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Original Article

Clinical efficacy of the combined use of inferior vena cava filter and catheter-directed thrombolysis in treating lower extremity deep venous thrombosis and the effect of this method on the level of inflammatory factors

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Abstract: Objective: We aimed to investigate the efficacy of the combined use of inferior vena cava filter (IVCF) and catheter-directed thrombolysis (CDT) in treating deep venous thrombosis (DVT) of lower extremity and the effect of this method on the level of inflammatory factors. Methods: A total of 112 patients with lower extremity DVT were selected as subjects and randomized to either a control group or an observation group of 56 cases each. Patients in the control group received antegrade thrombolysis via dorsal superficial vein of foot, and patients in the observation group were implanted with inferior vena cava filter in combination with CDT. The clinical efficacy, swelling reduction in lower extremity, levels of C-reactive protein and interleukin-6 in peripheral venous blood, and incidence of adverse reactions were compared between the two groups. Results: The observation group achieved better results in terms of efficacy and swelling reduction than the control group, and the levels of inflammatory factors and incidence of pulmonary embolism were lower in the observation group than those in the control group (all $P<0.05$). Conclusion: The combined use of IVCF and CDT can significantly improve the clinical outcome in treating lower extremity deep venous thrombosis and can decrease inflammation and incidence of lower extremity edema, which can be recommended for clinical application.

Keywords: Inferior vena cava filter, catheter-directed thrombolysis, lower extremity deep venous thrombosis, inflammatory factor, clinical efficacy

Introduction

Lower extremity deep venous thrombosis (DVT) is a common critical illness in vascular surgery, with morbidity of about 117 in every one million people. The high-risk factors of this disease include trauma, immobilization after orthopedic surgery, tumor, and senility [1, 2]. In the treatment of lower extremity DVT, effective measures need to be taken in a timely manner, otherwise, venous return can be obstructed leading to limb swelling, muscular tension increase, muscle soreness, and motor and sensory dysfunction; in some severe cases, thrombus can be detached from the wall and move its way back to the lung to induce acute pulmonary embolism (PE) [3-5]. Moreover, the residual thrombus on the vessel wall, even though will not cause acute PE, can be organized in the vessel wall, which eventually leads to venous valve dysfunction and various symptoms [6, 7]. Currently, anticoagulant and thrombolytic therapies are common methods for treating lower extremity DVT, however, the potential risk of PE induced by autolysis of blood clot still exists [8, 9].

Some studies have shown that the occurrence of DVT is closely associated with the levels of inflammatory factors [10]. The inflammatory response can damage intima of vein, while intima damage can trigger clot reaction, leading to thrombosis. Moreover, thrombosis can aggravate the inflammatory response in the body, thus further accelerating the formation of thrombus [11]. C-reactive protein (CRP) and interleukin (IL)-6 are two essential markers to be monitored for assessing the inflammatory

conditions in patients; reduction in the levels of these markers can suggest that the therapy can alleviate the inflammatory response, which, as a result, slows down the occurrence and progression of thrombus [12].

Catheter-directed thrombolysis (CDT) has been found to be an effective method for treating arterial thrombosis, while the use of inferior vena cava filter (IVCF) in conjunction with CDT can effectively prevent deep vein thrombus from entering the pulmonary circulation, thereby achieving good clinical outcome [13]. In this study, we investigated the efficacy of the combined use of CDT and IVCF in treating patients with lower extremity DVT and the effect of this method on the levels of inflammatory factors, in order to provide more theoretical basis and find out new intervention target for the treatment of this disease.

Materials and methods

Baseline data

This study was a prospective, randomized, single-center, double-blinded, controlled trial. A total of 112 patients treated in Dezhou Municiple Hospital between January 2016 and December 2018 for lower extremity DVT were selected as subjects and were assigned to either a control group or an observation group according to a random number table.

Inclusion criteria were as follows: 1) Patients with lower extremity DVT as confirmed by anterograde phlebography; 2) Patients with no pulmonary embolism as examined by pulmonary angiography; 3) The onset was within one week.

