Balloon-assisted catheter-directed thrombolysis: A novel approach for acute deep vein thrombosis in the lower extremities

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A B S T R A C T

Background: Deep vein thrombosis (DVT) is a common cardiovascular emergency that may have life-threatening complications, including pulmonary embolism (PE) and post-thrombotic syndrome (PTS). Conventional anticoagulant medication does not completely dissolve the clots and does not decrease the risk of DVT complications. Invasive catheter-directed thrombolysis (CDT) is an approach that has been reported to reduce the reoccurrence of PTS during acute DVT. We compared balloon-assisted CDT with routine CDT in the treatment of acute DVT and evaluated the clinical efficacy and safety of balloon-assisted CDT.

Methods: This retrospective cohort study included 94 patients diagnosed with a first episode of DVT in the lower extremities and treated from September 2008 to February 2018. The patients underwent routine CDT (group A, n = 50) or balloon-assisted CDT (group B, n = 44) based on their enrollment date. We obtained the circumference difference between the limbs, the degree of clot lysis, and the lysis rate as parameters for evaluating the two approaches. The PE incidence and bleeding amount were recorded. We also compared the total urokinase dose, treatment duration, and retrieval rate of optional filters.

Results: Swelling was significantly alleviated in both groups, as indicated by a reduction in the limb circumference. Patients who underwent balloon-assisted CDT exhibited significantly lower thrombus scores compared with the routine group (S = 1403.50, Z = −5.7702, $P < 0.0001$). Additionally, the duration of balloon-assisted CDT was significantly shorter (6 vs. 10 days [S = 1039.0, Z = −8.0358, $P < 0.0001$]). The mean urokinase usage per patient was decreased in the balloon-assisted group ($P < 0.0001$). Bleeding occurred in both groups, with no statistical significance. The filter retrieval rate in the balloon-assisted group was significantly higher than that in the routine CDT group ($X^2 = 4.829, P = 0.028$).

Conclusions: Balloon-assisted CDT is an effective, cost-efficient, and safe method for the treatment of acute DVT. It exhibited advantages over routine CDT, including less lysis medication, decreased procedure duration, and higher patency rates. Inferior vena cava filtration is mandatory in balloon-assisted CDT. After thrombus removal, the risk of symptomatic PE did not increase in this approach.

Introduction

Deep vein thrombosis (DVT) is a prevalent cardiovascular emergency involving blood clot accumulation in the deep veins. It affects approximately 2 million people in the United States and European countries yearly. DVT has been well documented as the major cause of venous thromboembolic diseases, leading to morbidity and mortality. Pulmonary embolism (PE) is one of the life-threatening complications of DVT, with a mortality rate of up to 15%.[1] The long-term complications of DVT include post-thrombotic syndrome (PTS).[2]

The routine treatments for DVT are anticoagulation, compression therapy, and mobilization. Although anticoagulation is beneficial against clot propagation, PE development, and DVT recurrence,[3] it is not helpful in patients with severe and extensive DVTs.[4] The American College of Chest Physicians (CHEST) guidelines suggest that catheter-directed thrombolysis (CDT) can be used to achieve patency in affected vessels and to reduce the risk of PTS development.[2] Percutaneous mechanical thrombectomy (PMT) combined with CDT and ultrasound-accelerated thrombolysis (UAT) are new clinical interventions.[4–8] However, the application of PMT or UAT may induce device-related complications, such as hemolysis, renal failure, bradycardia, and venous valve injuries.[9] In addition, the high clinical costs of PMT or UAT devices limit their worldwide use.

Therefore, to avoid potential device-related complications, we proposed a cost-efficient method, balloon-assisted CDT, for acute DVT in the lower extremities. In this study, we aimed to demonstrate that balloon dilation in the deep veins can fragment thrombi in the lower extremities before CDT. The fragmentation of thrombi can increase the exposed surface area and theoretically enlarge the venous flow for medication. Further, we aimed to evaluate the clinical efficacy and safety of balloon-assisted CDT for thrombolysis and to demonstrate its advantages over routine CDT.

