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Clinical efficacy and the influence of fibrinogen, homocysteine and prognosis in acute ischemic stroke patients treated with tirofiban plus TERVO stent thrombectomy

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Abstract: To evaluate the clinical efficacy and the influence of fibrinogen, homocysteine, and prognosis in acute ischemic stroke (AIS) treated with tirofiban plus TERVO stent thrombectomy. A retrospective study was conducted among 82 patients with AIS admitted to the Department of Neurology in Hengshui People's Hospital from December 2018 to December 2020 and they were evenly divided into control group and study group according to different methods. The control group received TERVO stent thrombectomy; the study group received tirofiban plus. The clinical efficacy, modified thrombolysis in cerebral infarction (mTICI) grade, serum levels of fibrinogen and homocysteine, National Institute of Health stroke scale (NIHSS), and activity of daily living (ADL) scores were compared. Significant higher clinical efficacy was observed in the study group vs. control group (all $p<0.05$). The study group witnessed lower percentage of 0~1 grade of mTICI blood flow in relative to the control group (all $p<0.05$). After treatment, significant reduction was observed in FIB and HCY in both groups, but the treatment in the study group resulted in a greater reduction (all $p<0.05$). After treatment, both groups reported a significant increase in NIHSS score and ADL score, with more increase in the study group (all $p<0.05$). The safety profiles were similar in the two groups with respect to the adverse reactions ($p>0.05$). Tirofiban plus TERVO stent thrombectomy could improve vascular recanalization rate, reduce fibrinogen and homocysteine levels and improve short-term prognosis in AIS patients.

Keywords: Thrombectomy, tirofiban, TERVO stent, acute ischemic stroke, fibrinogen, homocysteine.

INTRODUCTION

Stroke is a cerebrovascular disease characterized by high morbidity, disability and mortality. Acute ischemic stroke (AIS), as a common clinical type of stroke, accounts for 80% of the stroke (Gong *et al*., 2020). Evidence suggests that early thrombolytic therapy plays a positive part in stroke with respect to efficacy and prognosis (Yang *et al*., 2019). Still, the time window was only 4.5h, resulting in a low recirculation rate and a high risk of bleeding. Cerebrovascular stent thrombectomy extends the opening time window to 6-24 hours, with an increased vascular recanalization rate (Pan *et al*., 2019). Intravascular interventional treatment, including intra-arterial thrombolysis and mechanical thrombectomy with endovascular stents, is a universally applied in AIS (Dannenberg *et al*., 2019), with the superior performance in expanding the contact area of thrombolytic drugs, shorting the use time of thrombolytic drugs and reducing the dosage of thrombolytic drugs compared with intravenous thrombolytic therapy (Huo *et al*., 2020). AIS would lead to over expression of inflammatory cytokines, which exacerbates symptoms of neurological deficits, and undermines the prognosis. Fibrinogen (FIB) and homocysteine (HCY) are common cytokines of cellular inflammation. To date, there has been little agreement on the whether their expression has impact on the treatment and prognosis of AIS patients (Sun *et al*., 2021). To fill the gap, this study aims to evaluate the clinical efficacy and the influence of FIB, HCY, and prognosis in AIS patients treated with tirofiban plus TERVO stent thrombectomy.

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MATERIALS AND METHODS

General Materials

A retrospective study was conducted among 82 patients with AIS admitted to the Department of Neurology in Hengshui People's Hospital from December 2018 to December 2020 and they were evenly divided into control group and study group according to different methods. The control group received TERVO stent thrombectomy, while the study group received tirofiban plus TERVO stent thrombectomy.

Inclusion Criteria

a) In accordance with the diagnostic criteria of *Expert Consensus on Early Endovascular Intervention Therapy for Acute Ischemic Stroke* (Sun *et al*., 2019); b) Confirmed by cranial CT and MRI examination; c) With age 20~80 years old; d) With onset time less than 12h; e) Patients who were informed of the study and signed the informed consent; f) This trial was approved by the hospital ethics committee.

Exclusion Criteria

a) With hemorrhagic stroke; b) With expected survival time less than 1 year; c) With severe heart, liver, and

kidney dysfunction; d) With allergies to contrast agents; e) With previous surgery within 1 month; f) With a large infarction displayed in CT. This trial was conducted in accordance with Declaration of Helsinki (Huo *et al*., 2020).

Methods

Main surgical instruments

8F Arterial Sheath and 0.035-inch Loach Guide Wire (150cm) provided by Terumo, Japan; 5F single-bend Contrast Catheter (100cm) and 8F Catheter (90cm) provided by Cordis, USA; 0.014-inch Loach Synchronous Neural Microguide Wire (300cm), Pro-18 Microcatheter (150cm) and TREVO stent (4mm× 20mm) provided by Stryker, USA. 6F Navien Intermediate Catheter provided by Edtronic, USA.

