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Original Article

Effects of the AngioJet system on levels of serum inflammatory factors and Angptl2 in patients with arterial thrombotic disease of the lower extremities

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Abstract: Objective: The aim of the current study was to investigate the effects of the AngioJet system on expression levels of serum angiopoietin-like protein 2 (Angptl2) and related inflammatory factors in patients with arterial thrombotic disease of the lower extremities. Methods: Retrospective analysis was performed using the clinical data of 18 patients with arterial thrombotic disease of the lower extremities, treated with the AngioJet thrombus aspiration system in vascular surgery. Results: All patients were cured and discharged from the hospital. Patients had significantly higher ankle-brachial indexes (ABI) after the operation than before the operation ($P < 0.05$). Compared with before the operation, Angptl2 and serum inflammatory factors, IL-8 and IL-6, of patients were significantly lower after the operation ($P < 0.05$). In addition, the 18 patients showed no acute kidney injuries. There were no statistical differences between preoperative and postoperative creatinine values ($P > 0.05$). Conclusion: AngioJet catheter aspiration for treatment of arterial thrombotic disease of the lower extremities is safe, effective, and less invasive. It can also reduce serum Angptl2, IL-8, and IL-6 levels of patients, with good clinical effects.

Keywords: Thromboembolism, lower extremity, AngioJet, serum inflammatory factor, angiopoietin-like protein 2

Introduction

Acute thrombosis and acute embolisms of lower extremity arteries are common emergencies in vascular surgery. Incidence is approximately 2 patients/10,000 persons. If active and effective treatment measures are not taken in time, diseased limbs will be amputated due to ischemic necrosis, with an amputation rate of 20%-40%. Patient lives will be endangered in serious conditions, with a mortality of approximately 25% [1]. Acute embolisms of lower extremity arteries are often caused by acute shedding of the left atrial appendage thrombus or mural thrombus of the arterial system in patients with atrial fibrillation. Acute thrombosis is more common in secondary arteriosclerosis obliterans in the lower extremities [2]. Acute embolisms of the lower extremities are treated by routine arterial embolectomies, catheter-directed intraarterial thrombolysis, and the AngioJet mechanical thrombus aspiration technique [3, 4].

Routine incisions, with great amounts of operative trauma, do not completely treat thrombus. They may lead to incomplete thrombectomies. The reperfusion reaction is large. Catheter-directed intraarterial thrombolysis is an effective treatment in clinical practice. Main mechanisms of the thrombectomy procedure are to place the Fogarty catheter on the distal end of the diseased artery. The catheter is then slowly dragged after the balloon is filled. The balloon filling degree is adjusted until the thrombus is removed. The procedure is stopped when blood returns in the arterial end. However, due to the considerable amount of time spent on thrombolysis, repeated angiographies and the use of anticoagulants may cause neurological and gastrointestinal bleeding. The AngioJet mechanical thrombus aspiration technique has gained recent popularity with the development of intraluminal treatment techniques and improvements in interventional machinery. Its principle of clearing is to soften and drag the thrombus through the pressurized normal sa-

line, sprayed at the end of the catheter. Finally, the thrombus is aspirated from the catheter [5]. Moreover, this treatment process only takes a few minutes, saving valuable time for patients and improving prognosis. Good clinical effects have been achieved in recent years using the AngioJet mechanical thrombus aspiration technique for acute pulmonary embolisms and myocardial infarction [6]. To this end, the current study reviewed application of the AngioJet system for treatment of acute thrombotic diseases of the lower extremities, with good clinical results.

Materials and methods

General information

Retrospective analysis was performed on 22 patients with arterial thrombotic disease of the lower extremities. They were diagnosed using color Doppler and were treated with the AngioJet thrombus aspiration system via vascular surgery at the 3rd Affiliated Hospital of Shenzhen University, between August 2016 to July 2017.

Exclusion criteria: Patients that could not complete interventional treatment; Patients with infectious diseases two weeks before the operation; Patients with immune system diseases, having taken immunosuppressive drugs; Patients with other tissue tumors; Patients with previous peptic ulcers; Patients with preoperative renal dysfunction; Patients with severe anemia and blood system diseases; Amputees failing to be treated; Patients with incomplete data.

