as the systemic blood pressure (BP) ⁽⁷⁾. A similar effect has been demonstrated in stroke-prone hypertensive rats, in which the incidence of both stroke and renal vascular disease can be diminished by a high K^+ diet ⁽⁸⁾.

In one study, hypokalemia in the year before a stroke of treated hypertensive patients was associated with an increased risk of incident ischemic and hemorrhagic stroke independent of diuretic use when compared to normal serum K^+ levels ⁽⁵⁾.

Increasing dietary K^+ reduces neointimal formation after angioplasty and reduces atherosclerotic load. K^+ ameliorates oxidative stress by reducing free-radical formation, impairing vascular smooth muscle cells proliferation, and reducing monocyte adherence to vessel walls. Thus, K^+ retards the progression of atherosclerosis ⁽⁶⁾.

The aims of the study is to evaluate the level of serum K^+ in ischemic stroke (IS) patients in relation to non-stroke patients and the relation to hypertension (HT).

Methods

Study setting and design: The study was conducted in the wards of Internal Medicine/Neurology of Al-Imamain Al-Kadhmiyain Medical City. A hospital based case control study with an attempt to evaluate the level of serum K^+ in IS patients and the relation to HT. The period of data collection was one year started from Jan. 2012 to the end of Jan. 2013.

Selection of the study sample: A total number of 100 IS patients were examined from both sexes (50 males and 50 females), aged from 45-80 years old, who have an acute IS, were examined for serum K^+ , on (fasting) morning blood samples.

One hundred (50 males and 50 females) were selected from those suffering from other medical and neurological diseases other than stroke and cardiovascular events and considered as control group.

Baseline Examinations: The patients were assessed with full medical clinical examination for the diagnosis of stroke and exclusion of mimics, using a Computerized Tomography, Magnetic Resonance Imaging for Stroke confirmation and IS selection, complete blood count was done to exclude hematological disorders, basic biochemical investigations including fasting, random blood sugar, lipid profile (depending on total serum cholesterol, triglyceride, high density lipoproteins and low density lipoprotein for hyperlipidemia assignment), blood urea and serum creatinine to assess renal function.

Data collection: A Questionnaire was used to get information from studied population, which included general information from the patients and duration of stroke. Serum K^+ was measured with an autoanalyzer and the normal value of K^+ in both sexes was considered as 3.5-.5.5 mmol/L. ⁽⁶⁾

Statistical analysis

The collected data was organized, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 15. Values were expressed as mean ± SD. A comparison of continuous variables was performed by unpaired t-tests were used for categorical variables. The strength of associations between K⁺ and acute stroke was assessed by comparing stroke and control subjects. Significance levels were set at P values < 0.05 in all cases.

Results

The mean age of patients with IS was significantly higher than that of control group

(63±8.96 versus 53.86±9.29; *P* < 0.001). There was no significant association in distribution of cases according to gender (*P* = 0.832).

The mean serum K⁺ of patients with IS was significantly lower than that of control group (3.89±0.67 versus 4.19±0.56, *P* = 0.0001) as seen in fig. 1 and table 1.

The mean K⁺ for hypertensive stroke patients was significantly lower than non-hypertensive stroke patients (3.79±0.78 versus 4.26±0.72 *P* < 0.001), while there was no significant difference in K⁺ levels among the control hypertensive and non-hypertensive subjects (4.05±0.57 versus 4.43±.40; *P* > 0.05) table 2, 3.

