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Effects of Urinary Kallidinogenase on NIHSS score, mRS score, and fasting glucose levels in acute ischemic stroke patients with abnormal glucose metabolism

A prospective cohort study

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Abstract

Urinary kallidinogenase may assist recovery acute ischemic stroke. This study evaluated the effect of urinary kallidinogenase on National Institute of Health Stroke Scale (NIHSS) score, modified Rankin scale (mRS) score, and fasting glucose levels in patients with acute ischemic stroke (AIS) combined with diabetes mellitus and impaired fasting glucose.

Patients with AIS and abnormal glucose metabolism were enrolled in this prospective cohort study and divided into 2 groups. The human urinary kallidinogenase (HUK) group were treated with urinary kallidinogenase and standard treatment; the control group received standard treatment. NIHSS scores, mRS scores, and fasting blood glucose were evaluated and compared.

A total of 113 patients were included: 58 in the HUK group and 55 in the control group. NIHSS scores decreased with treatment in both groups (time effect $P < .05$), but were lower in the HUK group (main effect $P = .026$). The mRS score decreased in both groups from 10 until 90 days after treatment (time effect $P < .05$); the 2 groups were similar (main effect, $P = .130$). Blood glucose levels decreased in both groups 10 days after treatment (time effect, $P < .05$), but there was no significant treatment effect (main effect, $P = .635$). Multivariate analysis showed blood uric acid >420 μmol/L (odds ratio [OR]: 0.053, 95% confidence interval [CI]: 0.008–0.350; $P = .002$) and application of HUK (OR: 0.217, 95% CI: 0.049–0.954; $P = .043$) were associated with 90% NIHSS recovery. Baseline NIHSS score was independently associated with poor curative effect.

Urinary kallidinogenase with conventional therapy significantly improved NIHSS scores in patients with AIS. Urinary kallidinogenase also showed a trend toward lower fasting blood glucose levels, although the level did not reach significance.

Abbreviations: ACE = angiotensin-converting-enzyme, AIS = acute ischemic stroke, BBB = blood–brain barrier, HUK = human urinary kallidinogenase, KKS = kallikrein-kinin system, mRS = modified Rankin scale, PAI-1 = plasminogen activator inhibitor-1, SD = standard deviation, SUA = serum uric acid, VEGF = vascular endothelial growth factor.

Keywords: hyperglycemia, ischemia, kallikreins, stroke

1. Introduction

According to data released by the World Health Organization, stroke is the second leading cause of death in the world,[1] and it is also the main cause of disability.[2] In recent years, with the progress of prevention and treatment of stroke in various countries, although the incidence of stroke has decreased worldwide, it is still the main cause of death in China.[3] Ischemic stroke, owing to the acute reduction of the blood supply to the brain, accounts for 70% to 80% of all stroke patients.[4] Hence, prevention and treatment of ischemic stroke are particularly important for reducing the overall mortality and disability resulting from stroke. Ischemic stroke is caused by hypertension, diabetes, heart disease, age, heredity, and other risk factors.[5] This results in stenosis and occlusion of the cerebral vascular lumen, as well as reduced or interrupted blood supply to the nerve cells in the brain; thus, a hypoxic-ischemic necrosis appears.[6] Ischemic stroke manifests as a series of neurological deficits and signs as well as cognitive impairment, such as hemiplegia and aphasia.[7] Inflammation in the early stage after cerebral infarction is one of the important mechanisms of neuronal damage in infarcted and penumbra regions. In addition, it promotes the occurrence and development of atherosclerosis, resulting in unstable atherosclerotic plaques and plaque rupture, and thus aggravates thrombosis.[8] It has been confirmed that pretreatment with angiotensin-converting-enzyme inhibitors and aerobic physical exercise can improve the clinical outcomes of stroke patients in view of their anti-inflammatory properties.[9–11]] Hyperglycemia is the result of abnormal glucose