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Methods

Patients

Patients with a first episode of DVT in the lower extremities and who underwent interventional treatment from September 2008 to February 2018 in the First Affiliated Hospital of Soochow University were included in this study. The DVT diagnosis was confirmed by the presence of characteristic clinical manifestations and findings of Doppler ultrasound and/or venographic imaging. Patients who had swelling and/or pain in the lower extremities for <14 days were considered eligible. The exclusion criteria were isolated infrapopliteal DVT; recurrent ipsilateral DVT; a short life expectancy; and contraindications to contrast media, anticoagulation agents, or thrombolytic agents. Patients with the following conditions were also excluded: active internal bleeding, recent cerebrovascular accident, recent serious trauma, recent major surgery (<2 weeks), recent gastrointestinal bleeding, uncontrolled hypertension, pregnancy, allergy to thrombolytic agents, and coagulopathy.

Patients enrolled from September 2008 to December 2004 were treated with routine CDT (group A, n = 50) and those enrolled from January 2015 to February 2018 were treated with balloon-assisted CDT (group B, n = 44). The study was approved by the Institutional Ethics Committee of Soochow University, and all patients signed the informed consent form before participation.

Procedures

For anticoagulation, all patients were prescribed with subcutaneous low-molecular-weight heparin followed by oral warfarin (target international normalized ratio 2.0–3.0). The duration of anticoagulation was >1 year, which was slightly longer than the current guideline recommendations.[2] If the patients were compliant and bleeding was controlled, the treatment was continued. Inferior vena cava (IVC) filters (either retrievable [OptEase, Cordis] or permanent [VenaTech™ LP, B. Braun] filters) were routinely inserted in all patients before routine CDT or balloon-assisted CDT, through the contralateral common femoral vein. The retrievable IVC filters were removed within 2 weeks after placement.

Once the filter was in place, patients undergoing routine CDT were placed in the prone position and venous access was obtained through the ipsilateral popliteal vein under ultrasound guidance. A 6-F vascular sheath (Terumo, Japan) was placed at the puncture site to limit bleeding, and direct venography was performed to estimate the severity and extent of the filling defects. An infusion catheter with multiple side holes (UniFuse™, AngioDynamics) was positioned in the thrombus site, penetrating through the thrombus at the distal end. Once placed, the infusion catheter and sheath were fixed and assembled with a microinjection pump. Urokinase (Tianjin Biochem Pharma Co., Ltd., China) was continuously pumped through the catheter at $(4–10) \times 10^5$ U/24 h (in 50 mL of 0.9% saline). Surveillance venography was performed daily to visualize the thrombolysis and the position of the catheter for throbolysis The treatment was terminated when the following conditions were met: achievement of the maximal benefit as judged by the physician, presence of an increased risk for bleeding, occurrence of major clinical bleeding, or patient decision to terminate treatment.

In the balloon-assisted CDT group, balloon dilators (Φ 12–15 mm) were placed in the lumen of the deep veins (popliteal, femoral, external iliac, and common iliac veins) to fragment thrombi (note: this method different from percutaneous transluminal angioplasty for the treatment of May-Turner syndrome). Thereafter, the infusion catheter was extended to the distal end of the thrombus. If the thrombi migrated into the IVC filter, the infusion catheter was advanced to the filter for thrombolysis. The dosage of urokinase used was the same as that in the routine CDT group.

If the underlying iliac vein stenosis was >50% of the size before CDT at the end of thrombolysis, further adjunctive procedures, including percutaneous transluminal angioplasty and stent (Protege GPS™, ev3)

insertion, were conducted to ensure blood flow. All patients were advised to use knee-high elastic compression stockings (class II) daily for 24 months.

We recorded the parameters of the affected limbs by measuring the thigh at 15 cm above the knee joint and at 10 cm below the tibial tuberosity. We also documented the periprocedural complications.

