Wenli Wang, Yanfang Wu, Tao Fang, Dunyuan Xu*

Thrombectomy combined with indwelling-catheter thrombolysis is more effective than pure thrombectomy for the treatment of lower extremity deep venous thrombosis

Abstract: This study was a retrospective analysis of the efficacy of thrombectomy plus local catheter-directed thrombolysis (CDT) for the treatment of lower extremity deep venous thrombosis (LDVT).

The experimental group underwent thrombectomy plus LCDT, whereas the control group underwent thrombectomy plus systemic thrombolysis via the dorsalis pedis vein. Venography and vascular color Doppler ultrasound were performed 7 days after surgery and at follow-up. The differences in the thigh and calf circumferences of normal and affected limbs were compared between groups. The venous patency score and venous patency rate were used for outcome evaluation.
Compared with the control group, the experimental group showed a lower venous patency score and higher venous patency rate after treatment (P<0.05). Thirty patients were followed for 3 to 6 months, and according to the last evaluation, the differences in thigh and calf circumference between the normal and affected limbs remained lower in the experimental group than in the control group (P<0.05). Moreover, the venous patency score was lower, and the venous patency rate was higher in the experimental group than in the control group (P<0.05).

Conclusion. Thrombectomy plus CDT yields a higher venous patency rate and lower recurrence rate than pure thrombectomy for the treatment of LDVT.

1 Introduction

Lower extremity deep venous thrombosis (LDVT) is a common disease that is extremely harmful to human health. Approximately 56 to 122 cases of LDVT per 100,000 persons are diagnosed each year [1]. In the United States, almost 500,000 patients are diagnosed with LDVT each year, and approximately 10% of these patients ultimately suffer fatal pulmonary emboli (PEs) [2]. In the United Kingdom, LDVT is the third leading cause of cardiovascular disease after myocardial infarction and stroke, and LDVT-induced PE-related deaths account for more than 10% of total in-hospital deaths [3]. In China, DVT occurs in 47.1% of patients after prosthetic arthroplasty [4]. Additionally, data have shown that the incidence of DVT is rising annually [5]. Thus, finding appropriate treatments for LDVT has become a goal for clinicians and researchers worldwide.

Anticoagulation has long been considered an effective therapy for LDVT because of its unlimited treatment-time window and low complication rate. However, anticoagulation cannot quickly eliminate an existing thrombus. Moreover, despite the strict use of anticoagulation, 20% to 50% of patients with central DVT develop post-thrombotic syndrome (PTS) [6]. Traditional thrombolytic therapy, which is provided by administering thrombolytic drugs intravenously, is a riskier therapy than anticoagulation and is effective mainly against thrombi located in incompletely occluded blood vessels, as it dissolves only 10% of thrombi causing complete vascular occlusion [7]. Surgical treatment of acute LDVT offers the advantage of being able to eliminate thrombi rapidly and thoroughly. However,

*Corresponding author: Dunyuan Xu, No. 91 Jiefang Road, Zhifu District, Yantai 264001,China, Tel: 86-13105209222, E-mail: xudycn@yeah.net
Wenli Wang, Yanfang Wu, Tao Fang, Vascular surgery, Yantaishan Hospital, Yantai 264001, China

thrombectomy causes greater trauma and more blood loss than other treatments [8]. Moreover, an evidence-based study showed that surgical thrombectomy cannot significantly improve venous patency rates [9].

Catheter-directed thrombolysis (CDT), which builds on the traditional strategies of anticoagulation, thrombolysis and thrombectomy, has been proposed for the treatment of LDVT in recent years. CDT entails the direct infusion of high concentrations of thrombolytic drugs into thrombi via thrombolytic catheters and offers significant advantages over other treatments, as it restores deep vein patency and preserves deep vein valves [10-13]. The success rate of trans-catheter thrombolysis with urokinase is as high as 79% and does not appear to cause PE [14]. Early LDVT can be treated with CDT, which can safely and effectively restore venous patency [15]. CDT also improves health-related quality of life in patients with iliofemoral DVT [16]. After CDT treatment, the rates of venous patency in patients with acute iliac-femoral vein LDVT and acute femoral-popliteal vein LDVT were 87% and 79%, respectively [17]. Both the effectiveness and the safety of CDT are high [18]. Additionally, CDT can better protect the venous wall than other therapies, preserve venous valvular structure and function, avoid irreversible venous valvular damage, and reduce the incidence of PTS [19]. However, pure CDT has limitations, as it is associated with the risk of residual thrombi and deep venous valvular dysfunction. Furthermore, both antegrade and retrograde thrombolysis may damage venous valves. Additionally, the rate of catheterization in the correct location is low, and the effect of CDT on thromboses within the popliteal and deep veins in the calf is suboptimal [20]. Moreover, the mechanical action of the catheter during thrombolysis causes thrombi to fragment and loosen, which may result in their detachment, leading to PEs. It is thus essential to implant an inferior vena cava filter in affected patients prior to their undergoing surgery [21].

