Feasibility of Anticoagulation using Low Molecular-weight Heparin during Catheter-directed Thrombolysis for Lower Extremity Deep Venous Thrombosis

Yonghui Li  
the Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Junwei Wang  
Second Xiangya Hospital

Rongzhou He  
the First Affiliated Hospital of Sun Yat-sen University

Junmeng Zheng  
the Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Zhibo Chen  
Sun Yat-sen University Second Univeristy Hospital

Chen Yao  
the first affiliated hospital of Sun Yat-Sen University

Kai Huang  
the Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Research

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Abstract

Background: The optimal anticoagulant scheme during catheter-directed thrombolysis (CDT) for deep venous thrombosis (DVT) remains unknown. The present study is performed to evaluate the effectiveness and safety of anticoagulation therapy using low molecular-weight heparin (LMWH) during CDT for DVT.

Methods: The clinical data of DVT patients underwent CDT during the past 6 years were retrospectively collected and reviewed. According to LMWH dose, patients were divided into therapeutic-dose anticoagulation (TPDA) group and sub therapeutic-dose anticoagulation (sub-TPDA) group.

Results: A total of 61 patients involving 61 limbs were comprised. Acute and subacute DVT were identified in 39 (63.9%) and 22 (36.1%) patients, respectively. Thrombosis involving iliac vein was identified in 34 (55.7%) patients. Inferior vena cava filter placement was performed in 38 (62.3%) patients. Intraoperatively, adjunctive balloon, stent and thrombectomy were provided for 9 (14.8%), 4 (6.6%) and 1 (1.6%) patients, respectively. Twenty (32.8%) patients accepted TPDA therapy, while 41 (67.2%) patients were administrated with sub-TPDA therapy. Median urokinase infusion rates was 2.5 (0.83 to 5) x 104 U/h. Median infusion duration time was 4 (2 to 14) days, and median urokinase dose infused was 240 (60 to 1080) x 104 U. During CDT, 5 (8.2%) cases of minor bleeding were observed, and blood transfusion was not required. No major bleeding, symptomatic pulmonary embolism or death occurred. Complete (>90%) and partial thrombolysis (50~90%) were achieved in 56 (91.8%) patients. In comparison with sub-TPDA group, TPDA group exhibited no significant difference in baseline characteristics, clinical improvement, thrombolysis results and complications.

Conclusions: Anticoagulation therapy using low molecular-weight heparin during CDT for DVT is effective and safe. In comparison with sub-therapeutic-dose anticoagulation, therapeutic-dose did not improve the thrombolytic effect or increase the rate of complication.

Introduction

Deep venous thrombosis (DVT) is a common disease with an incidence of approximately 1 ~ 2 per 1000 persons per year.\(^1\) It could cause pulmonary embolism (PE), which led to more than 60,000 deaths annually in American.

Although anticoagulation therapy had been proved to be effective and safe in preventing PE and recurrence of DVT and improving patients’ quality of life,\(^2,3\) the management of DVT is still facing challenge since anticoagulation alone does not resolve the thrombus formed in the vein. Consequently, approximately 25 ~ 50% of proximal DVT patients develop post-thrombotic syndrome (PTS) because of valve incompetence and long-term venous hypertension.\(^4\)

Catheter-directed thrombolysis (CDT) has been proposed for symptomatic patients with severe DVT, particularly in the setting of limb ischemia.\(^5\) Numerous studies have reported the clinical benefit of CDT in
the treatment of symptomatic DVT. Despite the increased interest in CDT, consensus opinion has not been reached regarding the optimal anticoagulant scheme during CDT, including the use of low molecular-weight heparin (LMWH), safety and effectiveness of therapeutic-dose anticoagulation (TPDA) versus sub-therapeutic-dose anticoagulation (sub-TPDA) during CDT.

In the past 6 years, anticoagulation therapy with LMWH was used during CDT at our institution. This study was therefore performed to evaluate the effectiveness and safety of LMWH for CDT, and explore the optimal anticoagulation dose of LMWH during CDT.

**Methods**

**Data collection**

This retrospective study was approved by the Institutional Review Board and was performed in the Department of Cardiovascular Surgery, the Sun Yat-sen Memorial Hospital of Sun Yat-sen University. Patients who underwent CDT at our institution during the period from January 2014 to December 2019 were included. Informed consent was obtained from involved patients. Patients were diagnosed with DVT according to clinical features and ultrasound. Clinical data including demographics, co-morbidities, risk factors, ultrasound report, venography reports, operative note and complications were tabulated.

