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Original Article

Clinical efficacy and safety of urinary kallindinogenase combined with butylphthalide in the treatment of progressive cerebral infarction

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Abstract: Objective: To determine the clinical efficacy and safety of urinary Kallindinogenase (HUK) combined with butylphthalide (NBP) in the treatment of progressive cerebral infarction (PCI), to provide more choices for the clinical treatment of PCI. Methods: The clinical data of 94 with PCI admitted to our hospital from July 2015 to March 2017 were retrospectively analyzed in this study. In addition to basic treatment, the control group (n = 52) was treated with NBP and edaravone. The research group (n = 42) was treated with NBP and HUK. After 14 days of treatment, the clinical efficacy on the two groups was evaluated according to their neurological function deficit using the National Institutes of Health Stroke Scale (NIHSS). The functional recovery results after the stroke were measured using the Modified Rankin Scale (MRS). The independence rate of the two groups was compared. The activities of daily living (ADL) scale was adopted to evaluate the patients' life quality. The two groups were compared in the incidence of complications during treatment and the recurrence within 12 months. Results: The two groups of patients were not greatly different in basic data. After 14 days of treatment, the improvements in NIHSS, MRS, and ADL scores in the research group were more obvious than those in the control group. After 12 months of treatment, the research group showed a significantly higher independence rate than the control group. No serious adverse reactions were found in the two groups. There was no death during the treatment. After 12 months of treatment, the two groups were not greatly different in recurrence rate. Conclusion: HUK combined with NBP can reduce the neurological dysfunction and disability rate of patients and improve their independence rate and life quality. It is a safe and effective method for the treatment of PCI.

Keywords: Urinary kallindinogenase, butylphthalide, progressive cerebral infarction, clinical efficacy, safety

Introduction

As the population continues to age, the incidence of cerebral infarction is gradually increasing, and the sequelae gravely disrupts both the individuals and families [1]. Statistics show that strokes account for 9.5% of the annual global death toll [2]. Ischemic stroke is still a main cause of human death worldwide. In the United States and China, about 800,000 and 2 million people suffer from stroke each year, respectively [3]. Progressive cerebral infarction (PCI) is a brain disease triggered by insufficient blood supply, which can cause a rise to cerebral ischemia, necrosis, and hypoxia, and eventually lead to neurological deficit [4]. Patients with PCI account for 26%-43% of patients with cerebral infarction. PCI has a high disability rate and mortality rate, and 50%-70% of PCI survivors may suffer paralysis, aphasia, and dementia [5, 6]. PCI is far more dangerous than non-PCI, with a significantly higher long-term disability rate and an even worse progression than non-PCI [7].

The treatment of cerebral infarction is rapidly developing and continuously improving. Examples include vascular stent implantation, neuroradiology, and early rehabilitation. There is no ideal strategy to effectively prevent the progression of the disease [8]. In China, urinary kallidinogenase (HUK) and butylphthalide (NBP), the new first-class national drugs, are recommended in the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke* for improving cerebral blood circulation

of patients with stage 5 acute ischemic stroke (AIS) [9]. The two have been verified to be able to effectively promote cerebral perfusion and angiogenesis in ischemic areas after stroke [10, 11]. HUK combined with NBP are usually adopted for clinical treatment of some patients with AIS. One study by Qian et al. [12] has reported the effects of HUK combined with NBP that such combination can more effectively improve the long-term independence rate of patients with AIS than edaravone combined with NBP. Studies on HUK combined with NBP for patients with PCI are rare. This study analyzed the clinical efficacy and safety of HUK+NBP in the treatment of PCI, aiming at providing more choices for the clinical treatment of PCI.