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metabolism and is common in patients with acute stroke disease, even in patients who have not previously been diagnosed with diabetes.[12] Hyperglycemia is also closely related to an adverse outcome of ischemic stroke.[13] Elevated blood glucose can promote inflammatory response. Data from a study by Licata et al suggested that diabetic stroke patients exhibited higher plasma levels of plasminogen activator inhibitor-1 in comparison with nondiabetic ones.[14] Elevated blood glucose can also accelerate aortic atherosclerosis and microcirculatory disorders, and thus affect the formation of collateral circulation,[15] resulting in a reduction in blood circulation in the penumbra, the promotion of the death of neuronal cells death in the penumbra, and the increase of the infarct volume, thereby aggravating ischemic injury.[16]

Antithrombotic treatment is an important part of current treatment of acute ischemic stroke (AIS).[17,18] During onset of AIS, irreversible ischemia and hypoxic necrosis occur in the central area of the infarct lesion because of a reduced or interrupted blood supply. However, there are many surviving neurons in the ischemic penumbra of the marginal zone, which can restore their normal function if blood perfusion is recovered in a short time. However, owing to the short treatment window, most patients have missed the best time for thrombolysis at the time of treatment.[19] More recently, nerve repair therapy has been considered because it has a longer time window and applicable for most stroke patients. Angiogenesis plays a key role in the nerve repair process, which mainly occurs in the ischemic border zone. When the blood flow of the local brain tissue is blocked, the blood can flow to the ischemic area through other collateral branches. Newly generated blood vessels can then promote the processes of neurorestoration, including neurogenesis and synaptogenesis, thereby improving functional recovery.[20]

Ureklin kallidinogenase is a human urinary kallidinogenase (HUK), which exerts positive regulation through the kallikrein-kinin system (KKS) to catalyze the hydrolysis of low molecular weight kininogens to vasoactive kinins, and thereby activates bradykinin B1 and B2 receptors (B1R and B2R) and triggers a series of biological effects.[21] Of these, the activated B2 receptor can promote angiogenesis via the Akt-GSK-3β-VEGF-VEGFR-2 and Akt-eNOS-NO signaling pathways.[22] The protective mechanisms of kallikrein in ischemic brain injury include anti-inflammation, and antiapoptosis actions, and promoting angiogenesis and neurogenesis in hindlimb ischemia, myocardial infarction and renal ischemia.[23]

The purpose of this trial was to observe the effects of urinary kallidinogenase on the severity of stroke as measured by the National Institute of Health Stroke Scale (NIHSS) score and Modified Rankin Scale (mRS) score in patients with diabetes mellitus and impaired fasting glucose regulation with AIS. This will help accumulate basic data for evidence-based clinical application of urinary kallidinogenase for patients with AIS.

2. Methods

2.1. Participants

Patients with acute cerebral infarction who were hospitalized in the Neurology Department, of The Second Hospital of Hebei Medical University, China, between December 2016 and October 2017 were prospectively enrolled in this study.

The inclusion criteria for this study were as follows: aged 18 to 75 years (male or female); patients were admitted to hospital within 72 hours of stroke onset; diagnosis of acute ischemic stroke according to the criteria stated in the Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China (2010), and patients were confirmed as acute ischemic cerebrovascular disease by head computed tomography (CT) or magnetic resonance imaging (MRI) and diffusion-weighted imaging; NIHSS score ranged from 3 to 21 points; patients were previously diagnosed with type 2 diabetes, in which they were in line with the 2006 WHO diagnostic criteria for diabetes,[24] or they had fasting blood glucose of 6.1 to 6.9 mmol/L and glycosylated hemoglobin (HbA1C) of >6.1%; patients could cooperate with the test and evaluation of relevant indicators in the trial.

Exclusion criteria were: pregnant or lactating women; patients with severe heart, liver, and kidney dysfunction; patients with a history of cerebrovascular disease and who still suffered from serious neurological dysfunction that had an influence on the trial; patients with physical disabilities, joint deformities, or muscle lesions; patients were confirmed with intracranial hemorrhage by CT; patients were allergic to the study drug; patients suffering from severe systemic infection; patients who had participated in other clinical trials within 1 month; for any reason, the researchers believed that the subject was unlikely to complete the study (such as cerebral infarction caused by cerebral embolism, intracranial arteritis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and moyamoya disease; patients undergoing thrombolysis or thrombectomy after admission; patients and their families were unable to cooperate with follow-up.)

