Human Urinary Kallidinogenase Improve Short Term Motor Functional Outcome By Reducing The Corticospinal Tract Damage In Acute Ischemia Stroke Patients

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Study Protocol

- **Project name:** Human urinary kallidinogenase improve short term motor functional outcome by reducing the corticospinal tract damage in acute ischemia stroke patients
- **Background and Purpose:** The human urinary kallidinogenase (HUK) was used in China in the management of acute ischemic stroke(AIS) in recent years. However, the mechanism of HUK on the treatment of AIS has not been systematically investigated. This study aimed to assess the effect of HUK on motor functional outcome and relative corticospinal tract damage recovery in the patients with AIS.
- **The research participants：** The AIS patients in the Neurology Department of the Second Hospital of Hebei Medical University, North China, from July 2017 to March 2019 were eligible for inclusion according to the inclusion criteria below, The acute ischemic stroke diagnosis conformed to "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China 2014". This study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (2018-P023).

Inclusion and exclusion criteria

Inclusion Criteria: (1) The enrollment age was between 18 and 80 years old; (2) Within 72 hours of onset; (3) Diagnosed as acute ischemic stroke, and confirmed by MRI as an acute infarct with the unilateral corticospinal tract damage; (4) The patients' muscle strength of paralyzed side at the admission was below or equal to grade 4; (5) No history of cerebral infarction, or with cerebral infarction history but without residual physical activity disorder; (6) No other intracranial

lesions; (7) The patients or their surrogates voluntarily sign the informed consent.

Exclusion Criteria: (1) Intracranial hemorrhagic disease include cerebral hemorrhage, subarachnoid hemorrhage, etc; (2) Transient ischemic attack; (3) Intravenous thrombolysis and interventional thrombectomy; (4) Serious physical illness affects limb movement before enrollment; (5) Apply other neurotrophic and promote nerve regeneration drugs through the trial; (6) Unstable vital signs, severe liver and kidney diseases or malignant tumors; (7) Inability to understand and/or comply with the study procedures and/or follow-up due to mental disorders or emotional disorders.

- **Therapy**：With the random number table method, the patients were consecutively enrolled and divided into two groups: the HUK group and the control group. All patients were treated with standard therapy based on the Guideline, besides, the HUK group were given the HUK (Guangdong tianpu biochemical pharmaceutical co. LTD, National drug approval no. H20052065) for injection (0.15PNA diluted in 100ml physiological sodium chloride solution, 1 time/day, intravenous infusion) within 24 hours after admission. Both groups were treated continuously for 14 ± 5 days.
- **Data collection**：At admission and discharge, 2-3ml venous blood was collected, blood samples were centrifuged and serum were collected, the concentrations of VEGF and MBP were tested by ELISA (Wuhan Servicebio Technology Co., Ltd). At the same time, National Institute of Health Stroke Scale(NIHSS), Barthel

Index(BI), muscle strength were also assessed. Both groups underwent a brain MRI within 72h of onset and 14±5 days after treatment. The sequences included the axial and sagittal T2WI sequence (TR/TE, 5000/89 ms), the axial T1WI sequence (TR/TE, 500/8.4 ms), and the axial T2 FLAIR (Fluid-attenuated Inversion-recovery) sequence (TR/TE/TI, 9000/89ms), axial DWI sequence. The diffusion tensor imaging (DTI) examination adopted single excitation SE-EPI sequence, TR/TE: 3138/60 ms. DTI were performed to record the Dffusion Tensor Tractography(DTT) classification, Fractional anisotrophy(FA) and Apparent Diffusion Coefficient(ADC) parameters were to evaluate the injury degree of the corticospinal tract; The decline rate (the decline rate = [contralateral side - ipsilateral side] / contralateral side) was obtained, ΔFA and ΔADC represent the decline rate of the second time minus the first time. The severity of the corticospinal tract injury evaluated by DTT was classified as: Grade 1, with complete corticospinal tract; Grade 2, the corticospinal tract was slightly injured with the injury less than 50%. Grade 3, moderate corticospinal tract injury with the injury between 50%~75%; Grade 4, severe corticospinal tract injury, almost interrupted more than 75%. Besides, the Magnetic resonance angiography(MRA) was also performed, for persons with intracranial arteries $\geqslant$ 70% were diagnosed as severe stenosis.

- Primary outcome is the short-term motor function prognosis of the AIS patients in two groups, secondary outcomes are the recovery of corticospinal tract and the serum MBP and VEGF changes during treatment.