Somato Publications ISSN: 2643-265X

Current Research in Neurology and Neurosurgery

Research Article

Treatment with Human Urinary Kallidinogenase Improves Clinical Outcomes in Acute Ischemic Stroke Patients with Diabetes Mellitus

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Received: 02 May 2020; Accepted: 07 July 2020; Published: 08 July 2020

Citation of this article: : Dong, Y., Wang, Y., Xie, Y., Dong, Q. (2020) Treatment with Human Urinary Kallidinogenase Improves Clinical Outcomes in Acute Ischemic Stroke Patients with Diabetes Mellitus. Curr Res Neurol Neurosurg, 3(1): 01-06.

Abstract

Background

Patients with diabetes are at higher risk for stroke. Moreover, these acute stroke patients (AIS) often have worse outcomes than the non-diabetic population. Human urinary kallidinogenase (HUK) has been shown to be clinically beneficial in ischemic stroke patients. The present study aims to investigate the effects of HUK on the treatment of ischemic stroke patients with diabetes mellitus.

Methods

The present study was a retrospective study of pooled data from a phase IIb clinical trial and a phase III clinical trial, in which patient were allocated to receive either HUK injection or placebo. Clinical outcome were measured by the European Stroke Scale (ESS) and the Activities of Daily Living Scale (ADL). Safety was assessed the rate of severe adverse events. Outcomes in diabetic patients were analyzed and compared with non-diabetic patients.

Results

A total of 114 diabetes patients were included in the trials, with 83 in the HUK-treated group and 31 in the placebo group. Patients' demographic and baseline characteristics are similar. Logistic analysis of the data for this subgroup of patients showed that HUK was associated with greater improvements in functional and physiological outcomes. We also found that patients with diabetes were more likely to have greater improvement compared to non-diabetes patients.

Conclusions

HUK is potential benefit in AIS patients, especially in patients with diabetes mellitus.

Key words: Acute ischemic stroke, Human urinary kallidinogenase, Functional outcome, Diabetes mellitus

Introduction

Ischemic stroke, a leading cause of adult disability and death, accounts for approximately 43–79% of all strokes in China [1]. Diabetes mellitus (DM) is associated with significantly higher incidence of stroke compared with the non-diabetes population and also a risk factor for recurrent stroke [2]. Moreover, patients with diabetes were associated with less reperfusion and poor plasticity after infarction, which was associated with the risk of dependency [4]. Therefore, treatment of ischemic stroke patients with DM poses significant challenges.

The kinin-kallikrein system is a complex metabolic system. Lower kallikrein plasma levels are associated with a higher risk of ischemic stroke and stroke recurrence [5]. Human urinary kallidinogenase (HUK) is a tissue kallikrein extracted from urine. In animal studies, it has been found that HUK might act as a vasodilatator and as a pro-angiogenic agent [6]. Kallikrein can inhibit apoptosis and inflammation and promote neurogenesis and angiogenesis [7]. In rat, HUK was associated with better outcome and more reperfusion in the stroke model [8]. Subsequent clinical trials demonstrated its clinical benefits in stroke patients [9]. HUK was approved for treatment of acute ischemic stroke by the Chinese Food and Drug Association in 2008 based on promising results from a phase III clinical trial.

Furthermore, kallikrein protects against diabetic nephropathy [10] and cerebral reperfusion injuries [11] in diabetic rat models. Therefore, the present study was aimed to assess the benefits of HUK as a treatment for acute ischemic stroke patients with DM.

Methods

Trial design

The present study was a retrospective study of pooled data from a phase IIb clinical trial and a phase III clinical trial. Both the phase IIb trial and the phase III trial were multi-centered, prospective, double-blind, and randomized clinical trials. Written informed consents were obtained from all individual participants in the study. Both trial protocols were approved by the ethics committees of all participating hospitals.

Patients

Patients in the phase IIb trial were recruited from June 2002 to November 2003 and in the phase III trial, from September 2003 to December 2004. All strokes were diagnosed based on clinical presentation and CT/MRI imaging. Detailed inclusion and exclusion criteria are reported in Supplemental 1. Diabetes patients were defined if a patient was considered to have diabetes if the patient had a history of diabetes, a fasting glucose of greater than 7mmol/L, or an HbA1cof greater than 6.5%, identified by case report form.

