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Efficacy and safety assessment of urokinase plus tirofiban in acute cerebral infarction patients without clear criminal vessels

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Abstract: To determine the efficacy and safety assessment of urokinase plus tirofiban in acute cerebral infarction patients without clear criminal vessels. Totally 96 cases of acute cerebral infarction (ACI) patients without clear criminal vessels enrolled in our hospital from July 2017 to July 2020 were randomized to the control group (n=48) with urokinase (n=48) and the observation group (n=48) with urokinase and tirofiban. Clinical efficacy, National Institute of Health Stroke Scale (NIHSS) score, Barthel Index (BI), Clusterin (CLU), tumor necrosis factor-α (TNF-α), serum hypersensitive C-reactive protein (hs - CRP), interleukin-6 (IL-6) and safety were compared. The observation group outperformed the control group in terms of clinical efficacy. Before treatment, the NIHSS scores, BI scores and serum levels of CLU, TNF-α, hs - CRP, and IL-6 in the control group were similar to those in the observation group. After treatment, the above indicators were all decreased, and lower in the observation group. The observation group had a lower incidence of adverse reactions. Arterial thrombolysis of urokinase plus tirofiban in ACI patients without clear responsible vessels effectively reduces postoperative NIHSS score, improves self-care ability, relieves the level of inflammatory factors, with fewer adverse reactions and higher safety profile.

Keywords: Criminal vessels, acute cerebral infarction, urokinase, tirofiban, artery thrombolysis.

INTRODUCTION

Acute cerebral infarction (ACI) is a common clinical nervous system disease with high morbidity, high disability, and high mortality (Puri *at al.*, 2015). ACI has become a crucial cause of death in China due to population ageing (Lin *at al.*, 2016). ACI has long been an issue of great interest in medical progress. The role of thrombolytic therapy in ACI has captured growing attention for the merits of rapid progress and remarkable effect. One major issue in thrombolytic therapy concerned that (Lin *at al.*, 2018; Stevens *at al.*, 2019) in emergency arterial thrombolysis therapy, the deficits in neurological function in some patients are absent from digital subtraction angiography (DSA) (Tsivgoulis *at al.*, 2016). Controversy over the existence of an ischemic penumbra and the feasibility of thrombolytic therapy in ACI patients without clear criminal vessels has long existed in academia. To date, little consensus has been reached on the safety and effectiveness of arterial thrombolytic therapy. Accordingly, this study was designed to investigate the efficacy and safety of urokinase plus tirofiban arterial thrombolysis in ACI patients without criminal vessels to provide a basis for the selection of clinical treatment options and prognosis judgment in the future. The results are as follows.

MATERIALS AND METHODS

General information

A total of 96 ACI patients without clear criminal vessels admitted to our hospital from July 2017 to July 2020 were identified as research subjects. All patients were randomized to the control group and the observation group, with 48 cases in each group. The Ethics Committee of our hospital had approved the study. There were no significant differences in the general data of the two groups ($p>0.05$). As shown in table 1.

Inclusion criteria

a) Patients who met with the diagnostic criteria of Chinese Guidelines for diagnosis and Treatment of Acute Ischemic Stroke 2018 compiled by the cerebrovascular Disease Group of the Neurology Branch of the Chinese Medical Association (Lokeskrawee *at al.*, 2017); b) Patients who were admitted to the hospital within 4.5h after the onset; c) Patients with thrombolytic indications and without contraindications; d) Patients and their family members signed written informed consent.

Exclusion criteria

a) Patients with intracranial hemorrhage confirmed by cranial CT; b) Patients with malignant tumors, endocrine, immune, and blood system diseases; c) Patients with a history of major craniocerebral injury in the past 3 months; d) Patients with contraindications or a history of allergy to the drugs used in this study; e) Patients with poor compliance.