The present study gained approval from the ethics committee of The Second Hospital of Hebei Medical University (No.2016261). Written informed consent was provided by the study participants.

2.2. Therapeutic methods

According to administration of urinary kallidinogenase, patients were divided into the HUK group and control group. The treatment choice was made by the patients in consultation with their clinician. Both groups were given routine treatment for cerebral infarction, including antiplatelet aggregation, anticoagulation, lipid-lowering and plaque stabilizing, free radical scavenging, nerve nutrition, and brain protection. On the basis of this, patients in the HUK group were also given urinary kallidinogenase at 0.15 PNA unit/day, for a 10-day course. According to changes in their condition, patients were allowed to receive other appropriate treatments such as hypoglycemic, dehydration, and intracranial pressure lowering, blood pressure stabilizing, and correction of electrolyte imbalance, if it was necessary.

The withdrawal or termination criteria were as follows: patients who developed an apparent allergic reaction or phlebitis, which was considered related to the study drug; patients who were in a critical condition and needed to be transferred to another department; patients who suffered from a secondary cerebral hemorrhage, combined with subdural/external hematoma or subarachnoid hemorrhage; during the treatment, patients developed serious complications unrelated to the drug which might be life-threatening (such as cerebral palsy or stress ulcers), in which senior physician suggested to terminate the trial; patients or their families asked to quit the trial.

2.3. Data collection and follow-up

The medical data of the eligible patients during hospitalization were recorded, including name, sex, medical history (histories of

coronary heart disease, hyperlipidemia, cerebral infarction, hypertension, diabetes), smoking history and alcohol history, combined medication, and NIHSS score at admission, as well as related laboratory examinations. Fasting blood glucose was measured at admission and 10 days after admission. The NIHSS and mRS scores were followed up at 10 days, 30 days, and 90 days after admission; of these the data at 30 days and 90 days were obtained by telephone follow-up after discharge.

Evaluation of NIHSS score was done through following: general recovery was when NIHSS score was reduced by 90% to 100%; significant progress was when NIHSS score was decreased by 46% to 89%; progress was when NIHSS score was decreased by 18% to 45%; no change (invalid) was when NIHSS score was decreased or was increased by <18%; worsening was when the score was increased by >18%.

mRS score was evaluated as follows: 0, completely asymptomatic; 1, had symptoms, but no significant dysfunction; 2, mild disability; 3, moderate disability; 4, severe disability; 5, serious disability. Of these, a score of 0 to 2 points referred to a good curative effect, and 3 to 5 points referred to a poor curative effect.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 21.0 software (IBM Corp). Categorical variables were expressed as frequencies and percentages, and comparisons of ratios were made using the χ^2 test or Fisher exact test. Continuous variables were tested for normality. Normally distributed continuous variables were expressed as means ± standard deviation (SD) and were compared between 2 groups using Student *t* test. Non-normally distributed continuous variables were presented as median (range) and compared between groups using the Mann-Whitney *U* test. NIHSS score, mRS score, and fasting blood glucose were analyzed by 2-way repeated measures analysis of variance. Patient outcomes were analyzed with multivariate logistic regression analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 113 patients with acute cerebral infarction were included, including 55 patients in the control group and 58 in the HUK group. The baseline data of the 2 patient groups are shown in Table 1. The median age was 59 (range 36–77) in the HUK group and 60 (range 39–78) in the control group ($P = .868$). No significant differences in sex, histories of hypertension, diabetes, coronary heart disease, hyperlipidemia, cerebral infarction, and history of alcohol consumption were observed between the 2 groups. There were also no significant differences in laboratory examinations such as homocysteine, blood uric acid, hypersensitive C-reactive protein, and glycosylated hemoglobin between the 2 groups. Meanwhile, smoking history ($P = .027$), fasting blood glucose ($P = .043$), and hospital stay ($P = .047$) were significantly different between the 2 groups.

