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Safety and efficacy of pharmacomechanical thrombolysis for acute and subacute deep vein thrombosis patients with relative contraindications

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Abstract

To evaluate the safety and efficacy of pharmacomechanical thrombolysis (PMT) performed for patients with relative contraindications.

From June 2014 to December 2016, 112 patients with acute or subacute proximal deep vein thrombosis (DVT) were enrolled in this study. 60 patients (including 27 acute DVT patients and 33 subacute DVT patients) were treated with catheter-directed thrombolysis (CDT), and 52 patients with relative contraindications (including 25 acute DVT patients and 27 subacute DVT patients) with PMT. Assessment of venous recanalization was conducted using venography the time Inferior vena cava filter is removed, and complications were used to compare safety and efficacy between the groups.

The outcomes of acute DVT patients no matter which kind of therapy performed, CDT or PMT, were significant better than subacute DVT patients (P_{CDT} = .04 and P_{PMT} = .01). However, there was no significant difference between CDT acute group and PMT acute group or between CDT subacute group and PMT subacute group (P_{acute} = .80 and $P_{subacute}$ = .84). For complications of all patients, there was no mortality and major bleeding occurred.

PMT could be a safe and effective management for DVT patients with relative contraindications, and the acute DVT may achieve better outcomes when they receive CDT or PMT.

Abbreviations: CDT = catheter-directed thrombolysis, DVT = deep vein thrombosis, PMT = pharmacomechanical thrombolysis, PTA = percutaneous angioplasty, SAH = subaraclmoid hemorrhage.

Keywords: catheter-directed thrombolysis, deep vein thrombosis, efficacy, pharmacomechanical thrombectomy, safety

1. Introduction

Deep vein thrombosis (DVT) is a common cardiovascular condition with an incidence of approximately 1 to 2 per 1000 persons per year,[1,2] which is considered to be a significant source of mortality and morbidity.[3] Anticoagulation is the standard management for DVT to prevent pulmonary embolism and recurrence of DVT,[4] however its ineffectiveness at thrombus removal may prolong venous obstruction which may lead to post-thrombotic syndrome (PTS) even long-term morbidity.[5] Furthermore, there are 25% to 40% patients with DVT developing PTS within 2 years of the DVT episode,[6,7] which may not only lead to high economic burden but also significantly reduce patients' quality of lives.[8,9] Especially iliofemoral or iliocaval DVT, with proportion up to 28% to 38%, may be related to more risk of pulmonary embolism and worse risk of PTS.[10]

So far, catheter-directed thrombolysis (CDT) has been demonstrated to be an excellent way to effectively remove thrombus and significantly reduce the risk of PTS.[11–13] However, CDT could be chosen to treat for only selected patients with iliofemoral DVT symptoms for <14 days, good functional status, life expectancy of >1 year, and low risk of bleeding.[14] For patients with relative contraindications such as major trauma, major surgery, or aging patients,[15] pharmacomechanical thrombolysis (PMT) may be a better option.

Based on former studies and our clinical experiment, this study was carried out aiming to evaluate safety and efficacy of PMT performed for patients with relative contraindications.

2. Materials and methods

This study was approved by the Institutional Committee of Ethics in Research. From June 2014 to December 2016, consecutive patients with DVT in Third Hospital of Hebei Medical University were prospectively enrolled in this study. Patients were included based on the following criterions:

1) with a definite diagnose of unilateral iliofemoral or iliocaval DVT diagnosed using color duplex ultrasound imaging or ascending venography;

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XL and PC contributed equally to this work.

The authors have no conflicts of interest to disclose.

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2) acute DVT (<15 days) or subacute DVT (15–30 days);
3) informed consent form obtained. CDT was chosen for treating patients with iliofemoral DVT symptoms, good functional status, age <70 and low risk of bleeding.
4) Moreover, based on the Clinical Practice Guideline of the Society for Vascular Surgery and the American Venous Forum as well as American College of Chest Physicians Guidelines on Antithrombotic Therapy, PMT was chosen for treating patients with contraindications defined as recent cerebrovascular event (including transient ischemic attacks), neurosurgery (intracranial, spinal), or intracranial trauma (<3 months); recent major surgery, obstetrical delivery, or major trauma (<10 days);and age >70.[14–16]

Low-molecular-weight heparin (LMWH) was routinely administered for each patient daily after admission and interventional therapies were performed as soon as possible. Inferior vena cava filter insertions were performed to prevent fatal pulmonary embolism. Balloon dilation and stent implantation would be performed after thrombolysis if there was an underlying iliac vein stenosis greater than 50% or occlusion. Postoperative systematic anticoagulant would be utilized for 3 to 6 months generally and it may extend to 6 to 12 months if iliac vein stent was implanted.