A total of 18 patients were finally enrolled in the study. All patients were emergency admission. Clinical manifestations included distal "5P" (affected limb pain, paralysis, affected local paleness, loss of distal arterial pulsation, and dyskinesia) response of affected limbs. Risk classification of patients (Type I: no risk of necrosis in tissues; Type IIa: risk of mild necrosis; Type IIb: possibility of moderate necrosis; and Type III: irreversible necrosis) was performed according to the Rutherford model [7]. The AngioJet thrombus aspiration system was used for thrombectomies. Enrolled patients were informed of and agreed to this study. This study was approved by the Ethics Committee of the 3rd Affiliated Hospital of Shenzhen University.

AngioJet thrombus aspiration system treatment

Retrograde punctures of the healthy side of the femoral artery were routinely performed. The puncture needle successfully entered the affected femoral artery under the traction of the guide wire. After lesion locations were decided, the AngioJet thrombus aspiration system (Boston Scientific, USA) was used to complete thrombus aspiration using the following three steps: 1) Routine aspiration; 2) Spray thrombolysis; and 3) Fast thrombolysis. Routine aspiration: The catheter was sent to the target artery, gradually moving from the proximal end to the distal end for aspiration, at an aspiration speed within 2 mm/s; Spray thrombolysis: After the thrombus was aspirated, the guide wire was retained. A C2 catheter was inserted through, with thrombolytic drugs injected. Urokinase (Green Cross, Japan) was used as a thrombolytic drug and a dose of 250,000 U/50 mL of normal saline was prepared. After continuous thrombolysis through the C2 catheter, urokinase was injected at 400,000 units/day, assisted with low molecular weight heparin sodium as an anticoagulant (4,000 units, subcutaneous injection, 12 h/time); Fast thrombolysis: The AngioJet catheter was put through the thrombus, then slowly withdrawn. It passed through the thrombus, thereby clearing the thrombus. Afterward, angiographies (ominipaque from GE, 100 mL) were routinely carried out. If the procedure was not effective (no reduction in thrombus area), secondary aspiration or thrombolysis (small thrombus) was feasible.

Postoperative treatment

Routine anticoagulant therapy was performed, according to patient conditions, after the operation. For example, patients with atrial fibrillation took warfarin orally (Orion, Finland) for anticoagulation (adjusted according to International Normalized Ratio, controlled between 2.0 and 3.0). Patients with infective endocarditis and valvular vegetation were treated with cardiac surgery. Patients with no special history routinely took 100 mg aspirin (Bayer, Germany), orally, once daily.

Comparison of efficacy

Cooley criteria for postoperative efficacy: Cooley criteria were used to evaluate postopera-

Table 1. Baseline data of the subjects

Category	Statistics
Gender (male/female)	10/8
Age (year)	64.8 ± 11.0
Site (upper/lower extremity)	10/8
Course of disease (day)	2.8 ± 0.8
Combined disease	
Atrial fibrillation	9
Rheumatic heart disease	3
Infective endocarditis	1
Hypertension	11
Diabetes	3
Atherosclerosis	13
Rutherford classification	
Type I	2
Type IIa	8
Type IIb	8

tive efficacy in patients. 1) Healing: Review of the angiography indicated that lesions of blood vessels were completely open or the diameter of the arterial lumen was ≥ 70%. Blood flow was normal and the tissue was not necrotic. There was no sensory motor dysfunction. Postoperative ankle-brachial index (ABI) was > 0.6; 2) Good: Blood flow of the distal limb was recovered, symptoms disappeared, and vascular fluctuations were weaker than the contralateral side; 3) General: The blood supply of the distal limb was partially recovered and could be compensated; 4) Poor: Ischemic symptoms were not relieved and blood flow was not available, but could be compensated; and 5) Salvation failure: The limb was necrotic and amputated or the patient died [8].

Postoperative complications: This study mainly focused on renal function and bleeding. Bleeding included puncture site bleeding, visible hematoma, intracranial hemorrhages, and gastrointestinal bleeding.

Detection of inflammatory factors and angiopoietin-like protein 2 (Angptl2): Approximately 5-7 mL of peripheral venous blood was obtained from patients before the operation and on the 3rd day after the operation. The blood was added to the anticoagulant tube and centrifuged at 3,000 r/min. The supernatant was then stored at -80°C for use. Enzyme-linked immunosorbent assay kits (Infinite F50, Dickens, Switzerland; kit, Santa, USA) were used for detection of the serum content of IL-6 and IL-8. Specific methods were according to kit instructions. Changes in preoperative and postoperative Angptl2 levels were detected with the same method.

