

ORIGINAL RESEARCH

Effect of HUK on the outcome of ruptured intracranial aneurysm

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Fujian Key Research Project 2010D025

Abstract**Objective:** To evaluate the clinical efficacy of Human Urinary Kallidinogenase (HUK) on the outcome of patients with ruptured intracranial aneurysm.**Methods:** This was a prospective, open-label study. At the Department of Neurosurgery in our hospital, 127 patients were treated and operated due to ruptured intracranial aneurysm in the period 2015–2016. After surgery, all the patients received basic treatment and 70 patients received additional HUK treatment (HUK group) according to their willing. In detail, 0.15 PNA unit of HUK injection plus 100 ml saline in intravenous infusion was performed, with once a day for 14 consecutive days. The modified Rankin Scale (mRS) scores and favorable mRS rates (mRS 0–1) were analyzed 3-month after the treatment.**Results:** No difference was shown in the basic characteristics between the two groups ($p > 0.05$). Favorable mRS rate in the HUK group (71.43%) was significantly higher than that in control group (50.88%, $p < 0.05$). In addition, 3-month death rate was significantly lower in the HUK group. Delayed ischemic stroke rate was similar between the two groups.**Conclusion:** HUK can reduce morbidity and mortality of patients with ruptured intracranial aneurysm after surgery.**KEYWORDS**

aneurysm, Human Urinary Kallidinogenase, neuroprotection, Neurosurgery

1 | INTRODUCTION

Intracranial aneurysm is still a challenging health problem. Of all cerebrovascular accidents, it ranks the third, just behind ischemic stroke and hypertensive intracerebral hemorrhage. The incidence varies widely among populations; with an overall incidence about 9–20 per 100,000 (Steiner et al., 2013). 30-day mortality rate with conservative treatment is over 40% (Korja et al., 2013). About one-third of patients left with an untreated aneurysm will die from recurrent bleeding within 6 months after recovering from the first

bleeding (Lantigua et al., 2015; Pakarinen, 1967; Phillips, Whisnant, O'Fallon, & Sundt, 1980). Vasospasm, hydrocephalus, delayed ischemic deficit and other complications occur in a short or long time after intracranial aneurysm rupture will make the prognosis worse.

Human Urinary Kallidinogenase (HUK) is a glycoprotein extracted from urine of healthy men and has been widely used in the acute ischemic stroke. Numerous clinical trials have proved its efficacy (Zhang, Tao, Liu, & Wang, 2012) and have revealed that it can selectively dilate arterioles in the ischemic area, enhance angiogenesis and neurogenesis, increase regional cerebral blood flow, inhibit apoptosis and inflammation, promote glial cell migration, and improve neurological deficits after acute ischemic stroke (Ling

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et al., 2008; Lu, Shen, Yang, & Peng, 2008; Nagano, Suzuki, Hayashi, & Asano, 1992; Stone et al., 2009; Xia et al., 2006). Although HUK involves in many physiological and pathological functions, whether it can improve the prognosis of patients with ruptured intracranial aneurysm has not been studied yet. So we present our experience with HUK on ruptured intracranial aneurysm in this study.

2 | METHODS

2.1 | Patients

This study protocol was approved by the institutional review board of our hospital. All patients signed informed consent before treatment. Inclusion criteria were radiological confirmed aneurysmal by nonenhanced CT scan, CT angiography and catheter angiography, age 18–65 years. Exclusion criteria were patients with known hepatic impairment, pregnancy, taking warfarin-type drugs or suspected additional life-threatening disease. There were 137 patients enrolled in our study at the Department of Neurosurgery in our hospital. Age, male gender, preoperative SBP, preoperative DBP, history of subarachnoid hemorrhage, hypertension and diabetes mellitus, ruptured condition, intracranial hemorrhage, and cerebral infarct were collected and compared. Among them, 127 ruptured patients were treated and operated due to ruptured intracranial aneurysm in the period 2015–2016. The diagnosis was performed by nonenhanced CT scan, CT angiography and catheter angiography and the information of aneurysm variables also collected. After specific therapeutic interventions (clipping or coiling), according to their willing of treatment, the patients were divided into two groups: the HUK group with 70 cases and the control group with 57 cases.

