Original Article

Safety and Efficacy of Low Dosage of Urokinase for Catheter-directed Thrombolysis of Deep Venous Thrombosis

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Abstract

Background: Catheter-directed thrombolysis (CDT) has been a mainstay in treating deep venous thrombosis (DVT). However, the optimal dosage of a thrombolytic agent is still controversial. The goal of this study was to evaluate the safety and efficacy of low dosage urokinase with CDT for DVT.

Methods: A retrospective analysis was performed using data from a total of 427 patients with DVT treated with CDT in our single center between July 2009 and December 2012. Early efficacy of thrombolysis was assessed with a thrombus score based on daily venography. The therapeutic safety was evaluated by adverse events. A venography or duplex ultrasound was performed to assess the outcome at 6 months, 1 year and 2 years postoperatively.

Results: The mean total dose of 3.34 (standard deviation [SD] 1.38) million units of urokinase was administered during a mean of 5.18 (SD 2.28) days. Prior to discharge, Grade III (complete lysis) was achieved in 154 (36%) patients; Grade II (50–99% lysis) in 222 (52%); and Grade I (50% lysis) in 51 (12%). The major complications included one intracranial hemorrhage, one hematochezia, five gross hematuria, and one pulmonary embolism. Moreover, no death occurred in the study.

Conclusions: Treatment of low-dose catheter-directed thrombosis is an efficacious and safe therapeutic approach in patients with DVT offering good long-term outcomes and minimal complications.

Key words: Catheter-based Interventions; Deep Vein Thrombosis; Endovascular Treatment; Thrombolysis; Venous Disease

Introduction

Deep venous thrombosis (DVT), characterized by a blood clot which forms in deep veins (leg or pelvis) in the body, is a major medical problem worldwide. According to the statistical data, the annual incidence of DVT was about 0.1% and the mortality of DVT cases was 6%,[1] which makes it one of the most common and severe cardiovascular disease. Moreover, DVT, especially happened in iliofemoral vein, could frequently cause postthrombotic syndrome (PTS) and pulmonary embolism (PE),[2] which will result in high mortality and severe impairment of our normal life. Therefore, searching for the efficient therapy could relieve the burden brought by the disease.

Historically, the standard care for the patients with DVT has been anticoagulation treatment with heparin and coumadin. However, this form of therapy does not effectively treat the existing thrombus and will consequently lead to obstruction of the venous outflow and destruction of the valve function.[3] Optimal therapies which address the existing thrombus include surgical thrombectomy, systemic thrombolytic therapy, and catheter-directed thrombolysis (CDT). Among them, CDT is the most attractive method because it can effectively achieve the patency of lumen and remove the thrombus lining the venous valves.[4] Besides, several agents including streptokinase, urokinase, and recombinant tissue-type plasminogen activator (rt-PA) have been suggested to be efficacious in clinical practice in the past 30 years.[5] Among them, the second-generation PA urokinase is the dominant thrombolytic agent for CDT due to its consistency, predictability, and low costing.[6] In China, CDT with urokinase is also widely used, and the dosage is relatively lower than the report in western countries.[7] Until now, no report has focused on the safety and efficacy of low dosage urokinase for CDT.

Here, we performed a retrospective review on the safety and efficacy of low dosage urokinase for CDT in the Chinese population, and our results suggested low-dose urokinase with CDT is an efficacious and safe therapeutic approach for DVT patients.

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Methods

Patients

This study was approved by the institutional review board of the Second Affiliated Hospital of Soochow University and all participants provided written informed consent for the procedure. Inclusion criteria consisted mainly age range 18–80 years, suffered from acute DVT extending to the high femoral or iliac vein, symptom duration of less than 2 weeks, verified by ultrasound or digital subtraction angiography (DSA), good functional status, life expectancy of 1-year or more and low risk of bleeding. The following exclusion criteria were applied: Isolated infrapopliteal thrombosis, contraindications to contrast media or thrombolytic agents, stroke within 3 months, gastrointestinal bleeding or trauma within 3 weeks, uncontrollable hypertension, bacterial endocarditis, anemia, and renal failure.