Intervention

The patients included in the trials were randomized at a 2:1 ratio in the phase IIb trial and 3:1 ratio in the phase III trial to receive intravenous HUK (0.15 p-nitroaniline unit) or placebo. Both were administered over a period of 30 minutes daily for the first 21 days.

Assessments

Outcome were measured by the activities of daily living (ADL) scale for functional outcome and the European Stroke Scale (ESS). Functional outcomes were evaluated at baseline, on treatment day-7, day-14, and day-21by the ADL scale. An ADL scale score of higher than 85 was defined as functionally independent. Severity of stroke were evaluated by ESS at baseline, day 7, day 14, and day 21. Improvement was calculated as the changes of ESS scores from baseline.

Safety was measured the rate of severe adverse events (SAE), which were defined as death, life-threatening events, any events that could result in disabilities, events that lead to hospitalization or hospital lengthened hospital stay, or any event that was considered a serious adverse event by the investigator onsite.

Statistical analyses

Number (n) and percentage (%) were used to describe categorical data, while mean ± standard deviation (SD) was used to describe normally distributed continuous data and median (range) was used to describe continuous data that was not normally distributed. Data were blinded after all patients' clinical information for the trial was collected and entered into the database. Statistical analyses were performed with SAS software (SAS Institute Inc., USA).

Benefits of HUK were analyzed in the full analyze set (FAS) population, including all randomized patients who received at least one dose of trial medication and were assessed at least once for outcomes. The safety population included all patients who received at least one dose of HUK. The χ^2-test was used to test the differences in ESS and ADL scores between the study groups. The Wilcoxon

Table 1: Patients' demographic information and baseline characteristics with diabetes mellitus.

n (%)	HUK N=464	Placebo N=181	p
Sex, n (%)			
Male	276(59.48)	117(64.64)	0.23
Female	188(40.52)	64(35.36)	
Age (year, mean ±se)	62.10 ± 10.56	62.55 ± 9.89	0.62
BMI(kg/m2, mean ± se)	23.88± 2.83	23.69 ± 2.85	0.43
Family history of stroke, n (%)	119 (25.65)	43 (23.76)	0.62
Clinical history, n(%)			
Diabetes	83 (17.89)	37 (17.13)	0.82
Hypertension	291 (62.72)	121 (66.85)	0.40
Anginapectoris	39 (8.41)	19 (10.5)	0.40
Transient ischemic attack	77 (16.6)	19 (10.5)	
Comorbid conditions, n (%)			
Obese	111 (23.92)	44 (24.31)	0.92
Heart disease	231 (49.78)	87 (48.07)	0.69
Hypertension (>140/90 mmHg)	297 (64.01)	124 (68.15)	0.28
Hyperglycemia (>5.6 mmol/L)	185 (41.11)	66 (37.93)	0.47
Dyslipidemia	225 (48.49)	88 (48.62)	0.99
Characteristic of the treatment, n (%)			
Size of infarction (≥2 cm^2)	182 (57.23)	78 (62.40)	0.32
Onset of stroke (>24 h)	251 (54.09)	80 (44.44)	0.03

signed-rank test was used to test the difference in the movement items of the ESS between the study groups. The interactions between factors were analyzed by using a two-way ANOVA.

The multivariate logistic regression of ESS and ADL changes were conducted among study groups after adjusted.

Data availability

The data from this study for data validation and academic corporation are now made publicly available through direct request from study principal investigators (Q.D. at dong_qiang@fudan.edu.cn).

Results

A total of 114 diabetes patients were included in the trials, with 83 in the HUK-treated group and 31 in the placebo group. Patients' demographic and baseline characteristics are summarized in (Table 1).