Method

After admission, all patients received routine examinations, blood oxygen saturation and water-electrolyte balance, correction of acidosis, close monitoring of the vital signs and supportive treatment. Patients in the control group were given urokinase (Livzon Pharmaceutical Group Inc., SFDA Approval No. H44020646). 1.2×10^6 U urokinase was dissolved in 100 mL of normal saline and given through intravenous

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infusion for 30 min. Patients in the observation group were treated with urokinase and tirofiban (Yuanda Pharmaceutical Co. Ltd, SFDA Approval No. H20041165). The treatment method of urokinase was consistent with that of the control group. The tirofiban was given through transcatheter arterial infusion, 0.4μg/kg/min, for 30 min. Lipid-lowering, anti-platelet aggregation, and improvement of collateral circulation were performed postoperatively.

Observed indicators

(a) Clinical efficacy. If the patients had a decrease of National Institute of Health Stroke Scale (NIHSS) score over 90%, a disability level of 0, a Barthel index (BI) score over 95 points, and no visual, speech and other impairments, the efficacy is considered basically cured. If the patients had a decrease of NIHSS score between 45% and 89%, a disability level between 1 and 3 and a BI score between 75 and 94 points, the efficacy is considered markedly effective.

If the patients had a decrease of NIHSS score between 18% and 44%, a disability level between 4 and 6 and a BI score between 50 and 89 points, the efficacy is considered effective. The patients had a decrease of NIHSS score less than 18% and a BI score less than 50, the efficacy is considered ineffective. (Luo *at al.*, 2019) (b) Comparison of NIHSS score. Before treatment, 24 hours after treatment, 1 week after treatment and 2 weeks after treatment, the condition of neurological impairment was assessed from eleven components such as the vision, facial paralysis, speech, and consciousness level, with a total score of 42 points. The higher the score, the worse the neurological function. (c) Comparison of the activities of daily life. BI was adopted to evaluate the activities of daily life.

The higher the score, the stronger the activities of daily life. (d) Comparison of the serum levels of CLU, TNF-α, hs - CRP, and IL-6. Before treatment and 1 week after treatment, 3ml of fasting peripheral venous blood (non-anticoagulant) were collected, and serum Clusterin (CLU), tumor necrosis factor-α (TNF-α), serum hypersensitive C-reactive protein (hs-CRP), and interleukin-6 (IL-6) were determined, respectively. The serum levels of CLU, TNF-α, and IL-6 were determined with Elisa kits. The serum level of hs - CRP was determined by a fully automatic biochemical analyzer (Mindray BS - 620). (e) Comparison of the adverse reactions. The adverse reactions, including intracranial hemorrhage, skin ecchymosis, or bleeding in other parts were recorded and the incidence of adverse reactions was calculated.

STATISTICAL ANALYSIS

The data of the present study were analyzed using SPSS 17.0. Continuous data were summarized with the use of mean and standard deviation. The t-test was used for the comparisons between groups. The categorical data were summarized with the use of [n, (%)]. The chi-square test was used for the comparison of categorical data. The p-value < 0.05 indicates a significant difference.

RESULTS

Comparison of the clinical efficacy

The observation group outperformed the control group in terms of clinical efficacy (95.83% vs. 72.92%, p < 0.05).

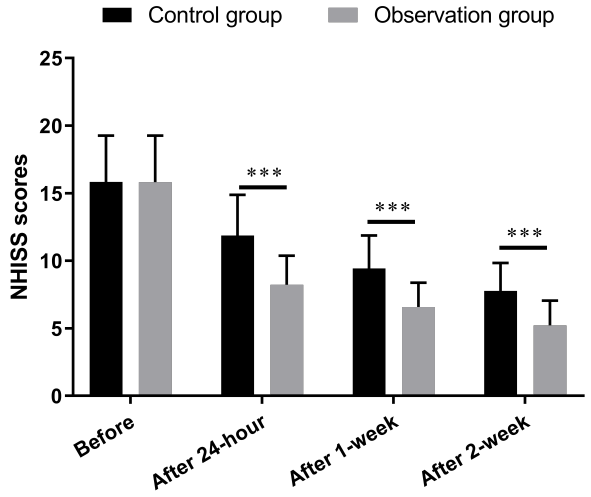

Fig. 1: Comparison of the NIHSS scores of both groups, *** indicated p<0.001.

Comparison of the NIHSS scores of both groups

The two groups had similar NIHSS scores before treatment (p>0.05). After treatment, the NIHSS scores of the two groups decreased, with lower results in the observation group than the control group (all p < 0.05). See fig. 1.