3.2. Change in NIHSS and mRS scores with treatment

The NIHSS scores of the 2 groups were similar at baseline ($P = .820$) and both groups showed a steady decrease over time from baseline (time effect, $P < .05$, Table 2). Comparison of the 2 groups showed a significant treatment effect in the HUK group (main effect, $P = .026$) and the changes were different in the 2 groups (interaction effect, $P = .001$).

The mRS score decreased in both groups from the first time point at 10 days after treatment until 90 days after treatment (time effect, $P < .05$, Table 2). There was no obvious treatment

Table 1

Comparison of baseline data between the different groups (N = 162).

Characteristics	HUK group N = 58	Control N = 55	*P*
Age, median (range)	59 (36–77)	60 (39–78)	.868*
Sex, n, %			.853
Male	41 (36.3%)	38 (33.6%)	
Female	17 (15.0%)	17 (15.0%)	
History of hypertension, n, %	14(12.4%)	19(16.8%)	.224
Type of diabetes, n, %			.915
Type 2 diabetes	51 (45.1%)	48 (42.5%)	
Impaired fasting glucose	7 (6.2%)	7 (6.2%)	
Insulin dependent (application of insulin), n (%)	9 (8.0%)	8 (7.1%)	.885
History of coronary heart disease, n (%)	11 (9.7%)	9 (8.0%)	.717
History of hyperlipidemia, n (%)	4 (3.5%)	2 (1.8%)	.440
History of cerebral infarction, n (%)	14 (12.4%)	17 (15.0%)	.420
History of smoking, n (%)	13 (11.5%)	23 (20.4%)	.027
History of alcohol, n (%)	15 (13.3%)	15 (13.3%)	.865
Homocycteine, μmol/L, median (range)	17.6[7,78]	17.7[8,78]	.419*
Blood uric acid, μmol/L, median (range)	261.5 (136–573)	265.0 (31.5–489.0)	.484*
hsCRP, median (range)	2.6 (0.4–205.2)	2.15 (0.3–35.2)	.271*
HbA1C (%), mean ± SD	8.6 ± 1.5	7.9 ± 2.1	.089†
Fasting blood glucose, mmol/L, median (range)	8.90 (4.64–17.70)	7.66 (4.09–17.99)	.043*
NIHSS score before treatment, mean ± SD	6.9 ± 3.2	7.0 ± 3.2	.820*
Hospital stay	13 (7–33)	12 (7–22)	.047*

hsCRP = high-sensitivity C-reactive protein, HUK = human urinary kallidinogenase, NIHSS = National Institute of Health Stroke Scale.

* *P* value from the independent sample Mann-Whitney *U* test; the other from the R × C χ^2 test.

† *P* value from the complete randomized 2-sample *t* test.

Table 2

Different time NIHSS and mRS scores with 2 groups of patients.

	HUK	Control	Main effect, *P*	Interaction effect, *P*	Time effect, *P*
NIHSS score (mean ± SD)			.026	.001	<.05
Before treatment	6.9 ± 3.2	7.0 ± 3.2			
10 days	5.2 ± 2.8	6.4 ± 2.8			
30 days	3.4 ± 2.4	5.0 ± 2.8			
90 days	2.1 ± 1.9	4.0 ± 3.0			
mRS score (mean ± SD)			.130	.146	<.05
10 days	3.2 ± 1.3	3.5 ± 1.3			
30 days	2.6 ± 1.2	3.0 ± 1.4			
90 days	2.1 ± 1.2	2.6 ± 1.5			
Blood glucose, mmol/L (mean ± SD)			.635	.001	<.05
Before treatment	9.33 ± 2.79	8.53 ± 3.25			
10 days	6.96 ± 1.85	7.33 ± 1.97			

HUK = human urinary kallidinogenase, mRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale.

effect in the HUK group (main effect, $P = .130$, interaction effect, $P = .146$).

3.3. Change in blood glucose with treatment

The blood glucose level also decreased from baseline in both groups over time (time effect, $P < .05$; interaction effect, $P = .001$, Table 2), but there was no significant treatment effect in the HUK group (main effect, $P = .635$), suggesting that HUK may not affect blood glucose level. However, a decreasing trend in blood glucose level was observed in the HUK group.