**Diagnosis**

DVT was diagnosed according to the clinical manifestation, the level of D-dimer, ultrasound. Only those patients with iliac or femoral vein thrombus were included. DVT Patients with duration time (calculating from onset of symptoms) ranging from 14 days to 1 month were classified as subacute DVT.

**Definition of variables**

Efficacy outcome included thrombolysis degree, clinical improvement, mid-thigh and mid-crus circumferences after CDT. Complete thrombolysis was defined as > 90% thrombus removal, and nearly no clot was found after the procedure. And the case with 50-90% thrombosis removal was scored as partial thrombolysis. Clinical improvement was defined as a significant decrease in pain and/or swelling of the affected extremity during hospitalization. Mid-thigh circumferences were measured 15 cm above upper margin of the patella, while mid-crus circumferences were 10 cm below lower margin of the tibial tuberosity.

Safety outcomes comprised CDT-related complications during hospital stay, including major and minor bleeding, symptomatic PE and death. Major bleeding and minor bleeding was defined as described. Systematic PE and intracranial hemorrhage were diagnosed with computer tomography, which was given for patients with sign of PE (anhelation, hyoxemia and so on) or intracranial hemorrhage (such as unconsciousness, powerless).

**Groups**
CDT was mainly performed by 2 surgical teams, and they provided anticoagulation treatment with different regimen of LMWH. According to the dose of LMWH, patients were divided into TPDA group and sub-TPDA group.

**Anticoagulation therapy**

All patients accepted a weight-based (1 mg/kg) twice-a-day regimen of LMWH (Lovenox; Sanofi, Paris, France) before and after CDT. During CDT, for sub-TPDA group, LMWH were given at a fixed-dose of 40 mg every 12 h, while TPDA group were administrated with the same weight-based (1 mg/kg) twice-a-day regimen.

**Catheter-directed thrombolysis**

A recyclable inferior vena cava filter (OptEase (Cordis, USA) or Celect (Cook, USA)) was implanted via the healthy femoral or jugular vein before CDT, and it was removed when the CDT ended. Retrograde catheterization of the femoral vein in the healthy lower extremity or antegrade catheterization of the popliteal vein in the affected lower extremity was performed. A 4F or 5F infusion catheter was advanced. The tip of infusion catheter was placed within thrombus, and its position changed according to ultrasound or venography. The length of the lateral-hole segment for placing into the thrombus was selected based on thrombus distribution. Urokinase (Livzon Pharmaceutical Group, Inc., China) was delivered at a speed of $0.83 \sim 5 \times 10^4$ U/h based on primarily the surgeon's preference, experience and risks of bleeding.

Coagulation function was tested daily. Infusion rate of urokinase dosage was adjusted according to Fibrinogen (FIB) concentration: infusion rate was slowed down by 50% if plasma FIB concentration decreased to $<1.5$ g/L; CDT was suspended and was restarted with a rate slowed down by 50%, if plasma FIB concentration dropped to $<1.0$ g/L.

For cases experienced complete thrombolysis, CDT was discontinued. If partial thrombolysis was confirmed on venography or ultrasound, whether CDT was continued depends on surgeons’ preference or experience. If CDT was continued, the catheter position might be adjusted. Adjunctive balloon, stent was used for those cases with iliac vein compression or residua stenosis after CDT. During CDT, patients were requested to rest in bed. The affected limb was elevated and extract of horse chestnut seeds tablets (Aescuven forte, CesraArzneimittelGmbH&CoKG, Germany) were used to alleviate swelling.

**Management of bleeding**

If patients manifested with major bleeding, CDT was discontinued. FIB, prothrombin complex or fresh frozen plasma was given. Proton-pump inhibitors were administrated for those patients experienced gastrointestinal bleeding. If patients had minor bleeding, CDT was suspended and resumed at a reduced dosage if minor bleeding could be well controlled. If the minor bleeding continued, CDT was discontinued permanently.
**Statistical analysis**

The continuous variables were expressed as the mean (standard deviation) or median (range), whereas the categorical variables were recorded as the number and percentage. A P value < 0.05 indicated a significant difference. Continuous data were analyzed with analysis of variance, paired t tests or Mann-Whitney testing, and categoric variables with Chi-square test or Fisher’s exact probabilities.