Assessment of venous recanalization

The degree of clot lysis was retrospectively and blindly evaluated using venography scoring.[10] It was analyzed at nine sites: IVC, common iliac, external iliac, common femoral, proximal femoral, distal femoral, popliteal, tibial, and profunda femoris veins. The veins were categorized according to the degree of thrombus, as follows: grade 0, thrombus-free (normal) segment; grade 1, 1–49% luminal reduction by the thrombus and/or stenosis; grade 2, 50–99% luminal reduction; grade 3, occluded. The lysis rate was calculated using the following formula: lysis rate = (pretreatment thrombus score - posttreatment thrombus score)/-pretreatment score.

Bleeding assessment

Bleeding was classified as major or minor. Bleeding was considered major when it was overt with a decrease of ≥2 g/dL in hemoglobin or when hemorrhage led to transfusion of 2 units of packed red blood cells or whole blood. Bleeding in a critical (intracranial, retroperitoneal, or pericardial) organ, or any life-threatening bleeding, was also defined as major bleeding. Bleeding around the catheter puncture site was considered minor.

Statistical analysis

Data are presented as mean ± standard deviation. The *t*-test was performed for statistical comparison between two groups. Data with a non-normal distribution are described as M (QL, QU), QL = P25, QU = P75, and further analyzed using Wilcoxon's test. Categorical variables were analyzed using the chi-square test.

Results

There was no difference in demographic and clinical characteristics between the two groups (Table 1). The DVT characteristics were similar, including DVT location, median duration since symptom onset, and DVT extension.

Table 1
Patient demographics.

	Group A	Group B
No. of patients	50	44
Sex		
Male	22 (44.0%)	18 (40.9%)
Female	28 (56.0%)	26 (59.0%)
Age (years)	50.3 ± 15.5	52 ± 17
Duration of symptoms (days)	9.73 ± 6.29	8.51 ± 6.50
Affected limbs (no. of patients)		
Left	38 (76.0%)	34 (77.3%)
Right	12 (24.0%)	10 (22.7%)
Site of thrombosis		
Proximal	5 (10.0%)	4 (9.1%)
Mixed	45 (90.0%)	40 (90.9%)
Distal	0 (0%)	0 (0%)
Causes		
Operation	23	24
Not clear	15	21
Trauma	4	4
Tumor	2	1

Limb circumferences

We observed considerable improvement of swelling and pain in the affected limb (100%) at discharge. The difference of thigh circumference between the affected and contralateral limbs decreased from 5.37 ± 1.97 to 2.96 ± 1.10 in group A (t = 8.35, $P < 0.0001$) and from 5.41 ± 2.22 to 1.78 ± 1.40 in group B (t = 12.35 $P < 0.0001$). The difference of calf circumference between the affected and contralateral limbs decreased from 4.14 ± 1.57 to 1.93 ± 0.84 in group A (t = 8.89, $P < 0.0001$) and from 4.05 ± 1.61 to 1.41 ± 1.17 in group B (t = 9.24, $P < 0.0001$) (Table 2).

Venous recanalization

Both treatments exhibited remarkable effects in terms of thrombolysis, with a mean lysis rate of 55.0% in group A and a median lysis rate of 94.5% in group B. The pretreatment thrombus scores did not significantly differ between the two groups (S = 1959.0, Z = −1.5172, $P = 0.1292$). However, at the end point of thrombolytic therapy, the mean thrombus score in group B was significantly lower than that in group A (S = 1403.50, Z = −5.7702, $P < 0.0001$). In addition, the mean CDT duration in group B was significantly shorter than that in group A (6 vs. 10 days [S = 1039.0, Z = −8.0358, $P < 0.0001$]). The total urokinase consumed per patient was less in group B than in group A (Table 3).

Complications

In group A, 19 (38.0%) patients experienced bleeding events. Of them, 1 event was classified as major and the other 18 were minor. The patient with major bleeding developed intracranial hemorrhage 2 days after CDT and died. The minor bleeding events included bleeding at the puncture site (n = 11), gross hematuria (n = 3), bleeding on the skin (n = 3), and blood in phlegm (n = 1). In group B, 10 (22.3%) patients experienced minor bleeding, including bleeding at the puncture site (n = 6), gross hematuria (n = 2), blood in phlegm (n = 1), and hemorrhage in muscle gaps (n = 1). The incidences of bleeding had no significant difference between the two groups ($X^2 = 2.5590$, $P = 0.1097$). No patient in both groups developed symptomatic PE (Table 3).