From July 2009 to December 2012, a total of 702 patients with DVT were registered for the study. In the initial phase, 261 patients were excluded for they were not suitable for the CDT therapy. In addition, 14 patients who refused to perform the CDT therapy were also excluded. Thus, altogether 427 patients with high femoral or iliac vein thrombosis were eligible for intervention with CDT in the study and electronic hospital records were interrogated with regard to patient demographics, co-morbidities, risk factors for DVT [Table 1].

Procedures

All interventional radiologic procedures were performed by experienced vascular surgeons under sterile operation. First of all, lower limb venography was performed under DSA (DSA, GE Innova 3100, USA) by injecting contrast media via dorsal metatarsal vein to determine the extent of the thrombus and the approach to place vena cava filter. Based on the angiographic results, permanent or temporary filter (OptEase Retrievable Vena Cava Filters, TrapEase Vena Cava Filters, Cordis, USA and Aegisy Vena Cava Filters, Lifetech, China) was inserted percutaneously via either contralateral femoral vein or internal jugular vein.

Table 1: Demographic data of the patients (n=427)

Parameters	Values
Age (mean±SD)	59.22 ± 14.15
Gender (male, *n*, %)	207 (48.4)
Risk factors (*n*, %)	
Spontaneous	246 (57.6)
Recent major surgery*	135 (31.6)
Cancer	10 (2.4)
Oral contraceptive use	12 (2.8)
Hypercoagulation statue	8 (1.8)
Immobilization†	10 (2.4)
Pregnancy	6 (1.4)

*Recent major surgery was defined as surgery experienced 30–90 days before the onset of DVT; †The scope for a classification of immobilization was 4–30 days before the onset of DVT. SD: Standard deviation; DVT: Deep venous thrombosis.

Next, with the patient in the prone position, venous access was achieved with a 4F micropuncture needle set through the ipsilateral small saphenous vein. Other appropriate venous access, such as popliteal vein, anterior or posterior tibial vein, the calf or inguinal veins, was chosen at the discretion of the operator. Then a 4F or 5F vascular sheath was carefully inserted into the vein in which all subsequent catheter and wire exchanges were performed. A 4F or 5F unifuse infusion catheter (length 20–40 cm, Unifuse Infusion Catheter, Angiodynamics, NY, USA) was then gently placed with the tip embedded in the proximal extent of the thrombus. Urokinase (UK, Lizhu Pharmacy Corp, Zhuhai, China) was first injected at a bolus dose of 200,000–300,000 U and followed by continuously infusions of 400,000–1,000,000 U/d pumped through the catheter. The dosage of urokinase was adjusted according to the level of fibrinogen measured by daily analysis of blood coagulation function. If the fibrinogen level dropped below 100 mg/dl, we immediately ceased the use of urokinase. Venographic controls were performed every 24 h to follow lysis, and the catheter was repositioned until >90% of thrombi was lysed. When there was no residual thrombus or the venography assessment indicated unchanged thrombus after 24 h, the infusion catheter was removed.

Contemporary low molecular weight heparin (LMWH, Aventis Intercontinental, France) was administered subcutaneously at 4000 U/12 h with a target of 1.2–1.7-fold level of activated partial thromboplastin time in comparison to reference values (target 40–60 s). Warfarin was started prior to hospital discharge and given in accordance with local routines based on international guidelines. The dosage of warfarin was adjusted to a target international normalized ratio of 2.0–3.0.[8] All the patients were recommended to wear compression stockings (Class II 30–40 mmHg) as standard adjunctive treatment. The subsequent anticoagulation therapy continued for more than 1-year. Clinical follow-up was scheduled in the outpatient department by venography or duplex ultrasound after 6 months, 1 year, and 2 years thereafter.