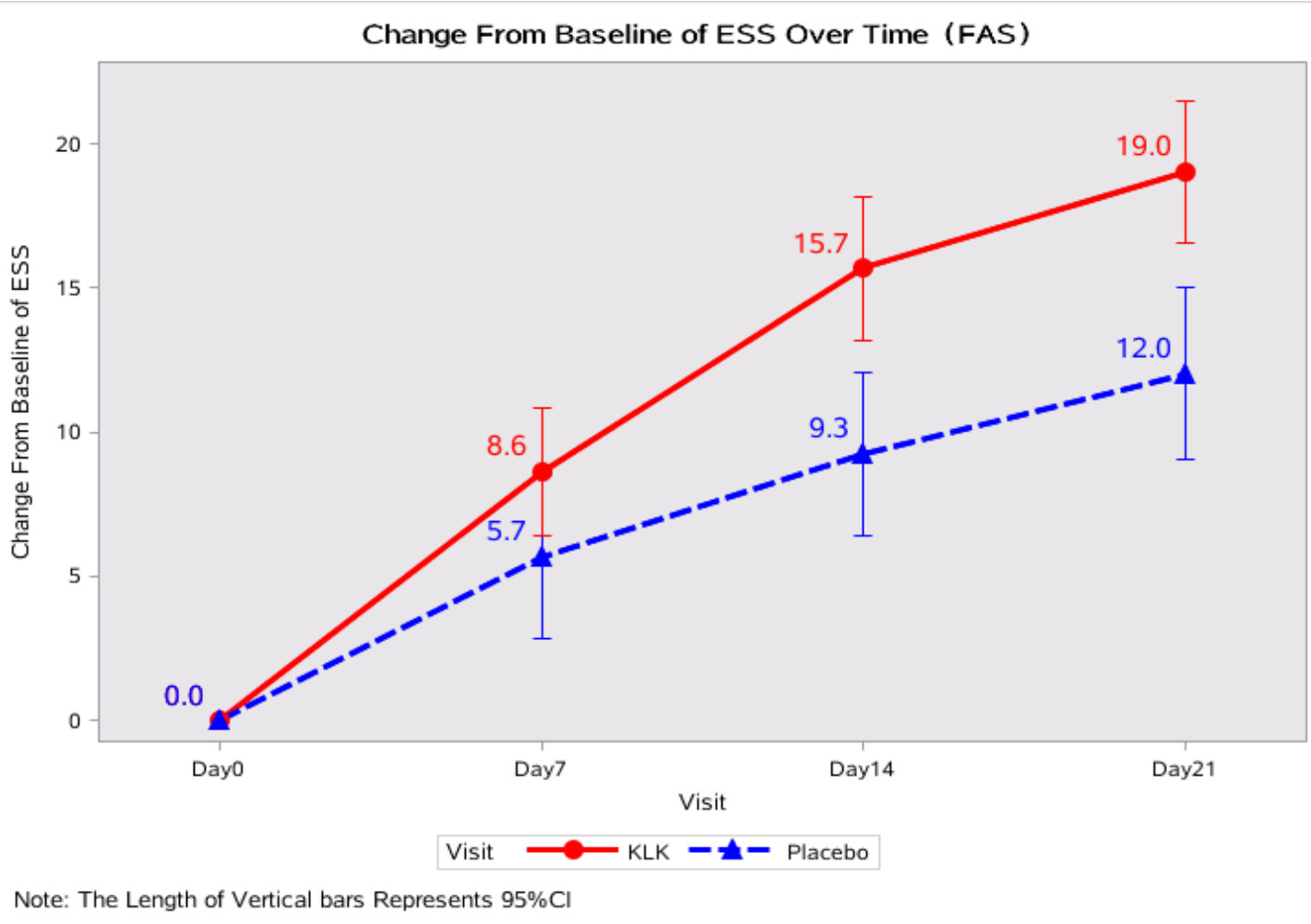
Functional outcome as assessed with the ADL scale is summarized in (Table 2). The vast majority of patients scored less than 85 on the ADL scale at the beginning of the trial, indicating that most of these patients were moderately to severely impaired and were dependent on a caregiver for their ADLs. Severity of stroke were measured by ESS (Figure 1). At baseline, the ESS score was 61.42±11.80 for the HUK-treated group and 59.64±13.10 for the placebo group. Treatment with HUK was associated with a significantly greater increase in ESS score compared with the placebo-treated group: on treatment day-21, patients in the HUK-treated group scored 80.28±24, significantly higher than the placebo group (scored as 70.29±16.64, p = 0.0019).

Logistic regression analysis of the data for diabetic sub-group of patients showed that HUK was associated with greater improvements in functional and physiological outcomes. We also found that patients with diabetes were more likely to have greater improvement compared to non-diabetes patients (Figure 2).

Table 2. Changes in ESS and ADL scores during the study period.