2.1. Interventional therapy

2.1.1. CDT. Percutaneous access was performed through popliteal vein or posterior tibial vein under guidance of ultrasound or veinography. A 5F or 6F sheath was inserted and ascending venography was obtained to examine the extent and location of thrombus after puncture. A suitable multiple-sidehole infusion catheter was chosen and placed within the thrombosis vessel with the aid of fluoroscopy. Urokinase was infused through catheter at a dose of 200,000 U within 15 to 20 minutes intraoperatively, which would continue to be infused at a rate of 600,000 U to 1200,000 U per day postoperatively. Unfractionated heparin was infused simultaneously through the access sheath at a dose of 125 U/h to prevent thrombus formation. The activated partial thromboplastin time (aPTT), hemoglobin, fibrinogen level, and platelet count were examined every 4 to 8 hours. Moreover, venography was performed via the sheath daily, based on types and doses of anticoagulation were modified. (Fig. 1)

2.1.2. AngioJet Ultra Thrombectomy. AngioJet system was performed by standard procedure. AngioJet catheter was inserted into the thrombosis vessel through the guide wire and thrombolytic therapy (200,000 U urokinase per 50 mL saline) was infused for 20 minutes. Then PMT was performed as catheter's first Mark near the thrombosis vessel at a rate of 2 mm/s.

In each procedure, percutaneous angioplasty (PTA) was performed when significant stenosis existed. And if there was residual stenosis of over 70% after repeat PTA, stenting could be adapted. (Fig. 2)

2.1.3. Assessment of venous recanalization. The outcome assessments were conducted by using venography the time Inferior vena cava filter being removed. Definition of successful recanalization is that residual thrombus has no influence on patency after clot lysis. The results of thrombolysis based on the residual thrombus in venous including popliteal vein, femoral vein, external iliac vein, and iliac vein, which were categorized as follows: level I means total length or multi-segment cumulative length of residual thrombus less than 1 cm with no influence on patency; level II means total length or multi-segment cumulative length of residual thrombus was more than 1 cm and less than 2