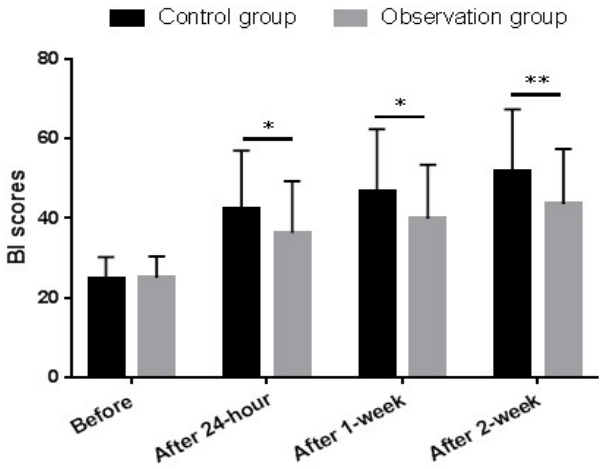

Fig. 2: Comparison of the BI scores of both groups, * indicated p<0.05; ** indicated p<0.01.

Table 1: Comparison of the general data of both groups

	Gender (Male/Female)	Age ($\bar{x}$±s, year)	time since ACI onset ($\bar{x}$±s, hour)
Control group (n=48)	25/23	55.26±11.54	2.53±1.12
Observation group (n=48)	26/22	55.29±11.65	2.55±1.13
$\chi 2$/t	0.042	0.013	0.087
p	0.419	0.990	0.931

Table 2: Comparison of the clinical effect of both groups [n, (%)]

	Basically cured	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=48)	20 (41.67)	14 (29.17)	12 (25.00)	2 (4.16)	46 (95.83)
Observation group (n=48)	13 (27.08)	12 (25.00)	12 (25.00)	11 (22.92)	35 (72.92)
$\chi 2$					7.686
p					0.006

NIHSS

Table 3: Comparison of the serum levels of CLU, TNF-α, hs-CRP, and IL-6 of both groups ($\bar{x}$±s)

	CLU(μg/ml)		TNF-α (μg/L)		hs-CRP (μmol/L)		IL-6 (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=48)	111.07± 20.50	91.97± 19.48*	69.97± 8.61	33.55± 7.73*	7.73± 1.69	5.54± 1.60*	194.01± 24.53	149.64± 27.05*
Observation group (n=48)	110.89± 20.43	80.06± 18.53*	70.06± 8.55	25.73± 6.68*	7.85± 1.75	4.22± 1.52*	193.28± 24.64	137.51± 26.80*
t	0.043	3.069	0.051	5.303	0.342	4.144	0.145	1.781
p	0.966	0.003	0.959	< 0.001	0.733	< 0.001	0.884	0.029

Note: * indicated $p < 0.05$ when compared with before treatment.

Table 4: Comparison of the adverse effects rate of both groups [n, (%)]

	Intracranial hemorrhage	Skin ecchymosis	Bleeding in other parts	Total rate
Control group (n=48)	1 (2.08)	0 (0.00)	0 (0.00)	1 (2.08)
Observation group (n=48)	3 (6.25)	4 (8.33)	1 (2.08)	8 (16.67)
$\chi 2$				6.008
p				0.013

Comparison of the BI scores

The two groups presented no significant differences in the BI scores before treatment ($p>0.05$). After treatment, the BI scores declined in the two groups significantly, with lower outcomes obtained in the observation group when compared with the control group (all $p < 0.05$). See fig. 2.

Comparison of the serum levels of CLU, TNF-α, hs-CRP, and IL-6 of both groups

The serum levels of CLU, TNF-α, hs-CRP, and IL-6 of the two groups were comparable before treatment ($p>0.05$). After treatment, the levels of the above indicators decreased, in which the observation group had a greater decrease than the control group (all $p < 0.05$). See table 3.

Comparison of the adverse effects rate of both groups

The observation group reported significantly fewer cases with adverse reactions than the control group (2.08 % vs 16.67 %, $p<0.05$). See table 4.