	Baseline	Increase from baseline	Increase from baseline	Increase from baseline
ESS score (mean ± se)		day-7	day-14	day-21
HUK (N = 464)	61.77 ± 11.64	8.72 ± 11.09	15.76 ± 12.43	19.62 ± 13.57
Placebo (N = 181)	59. 50 ± 12.76	6.46 ± 10.98	12.72 ± 12.68	16.69 ± 12.46
p	0.03	0.021	0.0074	0.0118
ADL Score (mean ± se)				
HUK (N = 464)	47.61 ± 18.60	12.58 ± 16.63	24.35 ± 20.59	30.73 ± 22.06
Placebo (N = 181)	44.23 ± 19.49	7.68 ± 15.71	17.30 ± 19.38	24.24 ± 21.06
p	0.04	0.0007	0.0001	0.0006

Figure 1: Comparison ESS changes between diabetic patients and non-diabetic patients.



Adverse event occurred in 2.69% of patients in the HUK-treated group and 0.54% in the placebo group.SAE occurred in 0.41% of patients in the HUK-treated group and 0.30% in the placebo group.

Discussion

In acute stroke patients with diabetes, we found that treatment with HUK was associated with significantly improved short-term outcomes. The HUK-treated diabetic patients scored 7.71 higher on the ESS score than the placebo group, whereas in non-diabetic patients, whole HUK-treated patients scored only 2.61 higher than the placebo group. Furthermore, HUK-treated diabetic patients scored 9.91 higher on the ADL scale than the placebo group; in contrast, HUK-treated non-diabetic patients scored 6.19 higher than the placebo group. These results indicated that HUK offers more clinical benefits for diabetic patients. The HUK-related AEs were few, and none were noted to occur in more than 1% of the study population. The present analyses confirmed the clinical benefits observed in ischemic stroke patients from previous clinical trials [12-15], and indicated that intravenous HUK significantly improved short-term functional outcomes in the diabetic subgroup of patients. Furthermore, HUK-treated diabetic patients showed greater improvements in functional and physiological outcomes than non-diabetic patients. It is also worth noting that the majority of patients included in the study had stroke onset for more than 24 hours. Therefore, HUK is a potential treatment in acute ischemic stroke patients with comorbid diabetes.

The main limitation of the study was that the sample size was small. In addition, the follow-up period was relatively short. As a result, we were not able to assess whether HUK could prevent a recurrent strokes, which are common among patients with diabetes. Further studies are needed in this group of patients.

Overall, diabetes is associated with worse outcome in ischemic stroke patients. Whether a tight glucose control protocol could improve outcomes in stroke patients with diabetes who also received tPA therapy has been explored [16]. The present study found that the treatment with HUK was associated with improved neuro physiological and functional outcomes, and the occurrence of adverse events in this subgroup of patients was limited. However, HUK as an optimal treatment for stroke patients, should be further explored, especially in patients with diabetes.

References

1. Liu, L., Wang, D., Wong, KSL., Wang, Y. (2011) Stroke and Stroke Care in China. Huge Burden, Significant Workload, and a National Priority. Stroke, 42(12): 3651-3654.
2. Bragg, F., Holmes, MV., Iona, A., Guo, Y., Du, H., Chen, Y., et al. (2017) Association Between Diabetes and Cause-Specific Mortality in Rural and Urban Areas of China. Jama, 317(3): 280-289.
3. Al-Rubeaan, K., Al-Hussain, F., Youssef, AM., Subhani ,SN., Al-Sharqawi, AH., Ibrahim, HM. (2016) Ischemic Stroke and Its Risk Factors in a Registry-Based Large Cross-Sectional Diabetic Cohort in a Country Facing a Diabetes Epidemic. J Diabetes Res, 2016:4132589.
4. Palacio, S., McClure, LA., Benavente. OR., Bazan, C 3rd., Pergola, P., Hart, RG. (2014) Lacunar strokes in patients with diabetes mellitus: risk factors, infarct location, and prognosis: the secondary prevention of small subcortical strokes study. Stroke, 45(9): 2689-2694.
5. Zhang, Q., Ding, H., Yan, J., Wang, W., Ma, A., Zhu, Z., et al. (2011) Plasma tissue kallikrein level is negatively associated with incident and recurrent stroke: a multicenter case-control study in China. Anna neurol, 70(2): 265-273.
6. Han, L., Li, J., Chen, Y., Zhang, M., Qian, L., Chen, Y., et al. (2015) Human Urinary Kallidinogenase Promotes Angiogenesis and Cerebral Perfusion in Experimental Stroke. PloS one, 10(7): e0134543.
7. Xia, CF., Yin, H., Yao, YY., Borlongan, CV., Chao, L., Chao, J. (2006) Kallikrein protects against ischemic stroke by inhibiting apoptosis and inflammation and promoting angiogenesis and neurogenesis. Hum Gene Ther, 17(2): 206-219.
8. Chen, ZB., Huang, DQ., Niu, FN., Zhang, X., Li, EG., Xu, Y. (2010) Human urinary kallidinogenase suppresses cerebral inflammation in experimental stroke and downregulates nuclear factor-kappaB. J Cereb Blood Flow Metab, 30(7): 1356-1365.
9. Miao, J., Deng, F., Zhang, Y., Xie, HY., Feng, JC. (2016) Exogenous human urinary kallidinogenase increases cerebral blood flow in patients with acute stroke. Neurosciences (Riyadh). 21(2): 126-130.
10. Liu, W., Yang, Y., Liu, Y., Lu, X., Guo, S., Wu, M., et al. (2016) Exogenous kallikrein protects against diabetic nephropa-