3.4. Multivariate analysis of factors related to patient outcome

The multivariate analysis of factors related to patients failing to achieve general recovery is shown in Table 3. Blood uric acid >420 μmol/L (odds ratio [OR] 0.053, 95% confidence interval [CI] 0.008–0.350; $P = .002$) and application of HUK (OR: 0.217, 95% CI 0.049–0.954; $P = .043$) were both independently associated with general recovery (Table 3).

Multivariate analysis of factors related to patients having a poor curative effect as measured by the 90-day mRS score ≥3 is shown in Table 4. The results showed that baseline NIHSS score was independently associated with poor curative effect (NIHSS 5–10, OR = 4.97, 95% CI 1.258–18.823, $P = .022$; NIHSS >10, OR = 58.98, 95% CI 5.314–654.77, $P = .001$).

4. Discussion

The aim of this study was to evaluate whether urinary kallidinogenase was beneficial when added to conventional treatment of AIS. The results show that NIHSS scores decreased with treatment in both groups but were lower in the HUK group with a significant treatment effect. The mRS score decreased in both groups from 10 days after treatment until 90 days after treatment, but the 2 groups were similar and there was no obvious treatment effect. Blood glucose levels decreased in both groups 10 days after treatment and were similar in the 2 groups with no significant treatment effect. So, these results suggest that treatment with urinary kallidinogenase helps improve neurological outcomes after AIS.

The main result in this study is the clear benefit in NIHSS scores to the patients with AIS in the HUK group. This result was supported by the multivariate analysis that showed HUK to be an independent factor related to general recovery. Other studies have also shown significant improvements in NIHSS score in patients randomized to receive urinary kallidinogenase as well as standard treatment. These include a study that randomized 200 patients with acute cerebral infarction after thrombolytic therapy,[25] a study of 58 patients with massive cerebral infarction treated with edaravone,[26] and a study of 47 patients with level 3 hypertension and ischemic stroke.[27] Another study looked at the treatment combination of urinary kallidinogenase with Maixuekang capsule and found that patients with ischemic stroke who received either urinary kallidinogenase in combination with standard treatment or urinary kallidinogenase in combination with standard treatment and Maixuekang capsule had significantly lower NIHSS scores after treatment than the control group.[27] A study using MRI to assess the effect of urinary kallidinogenase in patients with ischemic stroke found that alongside with observed improvements in stroke outcome, cerebral perfusion was enhanced and vascular endothelial growth factor (VEGF) and apelin expression were increased, suggesting a

Table 3

Multivariate analysis of factors related to nongeneral recovery (90-day NIHSS was reduced by <90%) for all patients.

		OR	95% CI	*P*
Blood uric acid	>420 vs ≤420 μmol/L	0.053	(0.008–0.350)	.002
Application of HUK	Yes vs no	0.217	(0.049–0.954)	.043

CI = confidence interval, HUK = human urinary kallidinogenase, OR = odds ratio.

Table 4

Multivariate analysis of poor curative effect (90-day mRS ≥3) for all patients.

	OR	95% CI	*P*
Baseline NIHSS score			
<5	Ref		.003
5–10	4.867	(1.258–18.823)	.022
>10	58.984	(5.314–654.77)	.001

CI = confidence interval, mRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale, OR = odds ratio.

possible mechanism for the action of urinary kallidinogenase.[27] These studies all show that further large-scale clinical studies into the use of AIS are needed,[28] but its use clinically shows a benefit to stroke outcome.