DISCUSSION

The ischemic penumbra theory is the most potent theoretical basis known in the treatment of arterial thrombolysis. In the literature on ACI, the main indication for thrombolytic therapy is clear total cerebrovascular occlusion with visible ischemic penumbra on DSA examination (Powers *at al.*, 2015). Intra-arterial thrombolysis plays a critical role in the treatment of patients with such symptoms, as timely restoration of blood supply to ischemic brain tissue areas before ischemic penumbra develops into irreversible damage maximizes the salvage of dying nerve cells to relieve the symptoms of neurological deficits. Therefore, the timing of thrombolysis is dominant in the treatment (Dorňák *at al.*, 2018). However, a great deal of previous research into ACI has revealed that some ACI patients with obvious neurological loss showed no clear criminal vessels in DSA examination (Tsivgoulis *at al.*, 2017), which may be

attributed to the two following reasons. Firstly, the degree of vessel occlusion is relatively small, and the resolution of the DSA machine is insufficient. Secondly, DSA cannot completely detect small infarcts because of the small size and the unclear number of perforating branches of the brain and cortical branches of the artery, resulting in occlusion of the perforating artery or natural dissolution of the embolus in the vessel (Gong *at al.*, 2020). The presence of an ischemic penumbra and the feasibility of thrombolytic therapy for patients with ACI without clear criminal vessels remain a pressing issue to be addressed. Accordingly, this study investigated the efficacy and safety of urokinase plus tirofiban arterial thrombolysis in ACI patients without clear criminal vessels.

Tirofiban, a kind of peptide platelet II b / III a receptor antagonist medicine, competitively and selectively binds to platelet GP II b / III a receptor and reversibly interdicts platelet activation pathways, thereby inhibiting thrombosis with the merits of the short half-life, no antigenicity, less adverse reaction, and good anticoagulant effect (Gruber *at al.*, 2019; Li *at al.*, 2016; Zhang *at al.*, 2019). Urokinase is a fundamental thrombolytic treatment with a short half-life, low antigenicity, low price, and easy acceptance by patients; however, it is associated with negative factors including rapid clearance *in vivo*, low specificity for thrombosis, short duration of action, and bleeding due to activation of systemic plasminogen (Wang *at al.*, 2021). Evidence has suggested a poor thrombolytic effect and a low rate of vascular recanalizatio of urokinase in occluded large vessels (Vilanilam *at al.*, 2019). In this study, the results showed that the observation group had greater clinical efficacy than the control group (95.83% vs 72.92%) and the lower NIHSS scores and BI scores were observed in the observation group. It indicated that urokinase plus tirofiban arterial thrombolysis reduces the postoperative neurological deficit score and improves the self-care ability of ACI patients without clear criminal vessels.

It is now well established that CLU level is closely related to the condition and prognosis of ACI with different degrees of neurological impairment and the lower the CLU level, the better the prognosis (Matsushita *at al.*, 2016). Consistent with the literature, results of the present study found a lower CLU level among patients who received urokinase plus tirofiban, indicating better anti-apoptotic and anti-inflammatory effects of the hybrid therapy in this study. It has been reported that the inflammatory reaction is positively related to the progression of ACI and the levels of TNF-α, hs-CRP and IL-6 are positively correlated with the severity of ACI (Liu *at al.*, 2018; Zhao *at al.*, 2020). IL-6 can induce the production of hs-CRP and participate in atherosclerosis, which leads to infarction in ACI patients. Results in this study showed that the serum levels of CLU, TNF-α, hs -CRP, and IL-6 in the observation group were lower than those in the control group, indicating that urokinase plus tirofiban arterial thrombolysis could effectively control inflammatory factors and improve the thrombolysis effect in ACI patients without clear criminal vessels. Moreover, the observation group obtained a lower incidence of adverse reactions than the control group (2.08% vs 16.67%), proving a higher safety of urokinase plus tirofiban.

CONCLUSION

Arterial thrombolysis of urokinase plus tirofiban in ACI patients without clear responsible vessels effectively reduces postoperative NIHSS score, improves self-care ability, relieves the level of inflammatory factors, with a low incidence of adverse reaction and a high safety profile.

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