Retrieval of IVC filters

In group A, permanent filters were inserted in seven patients (one with cervical carcinoma and six with age > 75 years) and retrievable filters were inserted in the other 43 patients. At the end point of thrombolytic therapy, the IVCs failed to be retrieved in five patients owing to a comparatively large residual thrombus in the iliofemoral vein, which had a high risk of detachment and a potential to induce PE. Therefore, the IVC filters were successfully retrieved in 38 patients, with a success rate of 88.37% (38/43). In group B, permanent filters were inserted in five patients (one with ovarian cancer, one with lung cancer, and three with age > 75 years) and retrievable filters were inserted in the other 39 patients. During thrombolysis, there were 12 cases of IVC occlusion (all in retrievable filters). We advanced the infusion catheters into the IVC filters to dissolve the occlusion. The retrieval of IVC filters was successful in all 39 cases (100% success rate), and no clots were observed

Table 2
Circumference difference between the affected and contralateral limbs ($\overline{x} \pm s$; cm).

	Prethrombosis		Post-thrombosis	
	Thigh	Calf	Thigh	Calf
Group A	5.37 ± 1.97*	$4.14 \pm 1.57^{\triangledown}$	2.96 ± 1.10*	$1.93 \pm 0.84^{\triangledown}$
Group B	5.41 ± 2.22**	$4.05 \pm 1.61^{\triangledown\triangledown}$	1.78 ± 1.40**	$1.41 \pm 1.17^{\triangledown\triangledown}$

*t = 8.35, $P < 0.0001$; **t = 12.35, $P < 0.0001$; $^{\triangledown}$ t = 8.89, $P < 0.0001$; $^{\triangledown\triangledown}$ t = 9.24, $P < 0.0001$.

Table 3
Summary of thrombosis outcomes and complications.

	Group A	Group B	*P* value
Thrombus score prethrombolytic treatment	9 (8, 10)	8.3 (7, 10)	0.1922
Thrombus score post-thrombolytic treatment	3.5 (2, 5)	0 (0, 1)	<0.0001
Percentage of thrombus resolution (%)	55.0 (42.3, 72.4)	94.5 (88.5, 100)	<0.0001
Duration of CDT (days)	10 (9, 12)	6 (5, 7)	<0.0001
Total dosage of urokinase used per patient (units)	$5.950 (5.525, 7.225) \times 10^6$ U	$4.100 (3.600, 5.050) \times 10^6$ U	<0.0001
Bleeding complications (% of patients)	38.0% (19/50)	22.3% (10/44)	0.1097
Major bleeding (incidence)	1	0	–
Minor bleeding (incidence)	18	10	–
Incidence of pulmonary embolism	0	0	–

within the filters. The filter retrieval rate in group B was significantly higher than that in group A ($X^2 = 4.829$, $P = 0.028$).

Discussion

Routine DVT treatment focuses on conventional anticoagulation to prevent PE occurrence and thrombus propagation. However, anticoagulation is not effective for severe thrombus formation. The CHEST guidelines indicate that CDT increases the opening of the affected tract and may reduce the incidence of PTS.[2] In 2012, an open-label, randomized trial compared CDT and standard venous treatment in acute iliofemoral DVT (CaVenT study). The authors found that CDT reduced the PTS risk by 14% in comparison with routine treatment.[11] However, CDT should be used with caution owing to the long treatment duration and associated complications. Previous studies reported that major bleeding occurred in 11–20% of patients treated with CDT.[10,11] In recent years, medical technological devices (PMT, UAT, and PCDT) have been used to overcome the limitations of CDT.[6,12] However, the disadvantages of current approaches include the potential development of hemolysis, renal failure, bradycardia, venous valve damage, and/or endothelial damage.[12] In addition, those devices are expensive.