Materials and methods

Research objects and treatment methods

The clinical data of 94 patients with PCI admitted to our hospital from July 2015 to March 2017 were retrospectively analyzed in this study. They were divided into two groups according to different treatment methods. All the patients were provided with basic treatment according to the 2013 AHA/ASA guidelines for early ASI [13], including antithrombotic therapy, control of blood pressure (BP) and blood glucose, statins, and dehydrating agents. The control group (con group, n = 52) was treated with both NBP and edaravone. The research group (res group, n = 42) was treated with both NBP and HUK. NBP was administered orally at 200 mg/time, 4 times a day, and edaravone was delivered through intravenous infusion at 30 mg/time, twice a day. HUK was delivered through intravenous infusion at 0.15 PNA unit each time, once a day. Each patient was treated continuously for 14 days. Butylphthalide soft capsule (State Food and Drug Administration (SFDA) approval number: H20050299) was purchased from CSPC NBP Pharmaceutical Co., Ltd., edaravone sodium chloride injection (SFDA approval number: H20193434) from Jiangsu CTFH Pharmaceutical Co., Ltd., and HUK for injection (SFDA approval number: H20052065) from Guangdong Techpool Bio-Pharma Co., Ltd. In conformity with the declaration of Helsinki, this study was carried out with informed consent forms signed by all enrolled patients and permission from the Medical Ethics Committee of our hospital, with ethical approval number of 2020 (ethnic) 081 (review).

Inclusion criteria

1. Patients who were over 18 years old; 2. Patients who met *2014 Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke* [14]; 3. Thrombolytic patients whose involved time was within the thrombolytic time window, and non-thrombolytic ones whose involved time was within one week; 4. Patients who suffered no severe consciousness disorder and were able to cooperate with the physical examination; 5. Patients with normal swallowing function.

Exclusion criteria

1. Patients with cerebral hemorrhage or massive cerebral infarction as indicated by brain CT and magnetic resonance imaging (MRI); 2. Patients with an estimated survival time less than 3 months; 3. Pregnant or lactating women; 4. Patients with serious metabolic diseases; 5. Patients with a history of coagulation disorder, hemorrhage, neutropenia, or thrombocytopenia; 6. Patients with severe liver, kidney, or lung dysfunction; 7. Patients with a National Institutes of Health Stroke Scale (NIHSS) score less than 4 points.

Outcome measures

Primary outcome measures: The neurological deficits of patients after 14 days of treatment were evaluated using the NIHSS [15]. A decrease in NIHSS score by 91-100% indicated a cure state; a decrease in NIHSS score by 46-91% and a decrease in disability degree by 1-3 levels indicated remarkably effective treatment; a decrease in NIHSS score by 18-45% indicated effective treatment; a decrease or increase in NIHSS score by 17% indicated ineffective treatment; and an increase in NIHSS score by 18% indicated a worsened condition. Death is the most serious outcome during treatment. The modified Rankin Scale (MRS) was adopted to evaluate the functional recovery after stroke. The independent rate of the two groups after 12 months of treatment was compared. MRS score ≤1 was defined as independence.

Secondary outcome measures: The activities of daily living (ADL) scale was adopted to evalu-

Table 1. Baseline characteristics

	The control group (n = 52)	The research group (n = 42)	χ^2/t	P
Gender			0.032	0.858
Male	30 (57.69%)	25 (59.52%)		
Female	22 (42.31%)	17 (40.48%)		
Age	63.77±13.36	62.34±12.58	0.530	0.560
Smoking history			1.123	0.289
Yes	28 (53.85%)	18 (42.86%)		
No	24 (46.15%)	24 (57.14%)		
Hypertension			0.592	0.442
Yes	40 (76.92%)	35 (83.33%)		
No	12 (23.08%)	7 (16.67%)		
Diabetes mellitus			0.667	0.414
Yes	19 (36.54%)	12 (28.57%)		
No	33 (63.46%)	30 (71.43%)		
Progression time (h)	29.58±18.46	27.43±16.84	0.584	0.561
LDL (mmol/L)	2.48±0.87	2.66±0.94	0.962	0.339
FBG (mmol/L)	5.77±2.24	6.69±3.21	1.633	0.106
GHb (%)	6.04±1.25	6.53±2.16	1.376	0.172
NIHSS	17.65±3.27	16.73±4.24	1.188	0.238

Note: The counting data were analyzed using the chi-square test, and the comparison of measurement data among groups was carried out using the independent-samples T test.

ate patients' quality of life. The complications during treatment and recurrence within 12 months were compared between the two groups.

Statistical analyses

SPSS19.0 was used for statistical analyses. Data in normal distribution was expressed as mean ± sd. Comparison of counting data (%) was conducted by the χ^2 test. The inter-group comparison of enumeration data was conducted by the t test. The paired t test was used to compare the data within groups. A $P < 0.05$ indicated a remarkable difference.