Surgical procedure

The survey was conducted with blood oxygen, blood pressure, and ECG monitored throughout. Patients who cannot cooperate well with the operator in supine position could be anesthetized by local infiltration of 1% lidocaine about 1.50cm above the right inguinal crepes and pulse of the common femoral artery. If agitation or persistent vomiting occurred, endotracheal intubation must be performed under inhaled anesthesia. Seldinger technique was adopted to puncture the right common femoral artery, then the 8F artery sheath was inserted. With the help of a 0.035-inch Loach guidewire, a 5F uncurved angiography catheter was introduced through the arterial sheath for cerebral angiography and the compensatory status of occluded vessels and collateral vessels were determined. Then 8F catheter was introduced through the loach guide wire. Under the guidance of the 0.014-inch synchronous nerve micro guide wire, the 6F Navien intermediate catheter was introduced as close as possible to the occlusion vessel; then the Pro-18 micro catheter was introduced through the nerve micro guide wire to the distal end of the occlusion vessel. The "smoke" of the micro catheter proved a correct place in the true lumen and that the distal artery was circulating well. Micro catheter was used to assist TREVO stent to thrombosis. Determined by the middle tube "pump," TREVO stent would be segmented effectively and completely cover the thrombus. With SWIM slow-release stent technology, the location and shape of TREVO stent was observed by radiography. Then the thrombosis was "pumped" out of the middle catheter. The stent was placed at the thrombosis for 4 ~ 5 min to determine whether the distal vessel is occluded. Then the micro catheter, the middle catheter and the thrombectomy stent were removed. A 50 ml syringe was adopted to continuously draw the middle catheter under negative pressure. After the thrombectomy stent and mediate catheter was removed, two 20 ml syringes were used to suction any clots that might have shed from the catheter. Next, the thrombectomy of the thrombectomy stent and the mediate catheter were examined and cerebral angiography was performed again to determine the recanalization effect of occluded arterial blood flow. If the recanalization was not ideal, the thrombectomy could be repeated. However, if it failed after 3 consecutive attempts, it should be stopped immediately. After continuous monitoring for 30 minutes, the surgery was completed successfully in the patients with good positive blood flow. The study group received 0.4μg/ (kg min) intravenous tirofiban for 0.5h after operation and then 0.1μg/ (kg min) for 24~48h.

Observation indicators

(1) Clinical efficacy was assessed at 4 weeks after operation by National Institute of Health stroke scale (NIHSS) scores and related symptoms. Basically cured, NIHSS scores decreased by more than 90%, symptoms disappeared; significantly effective, NIHSS score decreased > by 46% ~ 90%, symptoms were significantly improved; effective, NIHSS score decreased > by 18% ~ 46%, symptoms were improved; Invalid, NIHSS score decreased <18%, symptoms were not improved and even worsened. Total effective rate = (basically cured cases + effective cases + effective cases)/ total cases × 100%. (2) Modified thrombolysis in cerebral infarction (mTICI) grading at 3 days after the operation. Grade 0, there was no blood perfusion in the lesion segment, and the vessels were occluded; Grade 1, there was little blood flow through the occlusion segment with little or no perfusion; Grade 2a, the anterior perfusion was less than half of the downstream ischemic area; Grade 2b, the anterior perfusion was greater than half of the downstream ischemic area; Grade 3, Anterior flow was completely perfused into the downstream ischemic area (Li *et al*., 2016). (3) Detection of serum FIB and Hcy. 5ml of resting elbow blood was taken on an empty stomach in the morning and centrifuged at 3000r/min for 10min after anticoagulation. The upper serum was taken after standing for 15min and stored in the refrigerator at 30℃. FIB was detected by automatic blood coagulation instrument detector with nephelometry method. The kit was provided by Shanghai Yuchun Biotechnology Co., Ltd. HCY was detected by Selectra junior with a circulating enzymatic method. The kit was provided by Shanghai Fusheng Industrial Co., Ltd. Strictly followed the kit instructions to ensure the quality of the test. (4) NIHSS scores. Obtained before the treatment and at the end of 2 weeks, the lower the score, the better the neurological function. Activity of daily living (ADL) score: Obtained before and 3 months after the treatment. The higher the score, the higher the activity in daily life (Fu *et al*., 2020). (5) Adverse reactions: The vascular reocclusion (partial or complete recanalization of vessels after thrombolysis or thrombectomy during endovascular therapy and reocclusion occurred at the original occlusion site after reexamination), gastrointestinal bleeding, asymptomatic intracranial hemorrhage, urinary bleeding, and other adverse reactions were recorded for 3 months after the.