Outcomes definitions

Early efficacy of thrombolysis was assessed by venography using a contrast injection through the introducer and perfusion catheter. A thrombus score was evaluated for seven deep vein segment, including inferior cava vein, the common iliac vein, the external iliac vein, the common femoral vein, the proximal and distal segments of superficial femoral veins, and the popliteal vein. The score was 0 when patent vein, 1 when partially occluded, and 2 when completely occluded. Total thrombus score before and after lysis was calculated by adding each segmental score. The difference between the pre- and post-lysis thrombus scores divided by the prelysis score resulted in the percentage of thrombolysis, which was classified into three groups: Grade I ≤50%; Grade II = 50–90%, and Grade III = complete thrombolysis.[4] Lysis Grades II and III (≥50%) were considered as successful outcomes (marked lysis).

Long-term outcomes were assessed during follow-up after 6 months, 1 year, and 2 years. Iliofemoral patency was defined as regained when the following findings were present: Flow in the pelvic and femoral vein, compressibility of the femoral vein, and no functional venous obstruction.[9] PTS was diagnosed using the Villalta scale, consisting of five patient-rated leg symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and six physician-rated clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression).[10] Each sign/symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and the scores are summed up to produce a total score whereby a score <5 excludes PTS, a score of 5–14 indicates mild/moderate PTS, and a score ≥15 or venous ulcer indicates severe PTS.

The safety outcome calculated the adverse events such as bleeding, PE, and death. Bleeding complications were categorized as major if they were intracranial, retroperitoneal, or in critical organs. All other bleeding events were categorized as minor episodes.

Statistical analysis

All the statistical analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation while categorical data were expressed as counts and percentage. Student's *t*-test and Chi-square were employed for continuous data and categorical data, respectively. $P < 0.05$ was considered as statistical significance.

Results

Patient characteristics

A total of 427 patients received CDT procedures. Of them, 207 (48.4%) were male, and 220 (51.6%) were female. Mean age was 59.22 years (range, 20–79 years). The duration of symptoms before thrombolysis was 5.80 ± 4.73 days. Two hundred and sixty-nine cases of DVT were located in left limb while 158 in the right limb. The patient demographic data including risk factors to DVT are shown in Table 1.

Interventions

Permanent or temporary inferior vena cava filters were implanted in 361 patients to prevent the potential PE, and 313 were removed after a successful thrombolytic procedure. The filter retrieval rate reached 86.70%. Endovascular stenting (Boston Scientific Wallstent 53, Cordis SmartControll 19, Bard Luminexx 10) was performed in 82 patients with iliac vein stenosis or occlusion caused by May–Thurner syndrome. The primary patency rate of the stent was 97.5%. Early stent occlusion occurred in 2 patients who received secondary intervention with 10% increased the dosage of urokinase and regained complete patency.

Details of thrombolysis

The average overall daily infusion dose, total dose, and infusion time for urokinase were: $(5.87 \pm 1.19) \times 10^5$ U/d, $(3.34 \pm 1.38) \times 10^6$ U, and 5.18 ± 2.28 days. The duration of hospital stays was 6.22 ± 3.43 days [Table 2].

Early efficacy and long-term outcomes

As shown in Table 2, complete lysis (Grade III) was achieved in 154 (36%) of 427 patients, partial lysis (Grade II) in 222 (52%), and Grade I in 51 (12%) patients. Three hundred and seventy-six patients (88%) showed marked lysis (Grade II and III). The thrombus score was 8.26 ± 1.61 at the start of CDT and 1.91 ± 1.71 at completion. The thrombus score before and after CDT in patients classified by different grade are shown in Table 3. The thrombolysis rate was 76.88%. The patients achieved complete lysis, partial lysis, and Grade I lysis received an average dose of $(5.58 \pm 1.12) \times 10^5$ U/d, $(5.44 \pm 1.34) \times 10^5$ U/d, and $(5.25 \pm 1.18) \times 10^5$ U/d, respectively. The average dosage, the duration of symptoms, and treatment duration in patients categorized according to different grade are shown in Table 4.