Exclusion criteria: 1) Patients who had contraindications associated with anticoagulation, thrombolysis, and the use of catheters and filters; 2) Patients' venous thrombus was located in femoral vein or iliac vein; 3) Patients with coagulation disorder; 4) Patients who had infection over the past two weeks; 5) Patients who need to take glucocorticoid for immune diseases; 6) Patients who had tumor; 7) Patients with brain or cardiovascular diseases; 8) Patients with liver or kidney dysfunction.

Informed consent was obtained from all participants and the study was approved by the Ethics Committee of Dezhou Municiple Hospital.

Treatment methods

Treatment in the control group: Antegrade thrombolysis was performed in the control group. Urokinase for thrombolysis was administered to the patients at a dosage of 250,000-750,000 IU per day for 3-5 days. Pressure was applied over the ankle joint and below the knee joint by tourniquet to block the blood flow in superficial vein, and urokinase was micro-pumped via dorsal vein of foot for anticoagulation, meanwhile low-molecular-weight heparin and warfarin was also given. The drug dosage was adjusted based on the levels of coagulation markers.

Treatment in the observation group: In the observation group, IVCF implantation combined with CDT was carried out for thrombolysis. The recyclable IVCF complied with the relevant standards. During the procedure, local anesthesia was performed using 1% lidocaine, and femoral vein on the unaffected side was punctured using the Seldinger technique to implant the sheath (model 5F). Phlebography of inferior vena cava was conducted to locate the opening of the deep vein on both sides followed by placement of the filter. The popliteal vein on the affected side was then punctured using the Seldinger technique guided by color Doppler ultrasound, and the catheter sheath and wire were placed. Next, the infusion catheter was implanted and secured. During CDT, urokinase was continuously infused for 24 hours at a dosage of 50 IU/day until the thrombus was almost or completely dissolved. The duration of catheter placement was no more than two weeks [14].

Outcome measures

Main outcome measures: The main outcome measures included percentage of swelling reduction, clinical efficacy, and incidence of adverse reactions.

The percentage of swelling reduction in the two groups was calculated with the formula as follows: (circumference of the affected limb before treatment - circumference of the affected limb after treatment)/circumference of the affected limb before treatment ×100%.

Clinical efficacy was assessed after treatment and was classified into the following four levels

[15]. The efficacy was considered as excellent, if the circumference, tension, and range of motion of the affected limb became normal, the difference in circumference between the affected and unaffected limbs was no more than 1 cm, the blood flow was restored, no abnormal collateral vessel or no residual contrast agent was observed, and the inner wall of the blood vessel was smooth. The efficacy was considered as good, if the tension and range of motion of the affected limb became normal, the difference in the circumference between the affected and unaffected limbs was between 1.0 and 1.5 cm, the blood flow was partially restored, and a small amount of collateral vessel existed. The efficacy was regarded as fair, if the tension and range of motion of the affected limb became normal, the difference in the circumference between the affected and unaffected limbs was no less than 1.5 cm, many collateral vessels were present, a small amount of residual contrast media existed, and the vessel wall was rough. If the clinical results did not match any of the above criteria, the efficacy was regarded as poor. Total effective rate = total number of cases with excellent, good, or fair results/total number of cases in the group ×100%.

The incidence of pulmonary embolism was compared between the two groups. After treatment, each individual underwent pulmonary angiography for detecting the presence of embolism in pulmonary artery.

Secondary outcome measures: Variations in the levels of inflammatory factors after treatment were compared between the two groups. The peripheral venous blood before and three days after treatment were obtained (5-7 mL) and placed in anticoagulant tubes for centrifugation at 3,000 rpm. The supernatant was collected and kept at -80°C. The serum levels of IL-6 and CRP were detected using an ELISA kit (Santa, USA) and a microplate reader (Infinite F50, Tecan, Switzerland) according to the manufacturer's instructions.