**Results**

A total of 61 patients containing 61 limbs were treated. The average age was 56.2 years old, ranging from 21 to 88. Approximately half of them were female. Nine patients were addicted to smoking. Thirteen patients had a history of hypertension, and 5 patients were diagnosed with diabetes. Clinical characteristics were shown in Table 1.
Table 1
Clinical characteristics of 61 cases of DVT patients experiencing catheter-directed thrombosis.

| Variables                                           | No.(%) or median (range) |
|-----------------------------------------------------|--------------------------|
| Patents, n                                          | 61                       |
| Age, year                                           | 56.2 (21 to 88)          |
| Female                                              | 31 (50.8)                |
| Weight, kg                                          | 61.5 (43 to 82)          |
| Smoking                                             | 9 (14.8)                 |
| Symptom duration                                    |                          |
| Acute (0-2w)                                        | 39 (63.9)                |
| Subacute (2w-1m)                                    | 22 (36.1)                |
| Risk factors                                        |                          |
| Surgery within last 30 days                         | 10 (16.4)                |
| Immobilization                                      | 7 (11.5)                 |
| Malignancy                                          | 8 (13.1)                 |
| Childhood                                           | 1 (1.6)                  |
| Trauma                                              | 5 (8.2)                  |
| Oral contraceptive use                              | 1 (1.6)                  |
| Previous DVT or PE                                  | 3 (4.9)                  |
| Hypercoagulable state                               | 2 (3.3)                  |
| Cockett syndrome                                    | 2 (3.3)                  |
| Unknown                                             | 22 (36.1)                |
| Involving iliac vein                                | 34 (55.7)                |
| Co-existing PE                                      | 4 (6.6)                  |
| Preoperative mid-thigh circumference, cm            | 45.8 (4.9)\(^a\)         |
| Preoperative mid-crus circumference, cm             | 36.9 (3.4)\(^b\)        |

Twenty-two (36.1%) patients were classified as subacute DVT. As to risk factors, recent surgery within 30 days was the leading cause of DVT. And risk factors of 22 patients were unknown. Thrombosis involved
iliac vein was identified in 34 (55.7%) patients. The remaining 27 patients had femoropopliteal venous thrombosis. Co-existing PE was found in 4 (6.6%) patients.

Preoperative inferior vena cava filter placement was given for 38 (62.3%) patients. Intraoperatively, adjunctive balloon (Mustang, Boston Scientific, American), stent (Wallstent, Boston Scientific, American) and percutaneous mechanical thrombectomy (AnjioJet, Boston Scientific, American) was provided for 9 (14.8%), 4 (6.6%) and 1 (1.6%) patients, respectively. Twenty (32.8%) patients accepted TPDA therapy, while 41 (67.2%) patients were administrated with sub-TPDA therapy. Median urokinase infusion rates was 2.5 (0.83 to 5) x 10^4 U/h. Median infusion duration time was 4 (ranged 2 to 14) days, and median dose infused was 240 (60 to 1080) x 10^4 U.

During thrombolytic therapy, 5 (8.2%) cases of minor bleeding were identified, and no blood transfusion was required. No major bleeding, symptomatic PE, intracranial hemorrhage or death occurred. Among the 5 patients experienced minor bleeding, median thrombotic duration time was 7 (4 to 12) days. Median infusion rates were 3.75 (2.5 to 4.2) x 10^4 U/h. And median urokinase dose was 400 (180 to 990) x 10^4 U. In comparison with those patients without bleeding, patients experienced bleeding were given more urokinase (P = .029), and the urokinase was infused with a faster rate (P = .007). These cases with bleeding were managed by slowing down the infusion rate and suspending CDT. Intervention strategies were described in Table 2.

| Variables                                      | No. (%) or median (range) |
|------------------------------------------------|---------------------------|
| Balloon                                        | 9 (14.8)                  |
| Stent                                          | 4 (6.6)                   |
| Percutaneous mechanical thrombectomy           | 1 (1.6)                   |
| Inferior vena cava filter placement            | 38 (62.3)                 |
| Aspiration using catheter                      | 2 (3.3)                   |
| Low molecular heparin                         |                           |
| Therapeutic dose                               | 23 (37.7)                 |
| Subtherapeutic dose                            | 38 (62.3)                 |
| Median urokinase dose, 10,000U                 | 240 (60 to 1080)          |
| Median infusion rates, 10,000 U/hour           | 2.5 (0.8 to 5)            |
| Median duration time, day                      | 4 (2 to 14)               |
On coagulation function, a plasma FIB concentration < 2.0 g/L was found in 8 patents. Among these, FIB concentration < 1.5 g/L was identified in 2 patients. The infusion rate of urokinase was slowed down in these two patients. No FIB was infused.