The mean follow-up duration was 14.5 months (range, 6–24 months). Patency rates after 6 months, 1 year and

Table 2: Details and outcomes of thrombolytic therapy (*n*=427)

Items	Values
Details	
Infusion dose (U/d)	$(5.87 \pm 1.19) \times 10^5$
Total dose (U)	$(3.34 \pm 1.38) \times 10^6$
Infusion time (days)	5.18 ± 2.28
Duration of hospital stays (days)	6.22 ± 3.43
Outcomes	
Complete lysis (Grade III) (%)	154 (36)
Partial lysis (Grade II) (%)	222 (52)
Grade I lysis (%)	51 (12)
Significant lysis (Grade II + Grade III) (%)	376 (88)
Before CDT thrombus score	8.26 ± 1.61
After CDT thrombus score	1.91 ± 1.71
Thrombolysis rate (%)	76.9

CDT: Catheter-directed thrombolysis.

Table 3: Thrombus score before and after CDT in patients with different lysis grades

Lysis grade	*n*	Prelysis	Postlysis	*t*	*P*
I	51	8.10 ± 1.73	4.82 ± 0.97	14.98	<0.01
II	222	8.28 ± 1.55	2.47 ± 0.95	59.19	<0.01
III	154	8.29 ± 1.53	0.14 ± 0.35	89.27	<0.01

CDT: Catheter-directed thrombolysis.

Table 4: Urokinase dosage and treatment duration in patients with different lysis grades

Lysis grade	Number of patients (%)	Dose ($\times 10^5$ U/d)	Onset of symptom (days)	Treatment duration (days)
I	51 (12)	5.25 ± 1.18	7.25 ± 5.79	5.53 ± 2.34
II	222 (52)	5.44 ± 1.34	6.42 ± 5.35	5.13 ± 2.41
III	154 (36)	5.58 ± 1.12	5.03 ± 3.79*	5.12 ± 2.07

*Onset of symptom. $\chi^2 = 8.058$, $P = 0.018$; Treatment period $\chi^2 = 2.321$, $P = 0.313$.

2 years were 96%, 90%, and 87%, respectively. After 6 months, 94.5% of patients were free from PTS. The frequency without PTS at 1 year and 2 years were 90.6% and 87.4%, respectively [Table 5].

Complication rates

Major bleeding complications occurred in 7 (1.6%) patients within 3 days after CDT, including one intracranial hemorrhage, one hematochezia, and five gross hematuria. All the seven patients were applied with a urokinase dosage of 8.0×10^5 U/d. A total of 31 minor bleeding complications were reported. Of the minor bleeding patients, twenty were related to bleeding at the puncture site and the average urokinase dose was $(5.88 \pm 1.20) \times 10^5$ U/d [Table 6]. One patient experienced PE before the implantation of the filter, and the symptom was relieved by pulmonary CDT therapy. In addition, no death was found in the study.

Discussion

The latest guidelines from the American College of Chest Physicians have backpedaled and advocated medical treatments. However, the application of revolutionary new anticoagulation drugs cannot solve the poor outcomes, especially the high risk of PTS. Current international consensus recommends CDT as first-line treatment for selected patients with acute iliofemoral DVT.[11]

The primary goals in treating DVT are to: Stop the propagation of thrombus, prevent the thrombus from breaking off and lead to PE, prevent recurrence of DVT, and reduce the risk of PTS.[12] Anticoagulation therapy alone can accomplish the former three goals; however, it is not helpful in minimizing the PTS. Due to the high rate of long-term morbidity caused by PTS, management of patients with DVT should not only consider the prevention of acute complications such as embolization or propagation of the thrombus but also to maintain the cleared vein segments open during the procedure. Currently, CDT has shown its safety and efficacy in selected patients.[11] Our study confirmed this viewpoint. The frequency of PTS at 1 year and 2 years were 9.4% and 12.6%, respectively, which was consistent with that in Tone Enden *et al*.'s study.[13] A Cochrane review published in 2004 also revealed a risk reduction in PTS from 65% to 48% with CDT,[14] and a more recent meta-analysis reported the risk of PTS with systemic thrombolysis was decreased from 57% to 27% after CDT.[15] Besides, CDT exhibited several advantages, including no incision, minimal trauma, and vein valve function preservation.