ABI: An ABI detector (Shenzhen Weikangming Technology Co., Ltd., China) was used for measurement of systolic blood pressure of the posterior or anterior tibial arteries of the ankle and the brachial artery, obtaining the ratio between ankle arterial pressure and brachial artery pressure.

Data statistics

SPSS 20.0 statistical analysis software was used for analysis of data. Measurement data are expressed as mean ± standard deviation ($\overline{x}$ ± sd). Paired t-test was used for comparisons between groups, before and after treatment, with $\alpha = 0.05$ taken as the standard. When $P < 0.05$, differences are statistically significant.

Results

Baseline data

Baseline data of subjects in this group are shown in **Table 1**.

Postoperative situation of patients

Incidence of postoperative complications, postoperative hemoglobin reduction, and myoglobinuria of patients was observed. See **Table 2**.

Efficacy evaluation of AngioJet thrombus aspiration system treatment

All thrombectomy procedures were successful for the patients. A review of angiographies showed that the stenosis area was < 30%. Specific clinical effects are shown in **Table 3**.

Comparison of serum inflammatory factors IL-6 and IL-8 levels and ABI of patients before and after the operation

Results showed that patients had significantly lower serum IL-6 and IL-8 levels and significantly higher ABI after treatment with the AngioJet thrombus aspiration system, compared to before the operation. Differences were statistically significant. Results suggest that AngioJet treatment reduced inflammatory response and

Table 2. Postoperative general situation of patients

Category	Number of cases (n = 18)
Complications	
Bleeding in puncture site	2
Hematoma	0
Intracranial hemorrhage	0
Gastrointestinal bleeding	0
Postoperative proteinuria	11
Number of cases and degree of hemoglobin reduction (g/L)	18 (8.6 ± 2.7)

Table 3. Clinical effects

Clinical efficacy	Number of cases
Healing	12
Good	2
General	2
Poor	1
Salvation failure	1

increased hemodynamics. See **Table 4** for details.

Changes in serum Angptl2 levels of patients before and after treatment

Results suggest that, after interventional treatment removing the thrombus, patients had significantly lower serum Angptl2 levels than before the operation. Differences were statistically significant. See **Figure 1** for details.

Comparison of creatinine values of patients before and after treatment

Creatinine values, before and after treatment (the 3rd day after operation), showed that the 18 patients had no acute renal insufficiencies (ARI). The preoperative creatinine value was 74.6 ± 14.5 μmol/L and the postoperative creatinine value was 82.4 ± 13.8 μmol/L, without statistical differences. This indicates that AngioJet thrombus aspiration treatment had no significant effects on patient renal function. Thus, it is safe and reliable. See **Figure 2** for details.

Discussion

With changes in the human dietary structure and environment, as well as the advent of an aging society, incidence of atherosclerosis has increased year by year. Vascular system diseases have gradually become the main disease type threatening human public health [9]. Shedding of the attached embolus on the surface of atherosclerotic plaque has gradually become the main cause of acute arterial embolisms [10]. Therefore, it is important to improve diagnosis and treatment levels of acute arteries, improving the prognosis of these patients.

Most previous studies have focused on showing the effects of AngioJet thrombus aspiration for treatment of coronary and pulmonary embolisms, with good clinical effects. Present results also show the role of the AngioJet system in the treatment of lower extremity arteries. Postoperative ABI of patients was increased, significantly, showing good therapeutic effects. This is consistent with previous results [11, 12].

At present, there are relatively few studies concerning the effects of different operative methods on serum inflammatory factors and Angptl2. Serum inflammatory factors and Angptl2 have been closely related to the formation and prognosis of thrombus [13, 14]. The formation of thrombus is complementary to occurrence of inflammatory responses. On one hand, with the existence of inflammatory factors, blood tends to be in a high coagulation state. Thus, the formation of thrombus is accelerated. On the other hand, the release of inflammatory factors during the coagulation in the body aggravates inflammatory responses [15]. IL-6 and IL-8 are representatives of inflammatory factors. The former stimulates the liver to produce plasminogen activation inhibitors, reduces fibrinolytic function in the blood coagulation, and leads to thrombosis. The latter activates endothelial cells and monocytes to promote adhesion between inflammatory cells. In addition, it directly acts on endothelial cells, leading to the formation of local thrombosis [16]. Results of this study showed that, after treatment with AngioJet thrombus aspiration, patients had significantly lower serum IL-6 and IL-8 levels. Thus, interventional aspiration treatment significantly reduces inflammatory responses of the body,

Table 4. Comparison of serum inflammatory factors of patients before and after treatment

Inflammatory factors	Before treatment	After treatment	t	P
IL-6 (ng/L)	163.65 ± 18.43	103.79 ± 22.67	8.693	< 0.001
IL-8 (ng/L)	7.39 ± 0.47	4.50 ± 0.52	17.493	< 0.001
ABI	0.32 ± 0.09	0.65 ± 0.12	9.334	< 0.001

Note: ABI, ankle-brachial index.