Statistical analysis

SPSS 20.0 software was applied for the statistical analysis. Measurement data are expressed as mean ± sd. The comparisons between groups were performed by independent samples t-test and the comparison between pre and post-treatment within a group was performed by paired t-test. Count data were compared by χ^2 test. $P<0.05$ indicated a statistically significant difference.

Results

Baseline data

All patients displayed noticeable symptoms, including swelling in lower extremity, local cyanosis, and pain. No intergroup differences in the baseline data such as age, gender, course of the disease, and location of thrombus were observed (all $P>0.05$), indicating that the results of the two groups are comparable. See **Table 1**.

Swelling reduction in the affected limbs

Both groups had similar circumferences of the thigh and cnemis before treatment (both $P>0.05$). After treatment, the circumferences of the affected limbs reduced in both groups, while the magnitude of decrease in the observation group was greater than that in the control group ($P<0.05$). Meanwhile, the swelling reduction in the thigh and cnemis in the observation group was greater than that in the control group, suggesting that the combined use of IVCF and CDT helped to reduce swelling in the affected limbs of patients with lower extremity DVT (both $P<0.05$). See **Table 2**.

Changes in the levels of inflammatory factors

No intergroup differences in the serum levels of CRP and IL-6 were observed before treatment (both $P>0.05$). After treatment, both groups experienced reductions in the levels of these markers, and the observation group had a greater magnitude of decreases than the control group (both $P<0.05$), revealing that the use of IVCF combined with CDT could markedly lower the content of serum inflammatory factors in treating lower extremity DVT. See **Figures 1** and **2**.

Efficacy

The results showed that the clinical efficacy in the observation group was better than that in the control group ($P<0.05$), revealing that the combined use of IVCF and CDT could improve the clinical outcome of patients with lower extremity DVT. See **Table 3**.

Table 1. Baseline data in the two groups

Item	Control group	Observation group	t/χ^2	P
Gender (male/female)	38/18	36/20	0.040	0.842
Age (year)	58.13±9.45	58.32±9.87	0.104	0.917
Course of disease (day)	3.58±0.81	3.63±0.79	0.331	0.742
Limbs affected				
Both limbs	2	3	0.679	0.712
Left limb	38	34		
Right limb	16	19		
Complication				
Diabetes	5	7	0.093	0.76
High blood pressure	9	6	0.351	0.553
BMI	25.50±2.11	24.99±2.06	1.294	0.198
Height (cm)	170.20±22.34	169.87±23.91	0.075	0.940
Location of thrombus				
Both limbs	2	3	0.679	0.712
Left limb	38	34		
Right limb	16	19		
Cause of DVT				
Fracture	12	14	0.635	0.888
Immobilization after orthopedic surgery	20	22		
Child delivery	4	3		
Immobilization after other surgeries	20	17		

Note: BMI, body mass index; DVT, deep venous thrombosis.

Table 2. Swelling reduction in the two groups

	Circumference of thigh (cm)		Circumference of cnemis (cm)		Swelling reduction rate of thigh	Swelling reduction rate of cnemis
	Before treatment	After treatment	Before treatment	After treatment		
Control group	8.76±2.01	2.78±0.68*	4.89±1.29	2.46±0.89*	79.12±5.52	77.38±4.81
Observation group	8.68±1.99	1.22±0.59***	4.76±1.83	1.33±0.75***	88.56±5.34	89.82±4.01
t	0.212	12.967	0.434	7.266	9.198	14.866
P	0.833	<0.001	0.665	<0.001	<0.001	<0.001

Note: *P<0.05 vs. the control group before treatment; ***P<0.001 vs. the observation group before treatment.