2.2 | Therapeutic methods

Patients in the HUK group received basic treatment plus HUK injection treatment, patients in the control group received basic treatment only. Basic treatment was performed according to disease condition, with dehydrating agents, blood pressure, blood glucose and temperature controlling agents, thromboprophylaxis, and antiepileptic treatment. On that basis, 0.15 PNA unit of HUK injection (Trade name: Kailikang, Guangdong Techpool Bio-Pharma Co., Ltd. With approved medicine of H20052065) plus 100 mL saline in intravenous infusion was conducted in the HUK group, with once a day for 14 consecutive days. In the HUK group, during 24 hr before medication and in the treatment period, angiotensin converting enzyme inhibitor and steroid drugs were forbidden.

2.3 | Study design

This was a single-center, prospective, open-label study. Patients' baseline characteristics were obtained from our database system, and patients were divided into two groups according to the treatment they decided to receive: 70 cases in the HUK group and 57

cases in the control group. Baseline characteristics included gender, age, comorbidities, size of ruptured aneurysm, aneurysm location, Hunt-Hess scale score on admission and surgical methods. mRS scores and mortality rates at 3 months were obtained by telephone follow-up. Patients' baseline characteristics, favorable mRS score rate (mRS score 0–1), and 3-month mortality rate were also compared.

2.4 | Statistical analysis

Categorical variables were reported as number or percentage; continuous variables fitting the normal distribution were expressed as mean \pm standard deviation (SD), whereas median (1st to 3rd quartile, interquartile ratio) was used for nonfitting variables. Patients' baseline characteristics were compared by the Chi-squared test or Fisher's exact test as appropriate for categorical variables, and Student's *t* test for continuous variables. *p* values were two-tailed and considered statistically significant if less than 0.05. Data analyses were performed using IBM SPSS RRID:SCR_002865 Statistics v.19 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics of all the patients

We finally included 79 patients in HUK group and 58 patients in control group. There were 28 males and 51 females in the HUK group, with an average age at 53.97 ± 10.35 years old. The mean value of preoperative SBP is 142.81 ± 24.25 , and preoperative DBP is 88.18 ± 14.56 . Among them, 30 cases (37.97%) had hypertension, one case had previous subarachnoid hemorrhage and one case had diabetes mellitus. 70 patients had ruptured aneurysm, two cases had cerebral infarct. The mean maximum size of aneurysm was 5.73 ± 2.78 mm. In the control group, there were 28 males and 30 females with an average age at 52.32 ± 10.49 years old. 30 (51.72%) cases with hypertension, two cases had previous subarachnoid hemorrhage and one case had diabetes mellitus and mean maximum size of aneurysm was 5.24 ± 2.37 mm. The mean value of preoperative SBP is 143.17 ± 20.88 , and preoperative DBP is 87.78 ± 14.11 . 57 patients had ruptured aneurysm, two cases had cerebral infarct. We found no significant differences in age ($p = 0.361$), gender ($p = 0.131$), hypertension ($p = 0.109$), SAH history ($p = 0.574$), mean maximum size of aneurysm ($p = 0.318$). All the baseline clinical and demographic characteristics of participants were presented in Table 1. Aneurysm variables in ruptured participants and Hunt-Hess scale score on admission were presented in Table 2 and Table 3.