STATISTICAL ANALYSIS

All data analysis was performed with SPSS 22.0. Enumeration data and measurement data were expressed as mean ± standard deviation (mean ± SD) and (n, %) and verified by t-test and $\chi 2$ test. The conventional $p \leq 0.05$ was used to assess statistical significance.

RESULTS

Comparison of the general data of the two groups
The general data of the two groups were balanced (all $p>0.05$). See table 1.

Comparison of the clinical efficacy of the two groups
Significant higher clinical efficacy was observed in the study group vs. control group (all $p<0.05$). See table 2.

Comparison of the mTICI flow grade of the two groups
The study group witnessed lower percentage of 0~1 grade of mTICI blood flow in relative to the control group ($p<0.05$). See table 3.

Comparison of the serum FIB and HCY of the two groups
After treatment, significant reduction was observed in FIB and HCY in both groups, but the treatment in the study group resulted in a greater reduction (all $p<0.05$). See table 4.

Comparison of the NIHSS and ADL scores of the two groups
After treatment, both groups reported a significant increase in NIHSS score and ADL score, with more increase in the study group (all $p<0.05$). See table 5 and 6.

Comparison of the adverse reactions rate the two groups
The safety profiles were similar in the two groups with respect to the adverse reactions ($p>0.05$). See table 7.

DISCUSSION

As a common cerebrovascular disease, AIS features a high disability rate and needs long-term treatment and rehabilitation (Niu *et al*., 2019). In the course of AIS, complications are prone to occur, which may lead to disability and impose substantial economic burden and patients and their families pressure (Zhao *et al*., 2020). Additionally, most patients predipose to psychological and cognitive impairments, exerting a detrimental impact on their social ability (Zhou *et al*., 2020). It remains a major challenge for neurologists that how to effectively treat patients with ischemic stroke (Yu *et al*., 2018). Currently, thrombolytic therapy is an indispensable part of early AIS, including intravenous thrombolytic intervention and endovascular intervention (Wang *et al*., 2020). Though intravenous thrombolytic intervention opens occluded vessels and promotes blood flow recanalization by intravenous infusion of thrombolytic drugs, its limitations merit attention (Sporns *et al*., 2017). It time window is relatively narrow with not exceeding 4.5 hours. Otherwise, intravenous thrombolysis cannot be considered.

In the early stage, coronary heart disease was treated with the endovascular intervention (Massari *et al*., 2016). Since the 1980s, some scholars have employed it for AIS, but not been popularized yet (Tsumoto *et al*., 2017). Around 2015, the results of 6 clinical randomized controlled trials of mechanical thrombolysis have confirmed that for ischemic stroke patients with acute anterior circulation occlusion within 6 hours, the immediate recanalization rate and good prognosis rate in the group of intravenous thrombolysis combined with mechanical thrombolysis were better than those in the group of intravenous thrombolysis (Taglieri *et al*., 2019). Recently, a study screened suitable cases and extended the time window of intravascular treatment to 6~16h and 6~24h, further promoting the development of stent thrombectomy. However, there are vascular endothelial injury, platelet activation, local thrombosis, etc., which eventually lead to continuous thrombosis and vascular occlusion. Antiplatelet drugs can inhibit the formation of clots. Nevertheless, traditional oral antiplatelet drugs (clopidogrel and aspirin, etc.) take effect slowly, and the way of inhibiting platelet aggregation is single and incomplete, which cannot prevent the formation and growth of thrombosis quickly and effectively after vascular opening (Machi *et al*., 2017). Thus, it remains an issue to seek a new platelet inhibitor to replace enteric aspirin tablets and clopidogrel hydrochloride.

Tirofiban, a new effective and reversible peptide glycoproteins antagonist II b/IIIa receptor, could prevent platelet aggregation and crosslinking II b/IIIa receptor by preventing FIB from binding to platelet glycoprotein (Yu *et al*., 2018). Tirofiban, with its major advantage in small molecular weight (440.597), short half-life (1.4-1.8h), quick action (5min after intravenous administration), and rapid recovery of platelet function about 4h after withdrawal, serves as a safe and effective inhibitor of platelet aggregation. A meta-analysis including 12 studies (with 930 patients) evaluated the clinical efficacy and safety of tirofiban hydrochloride in the treatment of AIS (Zhou *et al*., 2020) and showed that tirofiban was superior in improving neurological deficits in patients with progressive stroke, and further study and observation are needed in terms of drug safety (Moulakakis and Lazaris, 2018). Consistently, our results were similar to the prior one in terms of the effectiveness profile. Moreover, we observed that the 0~1 grade of mTICI blood flow in the study group was significantly lower than the control group; after treatment, NIHSS scored had decreased and ADL scores had increased in both groups, with greater increase in the study group. Interestingly, the safety profiles were similar in the two groups.