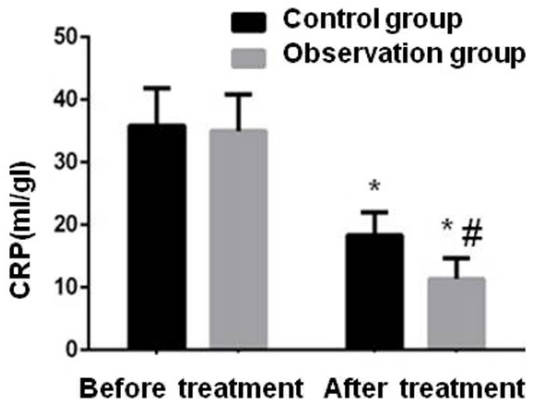

Figure 1. CRP level in the two groups. *P<0.05 vs. before treatment; #P<0.05 vs. the control group after treatment. CRP, C-reactive protein.

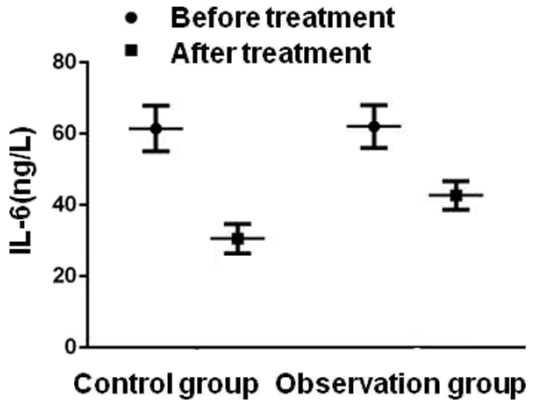

Figure 2. IL-6 level in the two groups. *P<0.05 vs. before treatment; #P<0.05 vs. the control group after treatment. IL, interleukin.

Table 3. Efficacy in the two groups

	Excellent	Good	Fair	Poor	Total number of effective treatments
Control group	30	15	6	5	51
Observation group	15	15	10	16	40
χ^2				5.861	
P				0.015	

Incidence of pulmonary embolism

The control group had a higher incidence of pulmonary embolism than the observation group (8 vs. 1, χ^2=4.350, P=0.037), suggesting that the implantation of IVCF could effectively prevent the break off of the blood clot, thus reducing the incidence of pulmonary embolism.

Discussion

Disturbance in the equilibrium between coagulation and anticoagulation is the major mechanism behind lower extremity DVT, and slow venous blood flow, damage to the blood vessel inner wall, and hypercoagulation are believed to be main factors of venous thrombosis [16]. Thus, measures against these factors are considered as interventions to prevent thrombosis. The occurrence of DVT can induce pulmonary embolism, which has a mortality rate of 10%. Some studies have shown that up to 90% of the emboli in patients with pulmonary embolism come from the deep vein of the lower extremity [17, 18]. Thus, it is of great clinical significance to find an effective treatment for lower extremity DVT.

Anticoagulation therapy is often applied for relieving the symptoms in the acute phase of lower extremity DVT, but the method cannot achieve good results for treating thrombus. Having an effective way to remove blood vessel occlusion caused by thrombus is essential for treating DVT. Previous studies have confirmed that anticoagulation combined with thrombolysis can achieve better clinical outcome in patients, and the results of our study displayed that the symptoms of the patients in the control group were alleviated to varying degrees and the effective rate reached 70%, which was consistent with the previous studies [19]. However, the combination of anticoagulation and thrombolysis cannot effectively prevent thrombus detachment, and risk of pulmonary embolism still exists. Moreover, due to poor blood flow of local vein, thrombolytic drugs can not completely reach the thrombus, thus affecting the therapeutic effect.

In the treatment with IVCF implantation combined with CDT, the potential risks of PE caused by blood clot break off can be prevented effectively, and the clots can be dissolved precisely directed by a catheter. Thus, this technique can make up for the shortcomings of anticoagulant therapy and improve clinical efficacy. In our study, the observation group achieved better results than the control group in terms of swelling reduction, recovery of circumference of thigh and cnemis, and effective rate, indicating that the IVCF implantation combined with CDT can improve the clinical outcome in treating lower extremity DVT. This finding aligns with the results of other studies [20, 21].