After CDT, complete and partial thrombolysis was achieved in 56 (91.8%) patients. Those patients with less than 50% thrombosis removed were all classified as subacute DVT. Among these, median urokinase dose were 180 (160 to 600) x 10⁴ U. The mid-thigh (45.8 ± 4.9 vs 43.6 ± 4.5, P < .01) and mid-crus (36.9 ± 3.4 vs 33.9 ± 2.5, P < .01) circumference (cm) significantly decreased after CDT. Clinical improvement was confirmed in 57 (93.4%) patients. Clinical outcome was shown in Table 3.

Table 3
Clinical outcome of 61 cases of DVT patients underwent catheter-directed thrombolysis.

| Variables                                      | No.(%) or mean (standard deviation) |
|------------------------------------------------|-------------------------------------|
| Thrombolysis degree                           |                                     |
| Complete                                       | 13 (21.3)                           |
| Partial                                        | 43 (70.5)                           |
| Clinical improvement                           | 57 (93.4)                           |
| Posteroperative mid-thigh circumference        | 43.6 (4.5)a                         |
| Posteroperative mid-crus circumference         | 33.9 (2.5)b                         |
| Complications                                  |                                     |
| Bleeding                                       | 5 (8.2)                             |
| Minor bleeding                                 | 5 (8.2)                             |
| Erhysis at the puncture site                   | 1 (1.6)                             |
| Dermal ecchymosis                              | 2 (3.3)                             |
| Menorrhagia                                    | 2 (3.3)                             |
| Major bleeding                                 | 0 (0)                               |
| PRBC transfusion                               | 0 (0)                               |
| Death                                          | 0 (0)                               |
| Allergy                                        | 1 (1.6)                             |

Note: a10 cm from lower margin of the tibial tuberosity; b15 cm from upper margin of the patella. PRBC = packed red blood cells
In comparison with Sub-TPDA group, TPDA group did not inhibited significant difference in demographic characteristics, lesion characteristics, use of urokinase and adjunctive strategies. And mid-thigh and mid-crus circumference, clinical improvement, rate of complete and partial thrombolysis and bleeding were similar between the two groups. Comparison outcome were described in detail in Table 4.

Table 4
Comparison outcome of therapeutic dose group and sub-therapeutic dose group.

| Variable                              | TPDA group | Sub-TPDA group | P value |
|---------------------------------------|------------|----------------|---------|
| Number                                | 23         | 38             | -       |
| Female                                | 9 (39.1)   | 22 (57.9)      | 0.155   |
| Age                                   | 57.4 (17.3)| 54.3 (13.7)    | 0.466   |
| Acute DVT                             | 15 (65.2)  | 24 (63.2)      | 0.871   |
| Subacute DVT                          | 8 (34.8)   | 14 (36.8)      |         |
| Thrombolytic treatment                |            |                |         |
| Median infusion rates 10,000U/hour    | 2.5 (0.8–4.2) | 2.5 (1.7-5)  | 0.891   |
| Median dose, 10,000U                  | 240 (60-1080) | 240 (80–480) | 0.456   |
| Median duration time, day             | 4 (2–12)   | 4 (2–14)       | 0.131   |
| Balloon                               | 3 (13.0)   | 3 (7.9)        | 1.000   |
| Stent                                 | 1 (4.3)    | 6 (15.8)       | 0.236   |
| Thrombosis degree                     |            |                |         |
| Undissolved                           | 3 (13.0)   | 2 (5.3)        | 0.665   |
| Partial                               | 15 (65.2)  | 28 (73.7)      |         |
| Complete                              | 5 (21.7)   | 8 (21.1)       |         |
| Clinical improvement                  | 20 (87.0)  | 37 (97.4)      | 0.146   |
| Decreased mid-thigh circumference, cm | 2.1 (2.4)  | 2.4 (1.8)      | 0.716<sup>a</sup> |
| Decreased mid-crus circumference, cm  | 2.2 (1.9)  | 3.1 (2.2)      | 0.268<sup>b</sup> |
| Bleeding                              |            |                |         |
| Major bleeding                        | 0 (0)      | 0 (0)          | 1.000   |
| Minor bleeding                        | 1 (4.3)    | 4 (10.5)       | 0.641   |

Note: w = week, m = month, DVT = deep venous thrombosis, <sup>a</sup>10 cm from lower margin of the tibialtuberocity; <sup>b</sup>15 cm from upper margin of the patella.
Discussion

Although various strategies had been applied for removing thrombus, the CDT remained the mainstream therapeutic strategy. CDT therapy could not only reduce mechanical trauma to the vessel wall compared with an open balloon thrombectomy procedure, but also manage thrombus in smaller distal vessels that are generally not accessible by a thrombectomy catheter. In clinical practice, CDT therapy was increasingly used in combination with percutaneous mechanical thrombectomy, creating a pharmacomechanical thrombectomy system.