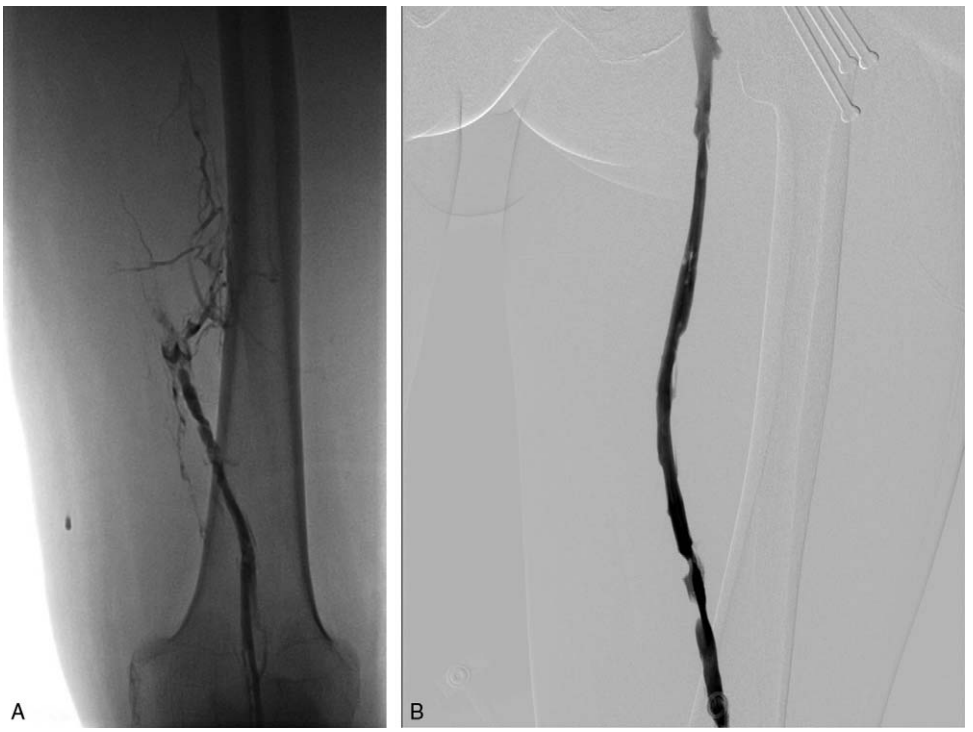

Figure 1. A 49-year-old man, who received internal fixation treatment for right femoral neck fracture 22 days ago, was diagnosed as subacute proximal DVT based on color duplex ultrasound imaging. It was confirmed by ascending venography, and CDT was performed after IVC implantation. (a) Initial venography revealed irregular stenosis of right superficial femoral vein. (b) After 5-day CDT treatment, venography was performed and there was almost no irregular stenosis except a residual thrombus less than 2 cm. This patient achieved successful recanalization with level II after treatment. CDT = catheter-directed thrombolysis, DVT = deep vein thrombosis, IVC = inferior vena cava.

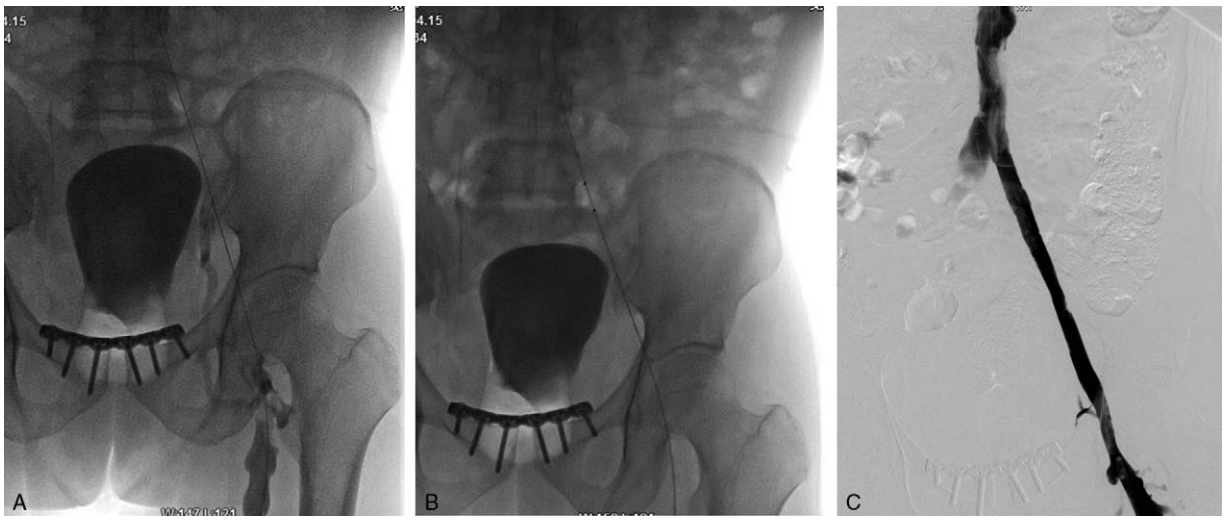

Figure 2. A 45-year-old man, with an internal fixation treatment for pelvic fracture 12 days ago, was identified as acute iliofemoral DVT diagnosed by color duplex ultrasound imaging. After IVC implantation pharmacomechanical thrombectomy was performed in prone position. (a) Initial venography revealed acute iliofemoral DVT. (b) The catheter progressed across the iliofemoral vein thrombotic segment as pharmacomechanical thrombectomy performed. (c) The final venography showed a patent iliofemoral vein, good antegrade flow, and no residual thrombus. That meant level I recanalization. DVT = deep vein thrombosis, IVC = inferior vena cava.

cm with no influence on patency; level III means total length or multi-segment cumulative length of residual thrombus more than 2 cm and less than 3 cm with no influence on patency; level IV means total length or multi-segment cumulative length of residual thrombus more than 3 cm and less than 4 cm with no influence on patency; level V means total length or multi-segment cumulative length of residual thrombus more than 4 cm with a slight influence on patency and the reduction effect with thrombolysis achieved; level VI any length of residual thrombus means significant influence on patency with no reduction effect.