Table 1: Comparison of the general data of the two groups

	Study Group (n=41)	Control Group (n=41)	χ^2/t	P
Sex				
Male/Female	24/17	25/16	0.097	0.352
Age (x±s, year)	58.87±5.79	59.36±5.32	0.465	0.132
Hypertension				
Yes/ No	25/16	26/15	0.162	0.624
Diabetes				
Yes/ No	7/34	9/32	0.231	0.636
Infarct volume (x±s, cm^3)	3.96±0.42	3.38±0.42	0.127	0.792
Time from onset to thrombolytic therapy (x±s, h)	3.52±0.39	3.38±0.42	0.975	0.174
SBP (x±s, mmHg)	147.05±4.21	149.36±4.11	0.869	0.258
DBP (x±s, mmHg)	85.16±3.15	85.69±2.74	0.458	0.560

Table 2: Comparison of the clinical efficacy of the two groups

	Basically cured	Significantly effective	Effective	Invalid	Total effective rate
Study Group (n=41)	9	14	5	13	28 (68.29)
Control Group (n=41)	16	18	5	2	39 (95.12)
χ2					5.867
P					0.002

Table 3: Comparison of the mTICI flow grade of the two groups

	Grade 0~1	Grade 2a	Grade 2b	Grade 3
Study Group (n=41)	7	6	11	17
Control Group (n=41)	1	3	8	29
χ2	4.297	1.559	0.893	7.336
P	0.036	0.203	0.337	0.044

Table 4: Comparison of the serum FIB and HCY of the two groups (x±s)

	FIB (g/L)				HCY (umol/L)			
	Before Treatment	After Treatment	t	P	Before Treatment	After Treatment	t	P
Study Group (n=41)	8.59±2.73	3.15±1.23	19.298	≤0.001	26.47±6.15	14.15±3.17	26.515	≤0.001
Control Group (n=41)	8.52±2.63	5.28±1.18	22.764	≤0.001	26.81±6.08	17.25±3.28	28.162	≤0.001
t	0.058	17.572			0.062	12.529		
P	0.932	≤0.001			0.854	≤0.001		

Table 5: Comparison of the NIHSS score of the two groups (x±s)

	NIHSS score			
	Before Treatment	After Treatment	t	P
Study Group (n=41)	13.19±1.12	7.27±1.46	25.172	≤0.001
Control Group (n=41)	13.09±1.05	9.37±1.03	26.521	≤0.001
t	0.082	15.321		
P	0.836	≤0.001		

Table 6: Comparison of the ADL score of the two groups

	Social function	Physical function	Mental health	Physical health
Study Group (n=41)	92.21±1.12	90.09±2.02	90.27±1.54	89.13±2.35
Control Group (n=41)	74.31±1.89	70.31±2.21	69.38±1.63	67.26±2.17
t	30.276	30.451	28.592	27.642
P	≤0.001	≤0.001	≤0.001	≤0.001

Table 7: Comparison of the adverse reactions of the two groups

	Reocclusion	Gastrointestinal Bleeding	Asymptomatic Intracranial Hemorrhage	Urinary Bleeding
Study Group (n=41)	2	2	17	4
Control Group (n=41)	3	4	18	5
$\chi 2$	0.012	0.067	0.015	0.019
P	0.934	0.709	0.952	0.941

To date, several studies have shown that in the occurrence and development of the acute ischemic cerebrovascular disease, brain tissue damage caused by inflammatory reaction always exists and higher levels of inflammatory factors will aggravate the injury of nerve function of ischemic brain tissue (Machi *et al*., 2017). Other studies have found that inflammation is one of the triggers of stroke, the improvement of related inflammatory factors thus can lay a foundation for improving the symptoms and prognosis of patients (Lejay *et al*., 2018). FIB and Hcy are common inflammatory cytokines, which are closely related to the occurrence and development of many acute ischemic cerebrovascular diseases. They are central indicators for monitoring AIS with high specificity and sensitivity. Hcy, in particular, has been proved to be an independent risk factor for acute ischemic cerebrovascular disease (Lejay *et al*., 2018). As an II kind of plasma protein, FIB is one of the markers of inflammation, has an impact on the circulation of blood and plasma viscosity. The higher the content, the higher the plasma viscosity. According to our study, FIB and HCY in both groups after treatment decreased, with greater decrease in the study group, suggesting that tirofiban could inhibit the expression of inflammatory cytokines in blood vessels. Taken together, although our study sheds light on the treatment of AIS patients, further prospective randomized controlled trials are warranted to evaluate its efficacy, safety and tolerability in larger, more clinically heterogeneous patient populations followed for longer intervals.

CONCLUSION

To sum up, tirofiban plus TERVO stent thrombectomy improves vascular recanalization rate, reduces FIB and HCY levels and improves short-term prognosis in AIS patients. Yet, further prospective randomized controlled trials are required in larger, more clinically heterogeneous patient populations.

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