Therefore, to avoid potential device-related complications, we proposed a novel and cost-efficient technique (balloon-assisted CDT) for the treatment of acute DVT in the lower extremities. The main novelty of balloon-assisted CDT lies in the application of balloon dilation in the lumen of deep veins to fragment the thrombi into small pieces (using an infusion catheter) before thrombolysis, which theoretically increases the exposed surface area and enlarges the venous patency. We demonstrated that balloon-assisted CDT had significantly better performance in terms of less urokinase use, shorter infusion duration, and more effective thrombolysis.

In our study, the medians of infusion time were 10 days in group A and 6 days in group B, which were slightly longer than the previously reported infusion time of 6 days in the CaVenT study.[11] This may be related to the late intervention, low investigation frequency, and low urokinase dose in our study. The patients underwent thrombolysis at 9.73 days after the onset of symptoms in group A and at 8.51 days in group B, and our patients had longer symptom durations than those in the previous study.[9,11] It has been reported that acute thrombi had a better response rate to thrombolysis than established DVTs, as thrombi stabilize over time.[13] As a result, late intervention may increase the difficulty of removing the thrombi. In this study, lysis was performed daily instead of every 6–8 h. Therefore, the record frequency may prolong the lysis duration. There is no global standard procedure for CDT, and the approaches are selected according to clinical experience.[2] In our study, the patients were treated with urokinase at $(4–10) \times 10^5$ U/24 h, according to the recommended dose 6×10^5 U/24 h.[14] However, recombinant tissue plasminogen activator is preferred in other countries.[11,15] The dose

of urokinase is much higher in other countries (e.g., 100,000–240,000 units/h).[16] A low dosage of urokinase may contribute to a long infusion time. Although both routine CDT and balloon-assisted CDT had a longer infusion time than that in the CaVenT study, balloon-assisted CDT had significant advantages in terms of effective thrombolysis, reduced urokinase usage, and shortened infusion time.

We found that bleeding is the complication of thrombolysis in both approaches. One patient, who had a medical history of cerebral trauma, developed intracranial hemorrhage. A circumspect review of medical history and an objective investigation of patients are crucial with respect to the administration of thrombolytic agents. Most of the bleeding events occurred at the puncture sites and were mainly caused by multiple punctures for popliteal vein access. This result indicated that ensuring one successful venous puncture may reduce the incidence of minor bleeding.

The use of balloon-assisted CDT for DVT management has the inherent risk of inducing PE. In our study, 12 of 44 (27.3%) patients experienced IVC filter embolization in the balloon-assisted group, whereas no symptomatic PE occurred. Complete lysis inside the IVCs was achieved in all 12 patients, and the retrieval of optional IVC filters was successful in all cases. Two intrinsic characteristics of acute DVT make filter embolization a transient phenomenon during balloon-assisted CDT. First, the thrombus segments captured in IVCs are newly formed and not yet stabilized in acute DVT patients; thus, they are easy to lyse.[13] Second, in acute DVT patients, blood still consistently flows through the IVC via the contralateral iliac vein. The blood fibrinolytic system prevents the formation of IVC embolization and, in turn, facilitates thrombolysis at the IVC site. Therefore, we recommend that IVC filtration should be mandatory in balloon-assisted CDT to prevent PE. After IVC clearance, balloon-assisted CDT with IVC filter placement does not increase the occurrence of symptomatic PE.

Our study had several limitations. This study was a single-center retrospective study involving a small sample population rather than a double-blind prospective randomized case-controlled trial. The patients were categorized according to the onset of symptoms but were not randomized at the same time. PTS and quality of life were not evaluated during the follow-up. The encouraging results demonstrating the advantages of balloon-assisted CDT during thrombolytic therapy require further large-scale prospective evaluation.

In conclusion, balloon-assisted CDT is a novel, cost-efficient, and promising modality for the treatment of acute DVT in the lower extremities.

Declaration of competing interest

The authors declare no conflict of interest.

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