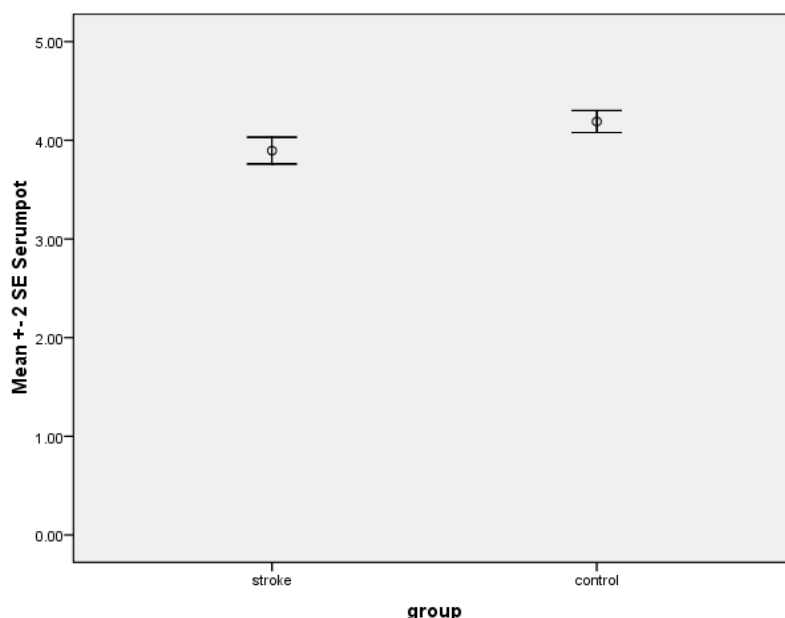


Fig. 1. Comparison of mean serum potassium between stroke group and control group

Table 1. Incidence of low serum potassium level in stroke and control groups

Serum potassium (mmol/L)	Stroke patients	Control group	Total
≥3.5	93	77	170
<3.5	7	23	30
Total	100	100	200

P = 0.002

Table 2. Comparison of mean serum potassium in patients with stroke versus control group

Serum Potassium mmol/L	Control Group		Stroke patients	
	non-hypertensive N = 35	Hypertensive N = 65	non-hypertensive N = 43	Hypertensive N = 57
Mean± SD	4.26±0.43	3.79±0.57	4.43±0.72	4.05±0.78
Minimum	3.80	2.80	2.80	2.10
Maximum	5.60	5.50	6.00	5.60
P Value	> 0.05		< 0.001	

Table3: Distribution of serum potassium level in stroke and control groups

Serum potassium (mmol/L)	Control		Stroke patients		Total
	non-hypertensive	Hypertensive	non-hypertensive	hypertensive	
≥3.5	35	58	38	39	170
<3.5	0	7	5	18	30
Total	35	65	43	57	200

P < 0.001

Discussion

In this study, the relation of K⁺ with stroke was examined. The study tried to compare epidemiological data from other studies that had linked K⁺ to stroke in human. Previous data revealed that K⁺ is an independent predictor of hypertension. Hypertension remains the second most common modifiable risk factor for stroke in the general population, including the elderly which exhibits that K⁺ levels were significantly lower in hypertensive than non-hypertensive patients (3.91±0.65 versus 4.2±0.54, P < 0.0001) consistent with the previous studies⁽⁹⁾. This study has shown that K⁺ levels were significantly lower in patients with ischemic stroke than the control group for other risk factors (3.89±0.67 versus 4.19±0.56, P = 0.0001). These results can suggest that hypokalemia may be an independent risk factor for the development of ischemic stroke. This study has shown the mean K⁺ for hypertensive stroke patients was significantly lower than non-hypertensive stroke patients (3.79±0.78 versus 4.26±0.72; P < 0.001), while there was no significant difference in K⁺ levels among the control hypertensive and non-

hypertensive subjects (4.05±0.57 versus 4.43±0.40; P > 0.05). These findings might be contributed that hypertension was the leading risk factor in this sample (57% of stroke patients were hypertensive). These data point that hypokalemia should be seriously considered in the hypertensive population as it was associated with significant increase in the risk of stroke in this particular group.

In 1997 Gariballa *et al* concluded that hypokalemia post stroke is common and may be associated with a poor outcome. They also found that on survival analysis, a lower plasma K⁺ on admission to hospital was associated with an increased chance of death, independent of age, stroke severity, history of hypertension, blood pressure level, or smoking history (hazard ratio 1.73 (95% CI: 1.03-2.9) for a 1 mmol/L lower plasma K⁺ concentration)⁽¹¹⁾. These results were also suggested by Moussavi *et al* in 2010 as they have found that patients with serum K⁺ levels below normal levels initially and at discharge have worse outcomes, especially in elderly patients⁽¹²⁾.