Results

Baseline characteristics

The con group consisted of 52 patients with a mean age of (63.77±13.36) years old, including 30 males and 22 females. The res group consisted of 42 patients with a mean age of (62.34±12.58) years old, including 25 males and 17 females. The two groups were not greatly different in gender, age, smoking history, hypertension, diabetes mellitus, progression time, and NIHSS score (all P>0.05, **Table 1**).

Clinical efficacy analysis

No patient died during the treatment. Compared with the con group, the res group showed a significantly higher cure rate and effective rate (both $P < 0.05$, **Table 2**).

NIHSS score

Before treatment, there was no notable difference between the two groups in NIHSS score (P>0.05). After 14 days of treatment, the res group had significantly lower NIHSS scores than the con group ($P < 0.05$, **Figure 1**).

MRS

After 14 days of therapy, the res group had significantly lower MRS scores than the con group ($P < 0.05$). After 12 months of therapy, the independence rate in the res group was significantly higher than that in the con group (78.57% *vs.* 46.15%, $P < 0.05$) (**Figure 2**).

ADL

Before treatment, there was no significant difference between the two groups in ADL score (P>0.05). After 14 days of treatment, the res group had significantly higher ADL scores than the con group ($P < 0.05$, **Figure 3**).

Adverse reactions and recurrence

There was no obvious adverse reaction in either group. In the con group, one patient showed BP decrease from 150/95 mmHg to 105/72 mmHg during the infusion of HUK. The patient's BP recovered to 126/80 mmHg after slow-down of the infusion speed, and the patient had no obvious discomfort. After one month of treatment, five patients in the con group had recurrent strokes. In the res group, one patient showed an increase in alanine aminotransferase (ALT), which reached 77 U/L on the 10th day of treatment. After corresponding treatment, the liver function of the patient returned to normal on the 14th day. After 12

Table 2. Clinical efficacy on the two groups after 14 days of treatment

	The control group (n = 52)	The research group (n = 42)	χ^2	P
Basically cured patients	26	31		
Patients with remarkably effective treatment	11	6		
Patients with effective treatment	5	3		
Patients with ineffective treatment	6	1		
Deterioration	4	1		
Death	0	0		
Cure rate	50.00%	73.81%	5.518	0.019
Effective rate	80.77%	95.24%	4.368	0.037

Note: The Chi-square test was used for analysis of counting data.

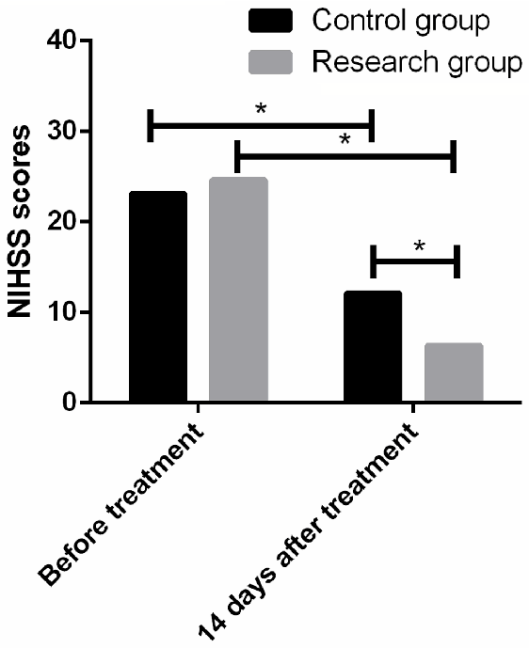

Figure 1. Changes in NIHSS scores of the two groups before and after treatment. Note: The independent-samples T test was adopted for inter-group comparison of measurement data, and the paired t test was adopted for intra-group comparison. *, $P < 0.05$.

months of treatment, 2 patients in the res group had recurrent strokes. The incidence of adverse reactions and recurrence rates of the two groups were not greatly different (P>0.05, **Table 3**).

Discussion

With a complex etiology, PCI has a high disability rate and mortality rate. Its etiology is still under investigation. Many scholars believe the etiology is correlated with pathophysiological phenomena such as thrombosis and collateral vascular compression [16, 17]. NBP has been widely used in patients with AIS in China since it has been approved by the State Food and Drug Administration in 2002. Multi-center and open label clinical studies in China have verified its effectiveness and safety [18]. HUK, a randomized controlled trial, included 24 trials involving 2433 patients. The trials had systematically confirmed that HUK injection can alleviate the neurological damage after acute ischemic stroke and improve the long-run prognosis [19].