3.2 | Outcomes and safety of HUK

In this study, 50 patients in the HUK group (71.43%) and 29 patients in the control group (50.88%) got favorable mRS score (mRS score 0–1), patients in HUK group had a higher ratio of good outcomes ($p = 0.018$). Four patients (7.02%) died within 3 month in the control

TABLE 1 Baseline clinical and demographic characteristics of participants

	HUK group (n = 79)	Control group (n = 58)	p Value
Age	53.97 ± 10.35	52.32 ± 10.49	0.361
Male Gender	28 (35.44%)	28 (48.28%)	0.131
Preoperative SBP	142.81 ± 24.25	143.17 ± 20.88	0.930
Preoperative DBP	88.18 ± 14.56	87.78 ± 14.11	0.875
History of SAH	1 (1.27%)	2 (3.45%)	0.574
History of HBP	30 (37.97%)	30 (51.72%)	0.109
History of DM	1 (1.27%)	1 (1.72%)	1.000
Ruptured case	70 (88.61%)	57 (98.28%)	0.044
Maximum size of aneurysm (mm, $\bar{x} \pm s$)	5.73 ± 2.78	5.24 ± 2.37	0.318
Cerebral infarct	2 (2.52%)	2 (3.45%)	1.000

TABLE 2 Aneurysm variables in ruptured participants

	HUK group (n = 70)	Control group (n = 57)
Location of aneurysm		
Anterior communicating	16 (22.86%)	16 (28.07%)
Posterior communicating	15 (21.43%)	11 (19.30%)
Ophthalmic	6 (8.57%)	1 (1.75%)
Vertebral basilar system	5 (7.14%)	3 (5.26%)
MCA	9 (12.86%)	10 (17.54%)
Internal carotid	6 (8.57%)	4 (7.03%)
ACA	3 (4.29%)	3 (5.26%)
AChA	2 (2.86%)	0 (<1%)
Multiple aneurysms	8 (11.42%)	9 (15.79%)
Coiling of aneurysm [Case(%)]	65 (92.86%)	50 (87.72%)
Clipping of aneurysm [Case(%)]	5 (7.14%)	7 (12.28%)

TABLE 3 Hunt-Hess scale score on admission

	HUK group (n = 70)	Control group (n = 57)
0 [Case(%)]	0 (0%)	0 (0%)
1 [Case(%)]	4 (5.71%)	3 (5.26%)
2 [Case(%)]	46 (65.71%)	32 (56.14%)
3 [Case(%)]	15 (21.43%)	9 (15.80%)
4 [Case(%)]	3 (4.29%)	10 (17.54%)
5 [Case(%)]	2 (2.86%)	3 (5.26%)

group while no patient died in the HUK group, the mortality of HUK group was significantly lower than that of control group ($p < 0.0001$). However, no statistically significant difference was found between the two groups in delayed ischemic stroke, with one patient in the HUK group (1.43%) and two patients in the control group (3.51%)

respectively (Table 4, $p > 0.05$). In addition, no adverse effect was reported in the HUK group.

4 | DISCUSSION

Between 1973 and 2002, ruptured aneurysm related SAH fatality rate decreased by approximately 17% (Nieuwkamp et al., 2009), and the possibility to recover an independent state has increased by 1.5% per year (Hop, Rinkel, Algra, & van Gijn, 1997). However, although surgical and medical treatments have improved, rupture of an aneurysm is still associated with high rates of case fatality (roughly one-third) and of severe disability (one-sixth) (Hop et al., 1997; Inagawa, 2001). Many factors associated with case fatality and functional outcome after aneurysm rupture, including the severity of the initial bleeding (Hop et al., 1997; Juvela, 2003), age (Kassell et al., 1990; Koffijberg, Buskens, Granath, Truskowski, & Alves, 2008; Lanzino et al., 1993), aneurysm site (Kassell et al., 1990) and size (Juvela, 2003; Kassell et al., 1990), history of hypertension (Juvela, 2003; Kassell et al., 1990), cigarette smoking (Weir et al., 1998), and heavy alcohol consumption (Juvela, 1992). Furthermore, disease-associated events (e.g., rebleeding, delayed cerebral ischemia, hydrocephalus), treatment-associated factors [surgical (clipping) or endovascular (coiling) complications] and complications associated with prolonged bed rest would all affect patients' prognosis.