The thrombolytic drug is another important factor in the treatment of DVT. In the past three decades, urokinase has been the dominant agent for peripheral thrombolytic therapy because it provided a consistent, predictive, effective, and safe solution in treating DVT. Dotter *et al*. first showed that intrathrombotic delivery of the first generation agent streptokinase generated a better effect in arterial thrombus lysis than systemic intravenous infusion.[16] However, it has been abandoned due to the allergic complications. Urokinase, a second-generation agent, showed a more efficacious and improved safety profiles than streptokinase. Although the current availability of new generation thrombolytic agent rt-PA, urokinase remained the dominant agent for its general acceptance and low price. Urokinase is also widely used in China because of its good pharmacoeconomics. In this study, the mean dosage and usage time of urokinase were 5.88 million units and 5.18 days. Mewissen *et al*. showed a mean dosage of 7.8 million units of urokinase in a mean duration of 53.4 h.[4] In a study of 53 patients, Park found that the average dose was 4.4 million units and the mean treatment duration was 40.6 h.[17] Xue *et al*. conducted a mean dosage and usage time of urokinase were 3.11 million units and 4.1 days, respectively.[18] Our results reconfirmed that a continuous infusion of low-dose urokinase in CDT could effectively remove the clot and restore the venous flow for the patients with DVT, which was similar to Xue's report. The duration of hospitalization in our study was significantly longer, and the dosage of urokinase was relatively lower than in some reports of western countries. The discrepancy might be produced by following reasons: (1) Previous clinical trials were mainly conducted by local centers in Europe and North America, where prefer high dosage in treating CDT. We believe the racial difference including weightiness variations and genes multiplicity might contribute to the discrepancy. (2) Novel adjunctive pharmacomechanical thrombolysis approaches such as Trerotola, AngioJet, and Trellis were presented, which make it possible to accelerate lysis and reduce the therapeutic time. Recent studies further indicated that percutaneous mechanical thrombectomy combined with CDT could improve venous patency rate and decrease lytic dose.[19] (3) Optimal dosage of urokinase has not been determined. Yamagami *et al*. reported a dosage of 240,000 U/d during the CDT,[20] which was significantly lower than the dosage used in Western countries, whereas the recommended dosage in China was 600,000–1,200,000 U/d.[21] We performed a

Table 5: Clinical follow-up after CDT

Villalta scale	6 months (n = 311)	1-year (n = 266)	2 years (n = 211)
Mean score	2.6 ± 2.0	2.2 ± 2.0	1.6 ± 1.8
No PTS (0–4 points) (n, %)	294 (94.5)	241 (90.6)	184 (87.4)
Mild PTS (5–0 points) (n, %)	17 (5.5)	22 (8.3)	22 (10.5)
Moderate PTS (10–14 points) (n, %)	0	3 (1.1)	5 (2.1)
Sever PTS (≥15 points or ulcer)	0	0	0

CDT: Catheter-directed thrombolysis; PTS: Postthrombotic syndrome.

Table 6: Complications after CDT

Complications	Number of patients (n, %)	Infusion dose of urokinase ($\times 10^5$ U/d)
Major bleeding	7 (1.6)	8.0
Intracranial hemorrhage	1	
Hematochezia	1	
Gross hematuria	5	
Minor bleeding	31 (7.2)	5.88 ± 1.20
Location (puncture site)	20	

CDT: Catheter-directed thrombolysis.

literature search on the dosage of urokinase during the CDT and used the most frequently reported dosage in this study.