In our study, the two groups were not greatly different in basic data, which indicated that there was no obvious selection or design deviation in this study. After 14 days of treatment, the improvements of NIHSS, MRS, and ADL scores in the res group were more significant than those in the con group. This indicated that NBP combined with HUK can effectively contribute to ameliorated neurological dysfunction and disability rate of patients with PCI and can improve their quality of life. The main functions of NBP are as follows: to keep platelet aggregation, to reduce oxidative damage triggered by ischemia, to improve microcirculation, to alleviate mitochondrial dysfunction, and to rebuild damaged neuron network [20, 21]. Edaravone was first authorized by the Japanese Ministry of Health in 2001 for the therapy of AIS. It can scavenge free radicals, inhibit the oxidative damage to brain cells, endothelial cells and nerve cells from lipid peroxidation, and alleviate the influence of cerebral ischemia and edema, finally alleviating the AIS-caused tissue damage [22, 23]. HUK can selectively dilate arterioles in ischemic areas, increase regional

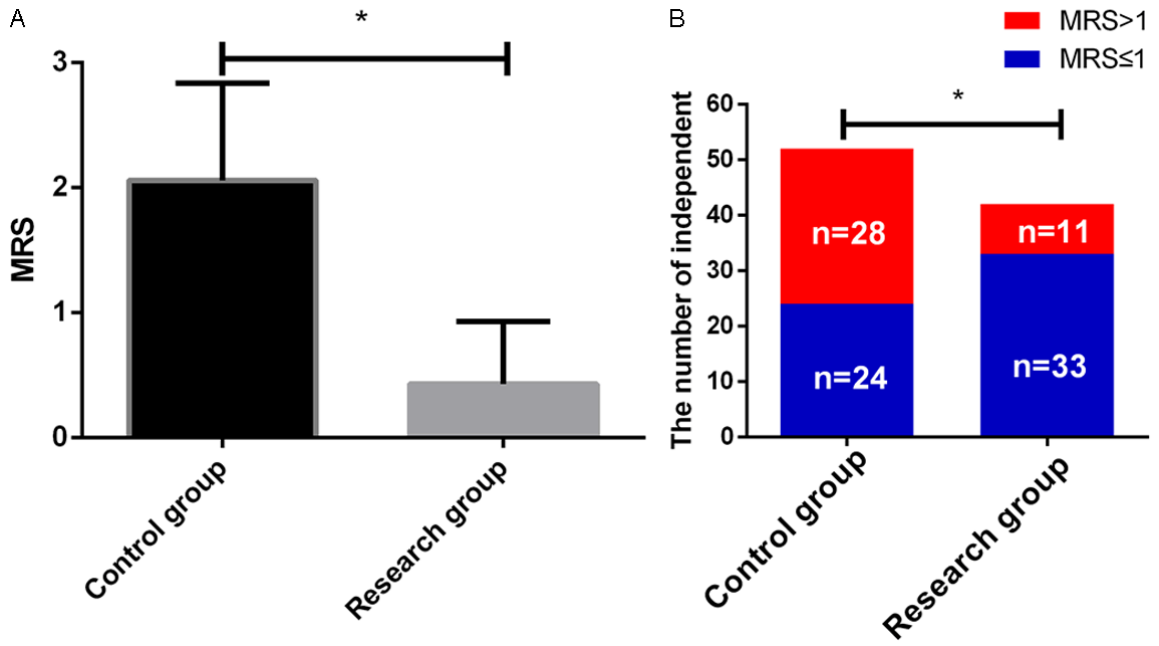

Figure 2. MRS changes and independent rate analysis of the two groups after treatment. A. Changes in MRS score of the two groups after 14 days of treatment. B. Analysis of the independent rate in the two groups after 12 months of treatment. Note: The independent-samples T test was adopted for inter-group comparison of measurement data, and the chi-square test was adopted for analysis of counting data. *, $P < 0.05$.