The aim of this study was to retrospectively analyze the differences in LDVT treatment outcomes between thrombectomy combined with local CDT and pure thrombectomy. The results of this study may provide clinicians with new ideas leading to the development of methods useful for treating LDVT.

2 Methods

2.1 Patients

The records of 20 patients with LDVT who underwent thrombectomy combined with local CDT at Yantaishan Hospital from January 2012 to February 2014 were analyzed in this retrospective study. LDVT was diagnosed on the basis of our observation of specific symptoms and laboratory findings, all of which were defined in the "Deep Venous Thrombosis Diagnostic and Treatment Guidelines (2nd Edition)" [22].

An additional 20 patients who underwent thrombectomy alone at the same hospital during the same period served as the control group. The general data for the two groups are summarized in Table 1.

This study was approved by the Ethics Committee of Yantaishan Hospital, which waived the requirement of written informed consent.

2.2 Inclusion and exclusion criteria

The following patients were included in this study: (1) patients aged 30-65 years; (2) patients with a clinical diagnosis of central lower extremity venous thrombosis, i.e., thrombosis within the iliac-femoral vein; and (3) patients with a clinical diagnosis of mixed lower extremity venous thrombosis, i.e., patients with a thrombus that originated in the calf muscle venous plexus, the antegrade extension of which affected the entire iliac-femoral venous system.

The following patients were excluded from the study: (1) patients with DVT recurrence, (2) patients with thrombosis extending beyond the superficial femoral vein, (3) patients with thrombi complicated by tumors and (4) patients with immunological disorders.

2.3 Treatment

2.3.1 Surgical procedures

The surgical thrombectomy was performed as follows: after the skin was incised longitudinally at a location inferior to the groin (namely, the location at which the greater saphenous vein converges with the lesser saphenous vein to form the femoral vein), the femoral vein and its superficial and deep branches in the affected limb were isolated. Then, the anterior wall of the femoral vein was incised longitudinally after blood flow was temporarily

occluded, and a 6F or 7F catheter (Fogarty balloon catheter) was used to remove as many of the proximal thrombi as possible. After blood backflow improved, 100,000 U of urokinase was administered into the venous lumen, after which the proximal veins were occluded, and the muscles and soft tissues were compressed in succession in an upward direction, beginning at the calf, to eliminate any remaining distal thrombi. After venous blood flow was restored, 100,000 U of urokinase was administered into the venous lumen of the distal vein. Then, the femoral vein was sutured.

2.3.2 Indwelling catheter thrombolysis in the treatment group

Regarding the indwelling catheter thrombolysis, after the thrombi were removed and the femoral vein was sutured, a branch of the greater saphenous vein was selected, and a Unifuse thrombolytic catheter was inserted into the proximal end of the iliac vein to serve as an indwelling catheter. The thrombolytic-guiding segment of the catheter was entirely within the primary thrombus area, and the catheter, which was fixed to the skin, drained at a location adjacent to the incision.

After surgery, 600,000 to 1,200,000 U/d of urokinase (2 infusions/day lasting 2 h each for 7 consecutive days) was continually pumped into the vein via the thrombolytic catheter while coagulation indices were monitored. Thrombus dissolution was monitored daily by color Doppler ultrasound examination, and treatment responsiveness was assessed by deep venous antegrade angiography of the affected limb on the 3rd and 7th days after surgery. If the results were satisfactory after 7 days of continuous medication, the indwelling catheter was removed. However, if the results indicated that no improvement had occurred, treatment was discontinued.

2.3.3 Venous thrombolysis in the control group

After surgical thrombectomy, urokinase was pumped into the dorsalis pedis vein of the affected limb (the dosage and duration were the same as those used in the experimental group). The fibrinogen level was detected, and thrombus dissolution was monitored daily by color Doppler ultrasound examination. Angiography of the lower limb was performed seven days after surgery.

2.3.4 Anticoagulation, anti-clotting therapy, and supportive treatment

Both groups received subcutaneous injections of low-molecular-weight heparin, as well as oral doses of warfarin. After 14 days, the patients were required to ambulate while wearing elastic stockings. They were also instructed to avoid strenuous or fatigue-inducing exercise, refrain from smoking, restrict their alcohol intake, elevate the affected limb, and undergo daily monitoring of blood coagulation parameters.