Serum K^+ has a fundamental role in BP regulation, and there is evidence highlighting the importance of K^+ homeostasis in hypertension. Pikilidou *et al* have concluded in their study the reverse relation between serum K^+ and BP supports a close pathophysiological connection between serum K^+ and essential HT. Moreover, they found that diuretic therapy is a significant cause of hypokalemia and requires systematic monitoring⁽⁹⁾.

The other important point needed to be taken in consideration is the effect of diuretics as a treatment for hypertensive patients. In 2003, Smith *et al* found that in adults with treated HT, hypokalemia in the year before a stroke was associated with an increased risk of incident ischemic and hemorrhagic stroke independent of diuretic use when compared to normal serum K^+ levels.⁽¹⁰⁾

Speculating on the mechanisms underlying their findings, they note that high serum K^+ levels are thought to inhibit processes such as free radical formation, platelet aggregation, and arterial thrombosis, thereby exerting a cardioprotective effect. Conversely, there is evidence that hypokalemia may increase the risk of cardiac arrhythmias in patients with underlying coronary disease. "A combination of these mechanisms may explain the association between hypokalemia and an increased IS risk," Smith *et al* conclude⁽¹⁰⁾.

In 2004, Drs. John Macdonald and Allan Struthers of Ninewells Hospital in Dundee, UK have produced an excellent summary of many consequences of hypokalemia in relation to cardiovascular disease. Among the highlights of their findings was High blood levels of K^+ inhibit platelet aggregation and thus help prevent IS and that adequate K^+ levels retard the progression of atherosclerosis⁽⁶⁾.

In 1999, Hiroyasu *et al* published a study that concluded low calcium intake, and perhaps low K^+ intake, may contribute to increased risk of IS in middle-aged American women⁽¹³⁾.

In contrast, K^+ supplementation appears to modestly lower the BP in some normotensive and hypertensive patients. The magnitude of

benefit was illustrated in two meta-analyses of randomized trials^(14, 15).

In the evidence of the above data and the findings of this study, it was shown that low serum K^+ is associated with IS and HT. Serum K^+ monitoring should be considered in populations who have other risk factors for stroke such as HT especially those groups treated with diuretics which may predispose them to develop hypokalemia. These groups may benefit from oral K^+ supplements to keep their serum K^+ within the acceptable range.

One of the most important limitations of this study was the sample size which reduced the power of the study. It is recommended that in the future to enroll a larger sample size and that patients may be followed over a period of time to estimate how serum K^+ levels may predict the development of IS especially in patients who are considered at high risk.

The measurement of serum K^+ , although easily accomplished, is seldom standardized. Indeed, the normal range for K^+ values is itself highly variable between laboratories; the lower limit fluctuates between 3.5 and 3.8 mmol/L and the upper limit between 5.0 and 5.5 mmol/L. Interpretation of a specific serum K^+ value initially requires an understanding of sampling conditions. For example, a serum K^+ value derived from a serum sample (red-top tube) is typically 0.1 to 0.3 mmol/L higher than one obtained from a plasma sample (green- or purple-top tube). Blood samples obtained using poor technique can also falsely increase serum K^+ values (pseudohyperkalemia). Prolonged use of a tourniquet above a venipuncture site or extended fist clenching produces tissue hypoxia and promotes the escape of K^+ from tissues into the plasma compartment⁽²⁾. Serum K^+ values also show evidence of a circadian rhythm (average peak-to-trough difference \approx 0.60 mmol/L, with lowest values at night).⁽¹⁶⁾

In conclusions, there was significant association between IS and low serum K^+ levels. Low serum K^+ level was significantly more evident in hypertensive than non-hypertensive patients.

Serum K⁺ should be taken in consideration as low levels are significantly associated with IS. A low serum K⁺ level in patients with IS is needed to be taken in consideration in hypertensive patients. Early detection and correction of low serum K⁺ in high risk patients for IS is recommended. Further studies are required to assess the value of K⁺ supplements in patients with other risk factors for IS.

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Author contribution

Dr. Haider A. Husain: acquisition of data, analysis or interpretation of data, statistical analysis. Dr. Hasan Azeez Al-Hamadani: revising the manuscript, study concept or design, study supervision. Dr. Munther T. Hamzah: collection of data.

Conflict of interest

No potential conflicts of interest.

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