Moreover, we reached significant lysis in 376 patients who underwent CDT with a low dosage of urokinase, with rest exhibiting Grade I lysis. This result here is comparable with that of others.[22,23] In previous reports, the rate of complete and partial lysis of acute DVT with symptom duration of >2–4 weeks varied between 70% and 90%. In this study, we also found there are correlations between lysis grade and onset of symptoms. The duration of symptoms within different grades was as follows: Class I: 7.25 ± 5.79 days; Class II: 6.42 ± 5.35 days, and Class III: 5.03 ± 3.79 days. The longer symptom duration could lead to worse lysis grade ($P < 0.05$). However, no significant differences were observed in different grades on the period of treatment [Table 4].

Bleeding is a horrible complication in thrombolysis. Major bleeding complications were found in 7 patients (1.6%). The incidence of bleeding is lower than that reported by Mewissen *et al*. in a multicenter register study of 473 treated limbs (11%),[4] and by Manninen *et al*. in a single center study of 56 patients (3.6%).[24] Notably, only one symptomatic PE (0.002%) was found in our study while Mewissen *et al*. reported a 1% incidence of PE,[4] and Grossman and McPherson showed a 0.9% incidence in 214 patients.[25] Furthermore, we encountered minor bleeding complication in 31 patients (7.2%), and 20 of them were presented in the puncture site. We found that there did not exist significant differences on the dosage between minor bleeding and uncomplicated patient and believed it might be associated with puncture technology. Thus, cautions should be taken to avoid inadvertent puncture of adjacent vessels such as the popliteal artery or the common femoral artery during the needle access to the vein. What's more, the dosage of urokinase was same (all 8.0×10^5 U/d) in 7 patients presented major bleeding, which had a higher average daily infusion than those with minor bleeding ($P < 0.05$). This result indicates that the higher dose has a significant correlation with major bleeding, which is in accordance with two previous studies.[26,27]

There are also some limitations in our study. Lacking of data about patients who received high-dose urokinase resulted in an inability to compare the results of patients treated with a different dose of urokinase. Another limitation of this study is its retrospective nature and differences from randomized controlled trials. Furthermore, adjunctive techniques to CDT were not employed due to higher cost.

In conclusion, our results showed that CDT with a low-dose infusion of urokinase was safe and effective for the patients with DVT. However, considering the application of more aggressive endovascular treatments, including adjunctive pharmacomechanical techniques with a fewer dosage of thrombolytic agent and anticoagulation agent, it is likely to accelerate clot lysis and shorten procedural time. These changes could not only lead to further improvements on patency of vessel and clinical outcomes but also decrease risk of complications. Thus, the optimal dosage of thrombolytic agent and adjunctive techniques with CDT might be performed in the further study.