2.4 Outcome measurements and follow-up

Patients' symptoms were monitored to determine whether they experienced adverse reactions, such as hemorrhage, PE, hematuria or other serious complications, after thrombolysis. The circumferences of the normal and affected thighs and calves were measured each day before and after treatment. Thrombus dissolution was monitored daily by color Doppler ultrasound examination, and vascular recanalization in the veins of the lower limb was assessed by antegrade angiography on the 3rd and 7th days after surgery in the treatment group and on the 7th day after surgery in the control group. The deep vein angiographic results after therapy were compared with the results before thrombolysis, and the venous patency rate was evaluated according to the Villalta scale [23]. Clinical follow-up was conducted 3 to 6 months later to reassess vascular recanalization, determine the venous patency rate, and evaluate the long-term effects of the above treatments.

2.5 Statistical analysis

The measurement data are expressed as the mean ± standard deviation and were analyzed using paired t-tests. Venous patency rate comparisons were made using chi-square tests. SPSS 13.0 software was employed for statistical analysis, and $P<0.05$ was considered statistically significant.

3 Results

3.1 Baseline data

There were no significant differences in gender, age, the condition of the affected limb, the time course of the

disease, or the cause of DVT between the two groups, as shown in Table 1. Among the patients enrolled in the study, 2 developed thrombi after abdominal surgery, 13 developed thrombi after surgery for bone trauma, 18 developed thrombi following soft-tissue injury, and 7 developed thrombi for unknown reasons.

3.2 Improvements in symptoms and signs and changes in angiography during hospitalization

The symptoms and signs of all the patients in the study improved significantly after treatment. The differences in thigh and calf circumference between the affected and unaffected limbs in the treatment group were both significantly less than the corresponding differences in the control group (P<0.05) (Table 2).

Additionally, the pre- and post-treatment venous patency scores were significantly lower in the treatment group than in the control group (P<0.05) (Table 3).

3.3 Follow-up

A total of 30 patients, or 75% of the patients enrolled in the study, were seen for follow up for a period ranging from 3 to 6 months. The average follow-up time was 4±1.5 months. As of the last follow-up, the differences in thigh and calf circumference between the normal and affected limbs of the treatment group were significantly less than those of the control group (P<0.05; Table 4). Moreover, the venous patency score of the treatment group was significantly lower than that of the control group (P<0.05), and the venous patency rate of the treatment group was significantly higher than that of the control group (P<0.05; Table 5).

3.4 Complications

No patients experienced PE, and no patients experienced hemiplegia or other manifestations of intracranial hemorrhage or anaphylactic shock. Gingival bleeding was observed in three patients during thrombolysis (two in the treatment group and one in the control group) but resolved after urokinase treatment was stopped and did not recur after the urokinase dose was adjusted. The incidence of adverse reactions during treatment was compared between the two groups, and the difference in the incidence of adverse reactions between the groups was

Table 1: Comparison of the baseline data for the patient groups

Item	Control (20)	Treatment (20)
Gender ratio (M/F)	14:6	13:7
Age (years)	52±9.1	53±4.3
Ratio of the types of thrombi in the affected limb (central:mixed)	7:13	8:12
Phlegmasia cerulea dolens	1	1
Phlegmasia alba dolens		1
Disease duration (days)	5.5±1.4	5.2±2.1
Post-abdominal surgery (n)	1	1
Post-bone trauma surgery (n)	7	6
Soft tissue injury (n)	9	9

Table 2: Differences in the thigh and calf circumferences between the affected and non-affected limbs in the patient groups before and after treatment

Group (n)	Before treatment		After treatment	
	Thigh	Calf	Thigh	Calf
Control (20)	5.51±2.36	4.49±2.13	2.97±1.48	1.91±1.34
Treatment (20)	5.68±2.15	4.26±1.89	2.01±1.56 *	1.26±1.04*

*P<0.05 compared with the control group

Table 3: Venous patency scores before and after treatment in the patient groups

Group (n)	Before treatment	After treatment	Venous patency (%)
Control (20)	9. 46±1. 52	6. 35±1.89	32. 81±3. 21
Treatment (20)	9. 58±1. 49	4. 74±1. 42*	50. 52±3. 89*

* P<0.05 compared with the control group

found to be statistically nonsignificant, as shown in Table 6.

4 Discussion

As the incidence of DVT is high worldwide, devising an appropriate treatment for the condition has attracted extensive attention from clinicians and researchers. Traditional therapies, such as anticoagulation, thrombolysis, and thrombectomy, and newer approaches, such as CDT and intravascular stents, have their own advantages and disadvantages. In this study, we retrospectively compared the outcomes of surgical thrombectomy combined with local CDT with those of pure surgical thrombectomy in patients with LDVT. The results of this study showed that the combination of thrombectomy and CDT integrates the advantages of both methods and may make up for the deficiencies of each modality.