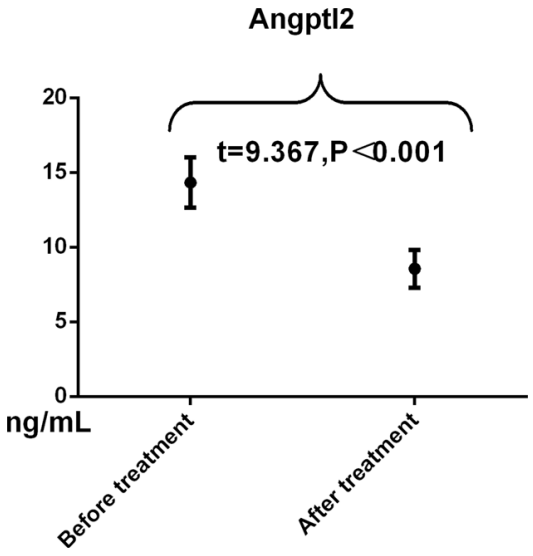

Figure 1. Changes in serum Angptl2 levels of patients before and after treatment. Angptl2, angiopoietin-like protein 2.

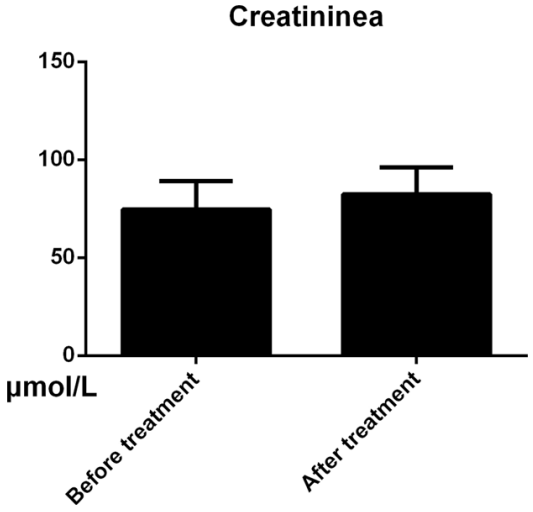

Figure 2. Comparison of creatinine values of patients before and after treatment.

confirming the effectiveness of its treatment and corroborating previous research [17].

Angptl2, a group of secreted glycoproteins regulated by Angptl2 genes, is associated with angiogenesis. It includes 8 members. Studies have confirmed that Angptl2 is related to the occurrence and development of cardiovascular diseases, such as coronary heart disease, aneurysms, and hypertension [18]. Its mechanism of promoting thrombosis may be through direct damage to vascular endothelial cells and the induction of platelet aggregation [19]. Patients had significantly lower Angptl2 after the operation than before the operation, indicating that AngioJet thrombus aspiration treatment can effectively remove intravascular thrombus and reduce content of thrombotic factors. This is consistent with previous results [20].

Evaluating the safety of AngioJet thrombus aspiration treatment mainly focuses on bleeding caused by anticoagulation and renal injuries possibly caused by red blood cell destruction [21]. Results of this study showed no cases of catastrophic bleeding of excessive anticoagulation. Moreover, the decline in hemoglobin levels in patients was also within the scope of clinical safety. In addition, there were no significant changes in preoperative and postoperative creatinine values and no ARI occurred. This further confirms the conclusions of previous studies, suggesting that AngioJet thrombus aspiration is safe and reliable.

However, this study was a single-center study with a small number of cases. Large-sample studies, with multi-center collaboration, are required to further confirm clinical efficacy. In addition, this study unilaterally evaluated AngioJet thrombus aspiration treatment. Thus, other treatments need to be compared, comprehensively evaluating clinical efficacy.

In summary, AngioJet thrombus aspiration for treatment of acute thromboembolisms of lower extremity arteries not only has good clinical effects, but also reduces levels of serum inflammatory factors and Angptl2. It has less impact on patient renal function. Therefore, it is relatively safer and more reliable.

Disclosure of conflict of interest

None.

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