2.2. Complications

The safety outcomes were evaluated by the occurrence of bleeding complications.[17] Major bleeding was defined as obvious bleeding enough leading to death, surgery, cessation of therapy, or blood transfusion including intracranial hemorrhage, gastrointestinal bleeding and retroperitoneal hematoma. It was considered as minor bleeding complications that other less severe bleeding events could be manageable with local compression, sheath upsizing, or dose alterations of a pharmacologic thrombolytic agent anticoagulant, or antiplatelet drug.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY). Continuous data including age and durations were reported as means ± standard deviation, and their significant difference was verified using Student *t* test. Nominal data including clinical characteristics and predisposing factors of patients were reported as the number of subjects and were analyzed using Wilcoxon–Mann–Whitney test. Statistical significance was defined a P value of $<.05$.

3. Results

One hundred twelve patients including 59 males and 53 females were enrolled in our study. 60 patients with 27 acute DVT and 23 subacute DVT were performed with CDT. 52 patients with relative contraindications such as major surgery recently including 25 acute DVT and 27 subacute DVT were treated with PMT.

The demographic information of those groups is listed in Table 1. No significant difference in sex or side was found among the 4 groups. Subacute DVT Patients receiving PMT were significantly older than subacute DVT patients treated with CDT. However

Table 1

Patients demographics.

	CDT(n = 60)		PMT (n = 52)			
	Acute (n = 27)	Subacute (n = 33)	Acute (n = 25)	Subacute (n = 27)	P_{acute}	$P_{subacute}$
Age	59.04 ± 7.23	59.45 ± 6.79	64.40 ± 13.37	65.11 ± 12.99	.08	.03
	$P_{CDT} = 0.82$		$P_{PMT} = 0.84$			
Sex (M/F)	15/12	17/16	14/11	15/12	.97	.75
	$P_{CDT} = 0.75$		$P_{PMT} = 0.97$			
Side (L/R)	17/10	18/15	13/12	15/12	.42	.93
	$P_{CDT} = 0.51$		$P_{PMT} = 0.79$			
Duration	6.44 ± 3.70	20.52 ± 5.30	7.04 ± 3.28	20.15 ± 3.54	.54	.75
	$P_{CDT} = 0.00$		$P_{PMT} = 0.00$			

P_{CDT} presents the difference between CDT acute group and CDT subacute group.
P_{PMT} presents the difference between PMT acute group and PMT subacute group.
P_{acute} presents the difference between CDT acute group and PMT acute group.
$P_{subacute}$ presents the difference between CDT subacute group and PMT subacute group.
CDT = catheter-directed thrombolysis, PMT = pharmacomechanical thrombolysis.

Table 2

Clinical characteristics and predisposing factors of patients.

	CDT (n = 60)		PMT (n = 52)			
	Acute (n = 27)	subacute (n = 33)	Acute (n = 25)	Subacute (n = 27)	P_{acute}	$P_{subacute}$
Smoking	7	5	6	8	.87	.18
	$P_{CDT} = 0.33$		$P_{PMT} = 0.65$			
Immobilization	5	8	6	6	.63	.85
	$P_{CDT} = 0.59$		$P_{PMT} = 0.88$			
Hypertension	10	8	9	11	.94	.17
	$P_{CDT} = 0.28$		$P_{PMT} = 0.73$			
CAD	3	5	3	4	.92	.97
	$P_{CDT} = 0.61$		$P_{PMT} = 0.77$			
Dyslipidemia	11	15	12	10	.60	.51
	$P_{CDT} = 0.71$		$P_{PMT} = 0.42$			
Diabetes	5	7	5	8	.89	.45
	$P_{CDT} = 0.79$		$P_{PMT} = 042$			
Thrombophilia	1	2	0	0	.33	.19
	$P_{CDT} = 0.72$		$P_{PMT} = 1.00$			
May-Thurner syndrome	8	6	9	6	.63	.70
	$P_{CDT} = 0.30$		$P_{PMT} = 0.27$			

P_{CDT} presents the difference between CDT acute group and CDT subacute group.
P_{PMT} presents the difference between PMT acute group and PMT subacute group.
P_{acute} presents the difference between CDT acute group and PMT acute group.
$P_{subacute}$ presents the difference between CDT subacute group and PMT subacute group.
CDT = catheter-directed thrombolysis, PMT = pharmacomechanical thrombolysis.

significant difference was not found for age between acute DVT patients and subacute DVT patients (both CDT and PMT groups). There was no significant difference in durations between CDT acute group and PMT acute group or between CDT subacute group and PMT subacute group. However, durations of CDT subacute group and PMT subacute groups were significantly longer than CDT acute group and PMT acute group.