It has been reported that both CRP and IL-6 participate in the process of thrombosis. CRP can stimulate monocytes to release tissue factors, thereby triggering coagulation in the body to induce thrombosis. IL-6 causes thrombosis by increasing the levels of various coagulants and decreasing the levels of thrombin inhibitors such as thrombase. Moreover, the formation of thrombus can further aggravate the inflammatory response, thus accelerating thrombosis [22, 23]. As a result, both CRP and IL-6 can serve as essential markers in evaluating the efficacy of DVT treatment. In our study, the levels of CRP and IL-6 decreased in both groups after treatment, but the magnitude of decrease in the observation group was higher than that in the control group, revealing that the IVCF implantation combined with CDT can effectively reduce the inflammatory factor level and improve the clinical outcome. This result is consistent with the results of other studies [24].

In conclusion, the combined use of IVCF and CDT can alleviate inflammation in the body, increase the swelling reduction in the affected limbs, restore the limb circumference, and achieve good clinical outcome, which can be recommended for clinical application. However, since the study was a singer center trial with small sample size, a multi-center clinical trial with a larger sample size needs to be carried out for further verification. Also, follow up need

to be conducted and adverse effects related to IVCF implantation and CDT need to be investigated in the future studies.

Disclosure of conflict of interest

None.

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References

[1] Gong M, Zhao B, He X, Gu J and Chen G. Feasibility of low-dose infusion of alteplase for unsuccessful thrombolysis with urokinase in deep venous thrombosis. Exp Ther Med 2019; 18: 3667-3674.

[2] Nguyen KP, Weber J, Samuel R and Moneta GL. Prospective study comparing the rate of deep venous thrombosis of complete and incomplete lower extremity venous duplex ultrasound examinations. J Vasc Surg Venous Lymphat Disord 2019; 7: 882-888.

[3] Liberman AL, Merkler AE, Gialdini G, Messé SR, Lerario MP, Murthy SB, Kamel H and Navi BB. Risk of pulmonary embolism after cerebral venous thrombosis. Stroke 2017; 48: 563-567.

[4] Fang MC, Fan D, Sung SH, Witt DM, Schmelzer JR, Williams MS, Yale SH, Baumgartner C and Go AS. Treatment and outcomes of acute pulmonary embolism and deep venous thrombosis: the CVRN VTE study. Am J Med 2019; 132: 1450-1457, e1.

[5] Tapson VF, Hazelton JP, Myers J, Robertson C, Gilani R, Dunn JA, Bukur M, Croce MA, Peick A, West S, Lottenberg L, Doucet J, Miller PR, Crookes B, Gandhi RR, Croft CA, Manasia A, Hoey BA, Lieberman H, Guillamondegui OD, Novack V, Piazza G and Goldhaber SZ. Evaluation of a device combining an inferior vena cava filter and a central venous catheter for preventing pulmonary embolism among critically Ill trauma patients. J Vasc Interv Radiol 2017; 28: 1248-1254.

[6] Rokosh RS, Ranganath N, Yau P, Rockman C, Sadek M, Berland T, Jacobowitz G, Berger J and Maldonado TS. High prevalence and mortality associated with upper extremity deep venous thrombosis in hospitalized patients at a tertiary care center. Ann Vasc Surg 2019; [Epub ahead of print].

[7] Hong J, Lee JH, Lee JY, Lee JO, Choi WI, Ahn S, Lim YH, Bang SM and Oh D. Prominent seasonal variation in pulmonary embolism than deep vein thrombosis incidence: a Korean venous thrombosis epidemiology study. Korean J Intern Med 2019; [Epub ahead of print].

[8] Hinojosa CA, Olivares-Cruz S, Laparra-Escareno H, Gomez-Arcive Z and Anaya-Ayala JE. Incidence of thrombotic events and complications associated to inferior vena cava filters in patients with and without anticoagulation therapy. Arch Cardiol Mex 2019; 89: 216-221.

[9] Ascher E, Chait J, Pavalonis A, Marks N, Hingorani A and Kibrik P. Fast-track thrombolysis protocol: a single-session approach for acute iliofemoral deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2019; 7: 773-780.