The multivariate analysis also showed that blood uric acid level >420 μmol/L was an independent factor related to general recovery. Univariate analysis showed no difference between the groups in uric acid level before treatment, but we did not measure the level after treatment. So, we will consider this in future studies. Uric acid is an antioxidant that plays a protective role against tissue damage.[29] Most antioxidants have reduced levels after stroke,[30] but uric acid may have a protective effect for neurons and protect against ischemic brain injury.[31] However, the relationship between uric acid and outcome after cerebral infarction is controversial. A study of 199 stroke patients showed that decreases in uric acid in the first week after stroke were associated with more severe stroke and poorer outcome.[32] In 317 patients with stroke treated with thrombolysis, excellent outcomes were associated with a significantly higher uric acid level, and the level of UA and the volume of final infarction were inversely correlated.[33] Another study of 1136 stroke patients showed clinical improvement was significantly higher in patients with high serum uric acid (SUA) levels at admission and uric acid level showed a positive correlation with clinical improvement, but uric acid level was an independent predictor for favorable stroke outcome only in patients receiving intravenous thrombolysis.[34] However, the study of 463 patients who had an acute ischemic stroke suggests that although a low SUA concentration is modestly associated with a very good short-term outcome, SUA may act more as a marker of the magnitude of the cerebral infarction than influence stroke outcome.[35] When differences in patient background were considered in 248 severe ischemic stroke patients treated with intravenous recombinant tissue plasminogen activator, excellent functional outcomes had a significant association with serum UA levels in men but not in women.[36] A study that measured SUA in 2498 patients with acute stroke found that higher levels predicted poor outcome.[37] This view is supported by a study of 435 patients after acute stroke where if SUA level was >0.47 mmol/L, then there was a high probability of early death.[38] Meta-analysis suggests that hyperuricemia may modestly increase the risks of both stroke incidence and mortality.[39] It is clear from the differences in the conclusions of these studies that further research is needed into the role uric acid has to play in stroke outcome.

The second finding of this study is a trend for decreasing fasting glucose level in the HUK group, although the level did not reach significance when the groups were compared. Studies have found that HUK can improve blood glucose utilization, promote glucose transfer, and improve insulin sensitivity.[40] This is likely to support the beneficial action of urinary kallidinogenase. Abnormal glucose metabolism is common in stroke patients and is significantly associated with the occurrence and damage of cerebral infarction. In ischemic stroke trials, hyperglycemic animals tend to present a higher incidence of cell death, hemorrhagic transformation, and larger infarct volume,[41] which is possibly associated with intracellular acidosis, increased free radicals, and blood-brain barrier (BBB) destruction which induces inflammation and leads to axonal degradation. The metabolic pathway plays a key role in the pathogenesis of ischemic stroke. For ischemic stroke patients with a normal blood glucose level, they suffer from cerebral ischemia and anoxia, reduced ATP synthesis, calcium overload in cells and mitochondria, which causes swelling of neuronal cells, degeneration of organelles, loss of membrane integrity, and ultimately leads to cell death. Meanwhile, for stroke patients with elevated blood glucose, the body can generate high-sugar complexes, which leads to an increase of excitatory release, upregulation of intracellular calcium, and increase of cytoplasmic cytochrome c, and thus induces death of neurons.[42] In addition, for cases with hyperglycemia, blood is stagnated and lactic acid is accumulated in the ischemic area, which is easier to trigger proapoptotic signals, reduces blood perfusion to penumbra, increases the final infarct volume, and leads to deterioration of neurological outcomes.[43] Applying urinary kallidinogenase in the acute phase of cerebral infarction can selectively dilate small arteries in the ischemic area, promote neovascularization, increase intracerebral perfusion in the penumbra, and improve blood supply and oxygen supply in the ischemic area, but also can inhibit apoptosis, slow neuronal damage, inhibit platelet aggregation, promote utilization of glucose, and promote neuroregeneration and angiogenesis in the ischemic area. Chen et al[42] showed that HUK also plays an important role in inhibiting edema and inflammatory mediators, improving nerve function and reducing infarct size.

This study has some limitations. The study population was quite small and from one center. A larger study would provide more evidence for these results. The patients were not randomized to their treatment groups; this is likely to have caused some bias in the results. The follow-up was quite short-term, so differences in the patient groups long term should be evaluated. Further study is needed to fully investigate uric acid levels after treatment.

5. Conclusion

The combination of urinary kallidinogenase and conventional therapy can significantly improve neurological deficits in acute ischemic stroke patients. Urinary kallidinogenase also showed a trend toward lower fasting blood glucose levels, although the level did not reach significance in this study.

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