As listed in Table 2, significant difference was not found in comparison of comorbidities among the groups with respect to hypertension, CAD, dyslipidemia, diabetes, thrombophilia, or May–Thurner syndrome.

Clinical characteristics of patients receiving PMT were listed in Table 3. There was no significant difference between those 2 groups regarding to total knee arthroplasty (TKA), total hip arthroplasty (THA), femoral fracture, pelvic fracture, >70 years, or subaraclmoid hemorrhage.

Table 3

Clinical characteristics of patients received PMT.

	Acute (n = 25)	Subacute (n = 27)	P_{PMT}
TKA	4	3	.61
THA	6	7	.99
femoral fracture	7	6	.63
pelvic fracture	5	5	.89
>70 years	4	5	.81
subaraclmoid hemorrhage	1	3	.34

P_{CDT} presents the difference between CDT acute group and CDT subacute group.
P_{PMT} presents the difference between PMT acute group and PMT subacute group.
P_{acute} presents the difference between CDT acute group and PMT acute group.
$P_{subacute}$ presents the difference between CDT subacute group and PMT subacute group.
CDT = catheter-directed thrombolysis, PMT = pharmacomechanical thrombolysis, THA = total hip arthroplasty, TKA = total knee arthroplasty.

Assessments of venous recanalization were listed in Table 4. The outcomes of acute DVT patients with CDT or PMT were significant better than subacute DVT patients($P_{CDT} = .04$ and $P_{PMT} = .01$). 7 patients (25.9%) of CDT acute group and 10 patients (40.0%) of PMT acute group were level I. Meanwhile, only 2 patients (6.1%) of CDT subacute group and 2 patients (7.4%) of PMT subacute group were level I. However, there was no significant difference between CDT acute group and PMT acute group or between CDT subacute group and PMT subacute group ($P_{acute} = .80$ and $P_{subacute} = .84$).

For complications, there was no mortality and major bleeding occurred in all the patients. Only 1 minor bleeding (intraoperative hemorrhage) happened in the CDT subacute group due to mis-operations. No symptomatic PE was found during the hospitalization.

4. Discussion

The most important finding of our study is that patients with relative contraindications treated by PMT may achieve a similar thrombectory efficacy with regular patients treated by CDT, and the thrombectomy outcomes of acute DVT patients were better than subacute DVT patients in both therapeutic method. Therefore, a better thrombectomy outcome would be achieved is the time PMT applied in acute phase for iliofemoral or iliocaval DVT patients with relative contraindications. A clinical significance of management for iliofemoral or iliocaval DVT patients with relative contraindications may happen.

Table 4

Assessment of venous recanalization.

		I	II	III	IV	V	VI	P
CDT	Acute (n=27)	7 (25.9%)	9 (33.3%)	4 (14.8%)	4 (14.8%)	2 (7.4%)	1 (3.7%)	P_{CDT}=.04
	Subacute (n=33)	2 (6.1%)	4 (12.1%)	10 (30.3%)	8 (24.2%)	7 (21.2%)	2 (6.1%)	P_{acute}=.80
PMT	Acute (n=25)	10 (40.0%)	8 (32.0%)	3 (12.0%)	2 (8.0%)	2 (8.0%)	0 (0.0%)	P_{PMT}=.01
	Subacute (n=27)	2 (7.4%)	4 (14.8%)	8 (29.6%)	7 (25.9%)	4 (14.8%)	2 (7.4%)	$P_{subacute}$=.84

P_{CDT} presents the difference between CDT acute group and CDT subacute group.
P_{PMT} presents the difference between PMT acute group and PMT subacute group.
P_{acute} presents the difference between CDT acute group and PMT acute group.
$P_{subacute}$ presents the difference between CDT subacute group and PMT subacute group.
CDT = catheter-directed thrombolysis, PMT = pharmacomechanical thrombolysis.