References

1. White RH. The epidemiology of venous thromboembolism. Circulation 2003;107 23 Suppl 1:I4-8.
2. Augustinos P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. Circulation 2004;1109 Suppl 1:I27-34.
3. Elsharawy M, Elzayat E. Early results of thrombolysis vs. anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. Eur J Vasc Endovasc Surg 2002;24:209-14.
4. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: Report of a national multicenter registry. Radiology 1999;211:39-49.
5. Olgun H, Buyukavci M, Ceviz N, Sahin IO, Yildirim ZK, Colak A, *et al.* Clinical experience with recombinant tissue plasminogen activator in the management of intracardiac and arterial thrombosis in children. Blood Coagul Fibrinolysis 2014;25:726-30.
6. Sugimoto K, Hofmann LV, Razavi MK, Kee ST, Sze DY, Dake MD, *et al.* The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. J Vasc Surg 2003;37:512-7.
7. Lei F, Li X, Qian A, Yu X, Rong J, Sang H, *et al.* Therapy of catheter-directed thrombolysis for inferior vena cava thrombosis after filter implantation. Zhonghua Yi Xue Za Zhi 2014;94:2197-200.
8. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;1336 Suppl:454S-545.
9. Enden T, Kløw NE, Sandvik L, Slagsvold CE, Ghanima W, Hafsahl G, *et al.* Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: Results of an open randomized, controlled trial reporting on short-term patency. J Thromb Haemost 2009;7:1268-75.
10. Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: A systematic review. Am J Med 2011;124:756-65.
11. Fahrni J, Engelberger RP, Kucher N, Willenberg T, Baumgartner I. Catheter-based treatment of ilio-femoral deep vein thrombosis-An update on current evidence. Vasa 2013;42:161-7.
12. Liu F, Lü P, Jin B. Catheter-directed thrombolysis for acute iliofemoral deep venous thrombosis. Ann Vasc Surg 2011;25:707-15.
13. Enden T, Haig Y, Kløw NE, Slagsvold CE, Sandvik L, Ghanima W, *et al.* Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): A randomised controlled trial. Lancet 2012;379:31-8.
14. Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database Syst Rev 2004;CD002783.
15. Alesh I, Kayali F, Stein PD. Catheter-directed thrombolysis (intrathrombus injection) in treatment of deep venous thrombosis: A systematic review. Catheter Cardiovasc Interv 2007;70:143-8.
16. Dotter CT, Rösch J, Seaman AJ. Selective clot lysis with low-dose streptokinase. Radiology 1974;111:31-7.
17. Park YJ, Choi JY, Min SK, Lee T, Jung IM, Chung JK, *et al.* Restoration of patency in iliofemoral deep vein thrombosis with catheter-directed thrombolysis does not always prevent post-thrombotic damage. Eur J Vasc Endovasc Surg 2008;36:725-30.
18. Xue GH, Huang XZ, Ye M, Liang W, Zhang H, Zhang JW, *et al.* Catheter-directed thrombolysis and stenting in the treatment of iliac vein compression syndrome with acute iliofemoral deep vein thrombosis: Outcome and follow-up. Ann Vasc Surg 2014;28:957-63.
19. Rao AS, Konig G, Leers SA, Cho J, Rhee RY, Makaroun MS, *et al.* Pharmacomechanical thrombectomy for iliofemoral deep vein thrombosis: An alternative in patients with contraindications to thrombolysis. J Vasc Surg 2009;50:1092-8.
20. Yamagami T, Kato T, Iida S, Tanaka O, Nishimura T. Retrievable vena

cava filter placement during treatment for deep venous thrombosis. Br J Radiol 2003;76:712-8.
21. Li XQ, Wang SM. The guideline for diagnosis and treatment of deep venous thrombosis (2nd) (in Chinese). Chin J Surg 2012;50:611-4.
22. Comerota AJ, Throm RC, Mathias SD, Haughton S, Mewissen M. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. J Vasc Surg 2000;32:130-7.
23. Sillesen H, Just S, Jørgensen M, Baekgaard N. Catheter directed thrombolysis for treatment of ilio-femoral deep venous thrombosis is durable, preserves venous valve function and may prevent chronic venous insufficiency. Eur J Vasc Endovasc Surg 2005;30:556-62.
24. Manninen H, Juutilainen A, Kaukanen E, Lehto S. Catheter-directed thrombolysis of proximal lower extremity deep vein thrombosis: A prospective trial with venographic and clinical follow-up. Eur J Radiol 2012;81:1197-202.
25. Grossman C, McPherson S. Safety and efficacy of catheter-directed thrombolysis for iliofemoral venous thrombosis. AJR Am J Roentgenol 1999;172:667-72.
26. Ouriel K, Gray B, Clair DG, Olin J. Complications associated with the use of urokinase and recombinant tissue plasminogen activator for catheter-directed peripheral arterial and venous thrombolysis. J Vasc Interv Radiol 2000;11:295-8.
27. Bjarnason H, Kruse JR, Asinger DA, Nazarian GK, Dietz CA Jr, Caldwell MD, *et al*. Iliofemoral deep venous thrombosis: Safety and efficacy outcome during 5 years of catheter-directed thrombolytic therapy. J Vasc Interv Radiol 1997;8:405-18.

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