[10] Rabinovich A, Cohen JM, Cushman M and Kahn SR; BioSOX Investigators. Association between inflammation biomarkers, anatomic extent of deep venous thrombosis, and venous symptoms after deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2015; 3: 347-353, e1.

[11] Jiang J, Tu J, Jia Z, Chen J, Cao H, Meng Q, Fuller TA and Tian F. Incidence and outcomes of inferior vena cava filter thrombus during catheter-directed thrombolysis for proximal deep venous thrombosis. Ann Vasc Surg 2017; 38: 305-309.

[12] Zhang T, Li Q, Wang L and Li G. Expression variations and clinical significance of MMP-1, MMP-2 and inflammatory factors in serum of patients with deep venous thrombosis of lower extremity. Exp Ther Med 2019; 17: 181-186.

[13] Wojtowicz D, Cholewa D, Faba AM, Domanska B, Kokoszka J, Kopacz K, Ficek R, Irzyniec T, Rotkegel SE and Chudek J. Diabetes decreases patency of tunneled catheters in hemodialysis patients after first effective thrombolysis with urokinase. Ren Fail 2018; 40: 384-389.

[14] Branchford BR and Carpenter SL. The role of inflammation in venous thromboembolism. Front Pediatr 2018; 6: 142.

[15] Mesters RM, Mikoteit T, Schiller M, Krings W, Ostermann H and Kienast J. Markers of coagulation activation for evaluation of the antithrombotic efficacy of heparin: a prospective study in acute deep venous thrombosis. Blood Coagul Fibrinolysis 1995; 6: 665-71.

[16] Shimizu Y, Tsuchiya K and Fujisawa H. Deep venous thrombosis with decreased cerebral blood flow to the thalamus was completely restored by factor Xa inhibitor. J Stroke Cerebrovasc Dis 2019; 28: e39-e43.

[17] Renczes J and Lindhoff-Last E. Modern treatment of deep vein thrombosis and pulmonary embolism. Internist (Berl) 2019; 60: 644-655.

[18] Karageorgiou J, Fowler K, Vedantham S and Saad N. Endovascular intervention for deep ve-

nous thrombosis in patients with inferior vena cava filters. Vascular Medicine 2016; 21: 459-466.
[19] Bloom AI, Farkas A, Kalish Y, Elchalal U and Spectre G. Pharmacomechanical catheter-directed thrombolysis for pregnancy-related iliofemoral deep vein thrombosis. J Vasc Interv Radiol 2015; 26: 992-1000.
[20] Stein PD, Matta F and Hughes MJ. Continuing use of inferior vena cava filters despite data and recommendations against their use in patients with deep venous thrombosis. Am J Cardiol 2019; 124: 1643-1645.
[21] Kwon SH, Park SH, Oh JH, Song MG and Seo TS. Prophylactic placement of an inferior vena cava filter during aspiration thrombectomy for acute deep venous thrombosis of the lower extremity. Vasc Endovascular Surg 2016; 50: 270-6.
[22] Wu J, Zhu H, Yang G, Wang Y, Wang Y, Zhao S, Zhao M and Peng S. IQCA-TAVV: to explore the effect of P-selectin, GPIIb/IIIa, IL-2, IL-6 and IL-8 on deep venous thrombosis. Oncotarget 2017; 8: 91391-91401.
[23] Kunutsor SK, Seidu S, Blom AW, Khunti K and Laukkanen JA. Serum C-reactive protein increases the risk of venous thromboembolism: a prospective study and meta-analysis of published prospective evidence. Eur J Epidemiol 2017; 32: 657-667.
[24] Nosaka M, Ishida Y, Kimura A, Hama M, Kawaguchi T, Yamamoto H, Kuninaka Y, Shimada E and Kondo T. Immunohistochemical detection of intrathrombotic IL-6 and its application to thrombus age estimation. Int J Legal Med 2015; 129: 1021-5.