thy. Kidney int, 90(5): 1023-1036.

11. Shi, R., Yuan, K., Hu, B., Sang, H., Zhou, L., Xie, Y., et al. (2016) Tissue Kallikrein Alleviates Cerebral Ischemia-Reperfusion Injury by Activating the B2R-ERK1/2-CREB-Bcl-2 Signaling Pathway in Diabetic Rats. Oxid Med Cell Longev.
12. Li, J., Chen, Y., Zhang, X., Zhang, B., Zhang, M., Xu, Y. (2015) Human Urinary Kallidinogenase Improves Outcome of Stroke Patients by Shortening Mean Transit Time of Perfusion Magnetic Resonance Imaging. J Stroke Cerebrovasc Dis, 24(8): 1730-1737.
13. Wang, YD., Lu, RY, Huang, XX., Yuan, F., Hu, T., Peng, Y., et al. (2011) Human tissue kallikrein promoted activation of the ipsilesional sensorimotor cortex after acute cerebral infarction. Eur Neurol, 65(4): 208-214.
14. Wang ,YX., Chen, Y., Zhang, CH., Li, CH., Dong, Z., Zhao, SN., et al. (2015) Study on the effect of urinary kallidinogenase after thrombolytic treatment for acute cerebral infarction. Eur Rev Med Pharmacol Sci, 19(6): 1009-1012.
15. Zhang, C., Tao, W., Liu, M., Wang, D. (2012) Efficacy and safety of human urinary kallidinogenase injection for acute ischemic stroke: a systematic review. J Evid Based Med, 5(1):31-39.
16. Bruno, A., Kent, TA., Coull, BM., Shankar, RR., Saha, C., Becker, KJ., et al. (2008) Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. Strok, 9(2): 384-389.

Supplemental Material

Supplemental 1: Inclusion And Exclusion Criteria

Inclusion Criteria Were As Follows:

1) Age Between 17 And 75 Years;

2) Onset of Ischemic Stroke Within 48 Hours;

3) Scored Greater Than 6 On The Consciousness Parameter And A Total From 40 To 80 On The European Stroke Scale (ESS).

Patients Were Excluded From The Study If They Met Any Of The Following Conditions:

1) Intracranial Hemorrhage As Assessed On A Computerized Tomography (CT) Scan;

2) Embolism Of Cardiac Origin;

3) Progressive Cerebral Infarction;

4) Posterior Circulation Infarction;

5) Having A History Of Cerebral Disease, Such As Intracranial Hemorrhage, Brain Tumor, Brain Trauma Or Ischemic Stroke;

6) Any Known Hereditary Or Acquired Hemorrhagic Diathesis;

7) Comorbid Pneumonia Or Systemic Infection;

8) Having Insufficient Cardiac Function,

9) Having Chronic Liver Or Kidney Disease (Increased Alanine Aminotransferase Or Serum Creatinine Level >1.5 Fold Of Normal Value);

10) Having Other Serious Systemic Or Visceral Diseases;

11) Having Serious Psychological Disorders, Including Intellectual Disability;

12) Blood Pressure ≤90/60 Mmhg Or ≥200/110mmhg During Treatment;

13) Pregnant Or Other Conditions.