As a state category I new drug approved by China's State Food and Drug Administration (CFDA), HUK has been widely used for acute ischemic stroke treatment in China with 87% efficacy rate (Emanuela & Madeddu, 2003). Clinical researches showed that HUK could improve patients' neurological deficits effectively and safely after acute ischemic stroke (Ding et al., 2007). HUK involves in many physiological and pathological functions, however, whether it can improve the prognosis of patients with ruptured intracranial aneurysm has not been studied. Our study found that HUK promoted good recovery in ruptured intracranial aneurysm, suggesting that HUK had the potential of regulating inflammation, coagulation and vasospasm in these patients.

TABLE 4 Main outcomes of ruptured participants

	HUK group (n = 70)	Control group (n = 57)	p value
Favorable mRS, 0-1 [Case(%)]	50 (71.43%)	29 (50.88%)	0.018
Delayed ischemic stroke [Case(%)]	1 (1.43%)	2 (3.51%)	0.582
Death [Case(%)]	0 (0%)	4 (7.02%)	<0.0001

Aneurysm rupture itself can cause stress hyperglycemia and increased blood coagulability, set a condition for delayed ischemic stroke and thromboembolic complications, and lead to poor outcomes (Dorhout Mees, van Dijk, Algra, Kempink, & Rinkel, 2003; Juvela & Siironen, 2006; Juvela, Siironen, & Kuhmonen, 2005; Lanzino et al., 1993). Hyperglycemia results in an increase in nuclear factor κ B (NF- κ B) binding, which leads to increased production of inflammatory cytokines and chemokines, such as tumor necrosis factor (TNF) and monocyte chemoattractant protein (MCP-1) (Dhindsa et al., 2004). Zhao and his colleagues (Zhao et al., 2003) found that a continuous supply of kallikrein (kinin in vivo) can suppress oxidative stress, thus protecting the cardiovascular, renal and central nervous systems against hypertension and associated type 2 diabetes. On the other hand, using of thromboprophylaxis in ruptured intracranial aneurysm is challenging because of the risk of rebleeding. The kallikrein-kinin system not only takes part in coagulation, it also promotes fibrinolysis (Moreau et al., 2005). Thus, conduction of HUK may regulate coagulation and fibrinolysis after intracranial aneurysm rupture.

Vasospasm occurs in 10%–15% of the patients with subarachnoid hemorrhage and is related to the bad outcome (Findlay, Nisar, & Darsaut, 2015; Inagawa, 2016). On angiography, it represents as a narrowing of the arterial blood vessel and it causes delayed ischemic deficit. HUK can activate kallikrein-kinin system (Sahan et al., 2013), transfer kininogen hydrolysis into kinin and kallidin, release NO and relax vascular smooth muscle (Ariturk et al., 2012; Perilli et al., 2012). Although did not reach a statistical difference, our study showed an extremely low rate of delayed ischemic stroke in aneurysm rupture patients (1.43%) 3-month after surgery, indicating the possible mechanism of the good clinical efficacy of HUK.

No side effect of hypotension, the most common adverse event of HUK, was reported in the HUK group, which proved the safety of HUK in the application of aneurysm rupture patients.

HUK could reduce morbidity and mortality of patients with ruptured intracranial aneurysm. Inflammation and coagulation regulation, glucose metabolism improvement and selective arterioles dilation might be it potential mechanism.

5 | CONCLUSION

HUK successfully reduce 3-month morbidity and mortality of patients with ruptured intracranial aneurysm.

CONFLICT OF INTEREST

There is no conflict of interest in this research.

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How to cite this article: Chen L, Lyu Y, Lin X, Sun M, Feng W, Tian X. Effect of HUK on the outcome of ruptured intracranial aneurysm. *Brain Behav.* 2018;8:e01060. <https://doi.org/10.1002/brb3.1060>