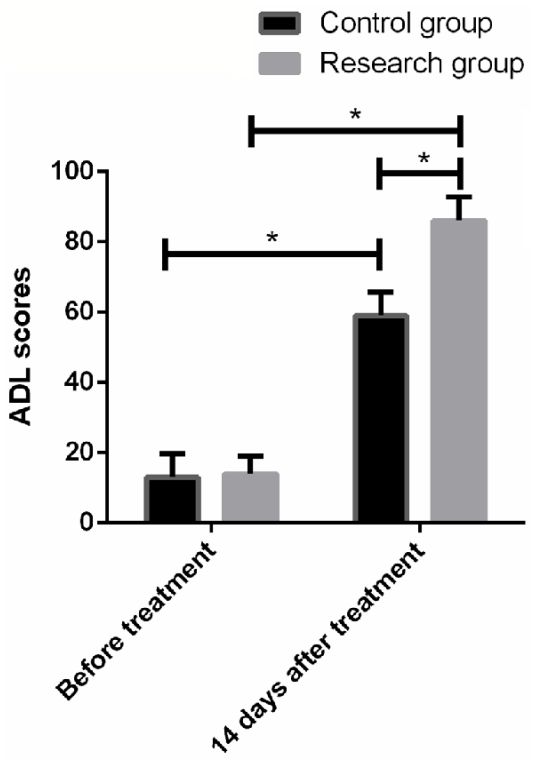

Figure 3. Changes in ADL scores of the two groups before and after treatment. Note: The independent-samples T test was adopted for inter-group comparison of measurement data, and the paired t test was adopted for intra-group comparison of them. *, $P < 0.05$.

cerebral blood flow, suppress apoptosis and inflammation, promote angiogenesis and neurogenesis, and alleviate neurological deficit after AIS [24, 25]. The pharmacological mechanisms of these three drugs are greatly different, making it possible to use them in combination. Since HUK ($71.5/day) and edaravone ($53.6/day) are costly in China, patients can only use one of them together with NBP ($7.5/day). HUK can induce vascular endothelial growth factor expression, promote the formation of brain collateral circulation [26], and inhibit oxidative stress through kallikrein-kinin system (KKS) [27]. Compared with edaravone, HUK has more pharmacological effects, which may be the reason why HUK combined with NBP can deliver better therapeutic effect. In our study, no serious adverse reactions occurred in the two groups, and no death occurred during the treatment. The results also indicated the safety of HUK combined with NBP for PCI.

Dong et al. [28] have carried out a randomized double-blind experiment. It is a phase IIb-stage and phase III trial. In the experiment, compared with the placebo group, the HUK group had significantly higher scores of European Stroke Scale (ESS) and ADL. HUK treatment was found to be related with a lower disability rate. The

Table 3. Adverse reactions and recurrence

	The control group (n = 52)	The research group (n = 42)	χ^2	P
Blood pressure decrease	1	0		
Alanine aminotransferase increase	0	1		
The incidence of adverse reactions	1.92%	2.38%	0.320	0.572
Recurrent stroke	5	2	0.246	0.620

Note: The Chi-square test was used for analysis of counting data.

incidence of adverse reactions among patients who received treatment in the experiment was 1.73%, which was like our result (2.38%). At the current stage, there are many studies on the mechanism of action of HUK. A previous study by Han et al. [10] has revealed that HUK can enhance the expression of VEGF and apelin/APJ in an ERK1/2-dependent manner, promoting angiogenesis and increasing blood vessel density. Another study by Lan et al. [29] has also found that HUK inhibits balloon-induced intimal hyperplasia of rabbit carotid artery and prevents vascular stenosis by transforming growth factor β1/smad2/3 signaling pathway. These studies provided an effective direction for us to analyze the mechanism of HUK in PCI in the future.

The present study has confirmed the value of HUK and NBP in PCI, but it still has limitations. In this retrospective study, the difference in sample size may lead to bias in statistical results. This study has only counted the recurrence of patients within one year but failed to follow up with the patients for a longer time, so the long-term effect of drug treatment on patients is still unclear. We hope to carry out randomized controlled trials in the follow-up study and carry out long-term follow-up to improve our research conclusions.

In conclusion, HUK combined with NBP can reduce the neurological dysfunction and disability rate of patients and improve their independence rate and quality of life. It is a safer and more effective method for the treatment of PCI. The number of cases enrolled in this study was small, so we suggest a larger sample size for a better confirmed conclusion.

Disclosure of conflict of interest

None.

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