Thrombectomy can facilitate a quick recovery and shorten hospital stays. Regarding the treatment of LDVT with CDT, catheter placement is closely related to the effectiveness of the treatment, as well as the risks of thrombolysis-related complications. Sequelae are inevitable in clinical practice, irrespective of the method used to treat the disease. However, if the femoral-iliac vein is recanalized, the swelling and pain in the lower limb can be significantly improved, thereby reducing the degree to which patients' lives and work are disrupted. This benefit may be due to compensatory blood flow through the deep femoral vein. Therefore, the main goal of treating lower limb venous thrombosis is to restore the patency of the femoral-iliac vein. The great saphenous vein has five branches. A Unifuse thrombolytic catheter was inserted into the proximal end of one branch and then directed to the iliac vein, where it served as an indwelling catheter. This approach ensures not only the correct positioning of the catheter but also the patency of the main vessel (the trunk of the great saphenous vein). The Unifuse catheter is a special catheter with a guidewire core and different segmental side holes at its head. Urokinase outflow occurs only via these side holes, which increases the extent and duration of contact between the thrombolytic drug and the thrombus. This unique structure permits the thrombolytic drug to be in full contact with the thrombus and directly perfused into it for a prolonged period of time, thus having a satisfactory thrombolytic effect [24]. Moreover, the use of this technique opens more collateral branches and thus significantly reduces the incidence of complications, such as systemic bleeding, thereby protecting deep

Table 4: Differences in the thigh and calf circumferences between the affected and non-affected limbs in the patient groups at the last follow-up

Group (n)	Before treatment		After treatment	
	Thigh	Calf	Thigh	Calf
Control (14)	5.51±2.36	4.49±2.13	2.57±1.591	1.71±1.24
Treatment (16)	5.68±2.15	4.26±1.89	1.83±1.86 *	1.06±1.05*

*P<0.05 compared with the control group

Table 5: Venous patency scores of the patients in each group at the last follow-up

Group (n)	Before treatment	Last follow-up	Venous patency (%)
Control (14)	9.46±1.52	5.91±1.78	38.81±3.21
Treatment (16)	9.58±1.49	3.74±1.52*	60.52±3.89*

* P<0.05 compared with the control group

Table 6: Comparison of the incidence of adverse reactions after treatment between the patient groups [n (%)]

Group (n)	Death	Stroke	Pulmonary embolism	Allergy	Mild bleeding	Total
Control (20)	0	0	0	0	1 (5%)	1 (5%)
Treatment (20)	0	0	0	0	2 (10%)	2 (10%)

venous valves and preventing additional thrombi. Taken together, these findings indicate that CDT helps reduce the high rate of recurrence after surgical thrombectomy.

In this study, the differences in thigh and calf circumference between the normal and affected limbs in the treatment group were smaller than the corresponding differences in the control group. Moreover, the venous patency score of the treatment group was lower than that of the control group, and the venous patency rate of the treatment group was higher than that of the control group. The beneficial effects of CDT remained evident at three to six months of follow-up. Other researchers have demonstrated the clinical advantages of this treatment over other treatments. For example, two studies showed that CDT can completely dissolve thrombi and relieve clinical symptoms, resulting in more positive long-term effects [25,26]. The results of our study are consistent with the findings of other studies showing that thrombectomy combined with indwelling catheter thrombolysis appears to have positive clinical effects with respect to the treatment of acute LDVT.

Local or systemic hemorrhage is the most important complication of CDT and can be characterized by bleeding into skeletal muscles, genitourinary system bleeding, gastrointestinal hemorrhage (3%), intracranial hemorrhage (<1%), and retroperitoneal hemorrhage (1%) [24]. No patients in this study experienced PE, nor did they experience hemiplegia or other manifestations of intracranial hemorrhage or severe complications, such as anaphylactic shock. Our results are similar to those reported in the literature [18] and are demonstrative of the safety of CDT. Therefore, surgical thrombectomy combined with indwelling catheter thrombolysis appears to be a safe and effective treatment for acute LDVT that can effectively prevent postoperative re-thrombosis and reduce the incidence of LDVT sequelae.

This study had a limitation. As this was a single-center retrospective study with a small sample size, bias may have affected its outcome. To address this issue, additional investigations with prospective multi-center study designs and larger sample sizes are needed.

In conclusion, thrombectomy combined with indwelling catheter thrombolysis is more effective than pure thrombectomy for the treatment of acute LDVT. The results of this study serve as additional evidence supporting the clinical use of thrombectomy combined with indwelling catheter thrombolysis for the treatment of LDVT.

Conflicts of interest: The authors declare no conflicts of interest regarding the publication of this manuscript.

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