PTS is 1 of the most common sequelas of iliofemoral or iliocaval DVT, which may result from venous valvular incompetence, VO obstruction, and calf muscle pump dysfunction following an acute episode of DVT.[18] The severity of PTS relates to the recovery of venous obstruction and developments of collateral bypass veins.[19] The rates of PTS following iliofemoral DVT was ranging from 25% to 46% when they are conservatively treated by anticoagulation.[7,20] Although application of CDT has been demonstrated rapid and effective dissolution of thrombus and significantly reducing rates of PTS,[15] according to guidelines of the American College of Chest Physicians, CDT can be chosen for treating patients with iliofemoral DVT symptoms for <14 days, good functional status, life expectancy of >1 year, and low risk of bleeding.[14] In clinic, some contradictions exist.

With an aged population as well as expanding indications, there is expected increases in the number of aged patients receiving orthopedic surgery such as arthroplasty, especially in our hospital specialized in orthopedic. As for orthopedics, the rates of DVT are relatedly high even in the absence of prophylaxis.[3] When it comes to the aging patients undergoing orthopedics surgery, the rates may be much higher. Therefore, for DVT patients with >70 years, subaraclmoid hemorrhage (SAH), or undergoing arthroplasty, it is a real severe problem to avoid PTS.

There are different kinds of PMT devices with their own advantages each,[21] and the Angiojet rheolytic thrombectomy system (Boston Scientific) might still be a widely utilized thrombectomy device introduced in 1996. Bunch of studies have been done to determine the outcome of PMT (most were Angiojet) with inspiring results. Tzu-Ting Kuo et al found that CDT and PMT have similar venous outcomes in patients with acute iliofemoral DVT, although PTS is less severe following PMT than after CDT.[18] The study of Eric Hager et al suggested that PMT may have the same efficiency as CDT in preserving valve function and preventing PTS.[22] Study of Chun-Yang Huang et al showed that there is a similar treatment efficiency for PMT with CDT, but the rate of PTS was lower.[23] What is more, David Vogel et al also found a similar conclusion that PMT may have advantages in protecting valve function compared with CDT.[24] Studies mentioned above are much more focused on the comparison between CDT and PMT.[23] Only few authors isolated patients with relative contraindications including >70 years, subaraclmoid hemorrhage (SAH), or undergoing arthroplasty. Based on our promising results, those patients treated by PMT could have the same thrombus removal efficacy as patients without contraindication treated by CDT.

For the diagnosis of DVT mostly based on symptom duration, duplex ultrasound imaging and D-dimmer level,[25] the diagnosis time of the lower extremity DVT may be later than its occurrence. Current DVT staging system is based on symptom duration and the definition of DVT stages might be relative. However, it could significantly affect safety and efficacy of thrombolysis that stratifies patient selection criteria and timing of intervention. Treatment of acute DVT could result in a better outcome than subacute DVT,[26] the same result as our study. No matter what kind of therapy they received, thrombus removal of most acute DVT patients achieved level I or level II, while subacute DVT patients level III or level IV. A small part of acute DVT patients results in level III or level IV with thrombus removal caused by old thrombus. Some subacute DVT patients with level I or level II thrombus removal were that the thrombus built up chronically slowing down progresses of thrombus organization although the durations of DVT were relatively longer.

There were no systemic bleeding complications happening among our patients. For some studies, patients receiving CDT were with the rate of major bleeding is 2% to 4%,[27] and the minor bleeding was estimated to 14.6%.[26] For the advantages of shortening treatment time and reducing the dose of urokinase,[21] major bleeding complications barely happened in patients receiving PMT.[28] Besides, the use of urokinase also has some impacts on the safety and efficacy of the thrombolysis. Among numbers of thrombolytic agents including streptokinase, urokinase, and recombinant tissue-type plasminogen activator (rt-PA),[29] the second-generation PA urokinase has been proved to be efficacious for CDT.[30] For its consistency, predictability and low costing, urokinase is wildly used in China.[31] However the dosage of urakinase for CDT might be lower in the Chinese population,[31] which is also an important factor to reduce the bleeding complications.

There were some limitations of our study. First, the sample size was small, a much larger group study is necessary to confirm our results. Moreover, longer follow-up is necessary to discover the patency, rate of PTS and quality of lives for patients with different levels of venous recanalization.

5. Conclusions

PMT could be a safe and effective management for DVT patients with relative contraindications, and the acute DVT may achieve better outcomes when they receive CDT or PMT.

Author contributions

Data curation: Xiangdong Liu, Yunsong Li, Jianing Zhao, Haitao Li.
Investigation: Liang Li.
Project administration: Yanrong Zhang.
Writing – original draft: Pengkai Cao.

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