Unfractionated heparin was preferentially used for anticoagulation therapy during CDT due to its shorter half-life and complete reversibility by using protamine. In this context, thought favorable results has been obtained, numerous studies have demonstrated risks of bleeding related to CDT therapy were alarmingly high, particularly in elderly patients. In comparison with unfractionated heparin, LMWH seemed to be equally effective and safer for venous thromboembolism. In addition, unfractionated heparin was given by intravenous continuous infusion during CDT, while LMWH was easier to use by subcutaneous injection. However, the evidenced of using of LMWH during CDT was limited.

In Chen et al study involving 46 patients with acute iliofemoral venous thrombosis, LMWH in combination with low dose urokinase were applied for CDT. According to the risk of bleeding, these patients were divided into high-risk group and low-risk group. CDT was given for high-risk with a median infusion rate of $1.0 \times 10^4$ U, while for low-risk group with a median infusion rate of $2.0 \times 10^4$ U. The rate of complete thrombolysis and clinical improvement was consistent with those studies using unfractionated heparin for CDT, and the rate of bleeding was lower.

A retrospective study performed by Graif et al included 45 patients accepting anticoagulation with LMWH during CDT for PE and 111 patients with unfractionated heparin. They found that therapeutic anticoagulation using LMWH during CDT for PE was safe. Their study did not find a significant difference between LMWH and unfractionated heparin with respect to hemorrhagic and general complication rates.

Favorable results were observed in the present study as well. Complete, partial thrombolysis and clinical improvement was achieved in over 90% patients. The rate is acceptable in comparison with other studies, given subacute DVT patients, who were thought to be poorly responsive to CDT), nearly accounted for one third of patient population in the present cohort. In addition, a relative low rate of adjunctive strategies, including balloon, stent and percutaneous mechanical thrombectomy, was applied, which might affect the thrombolytic result.

In a meta-analysis involving 45 studies, major bleeding occurred in 196 (7.9%) of 2467 patients experiencing CDT, and 18 (0.8%) of 2388 patients underwent CDT developed intracranial bleeding. No major bleeding or intracranial bleeding was identified in the present study. Minor bleeding occurred in 8.2% patients. The rate of minor bleeding was lower compared with those studies in which unfractionated heparin were used for anticoagulation therapy. On coagulation function assay, FIB concentration <
1.5 g/L was identified in 2 patients, and it was reversible by suspending CDT. These results indicated that it is of safety to use LMWH for CDT.

Nevertheless, the conclusions should be carefully quoted. We respectively reviewed the infusion rate, urokinase dose and thrombolytic duration of patients underwent minor bleeding. In comparison with those patients without bleeding, faster infusion rate and more urokinase were found in those patients with bleeding. The results showed that the risks of bleeding increased as the dose increased and infusion rate speeded up. Given the infusion rate and dose of urokinase was relatively low in the present cohort, the conclusion might be confined to low dose CDT.

The optimal dose of anticoagulation remained unclear during CDT. In comparison with sub-TPDA group, TPDA group neither improved the thrombolysis outcome, nor increased the risks of bleeding in the present study. The similar results could be explained as follow. Dose of urokinase and infusion rate had a larger effect on the clinical outcome, and the effect of anticoagulation therapy might be underestimated. And the relative limited number of patients involved might affect the power of statistical tests. Based on these results, both sub-therapeutic and therapeutic dose LMWH could be used for anticoagulation therapy during CDT.

Serial hematocrit levels and coagulation function assay should be mandatory, and it was performed daily in the present study. The frequency of testing was less than that accepting anticoagulation therapy with unfractionated heparin. We observed that parameters of blood coagulation were stable during CDT. Anti-factor Xa level could be used for monitoring of LWMH. However, the optimal anti-factor Xa level was unknown during CDT. The assay was not available at that time in our center. Further studies evaluating optima anti-factor Xa level during CDT should be performed.

**Limitation**

First, the present study was based on retrospectively collected data and shared the same flaws as other observational studies. Second, follow-up outcome variables were absent in the present study. Outcome variables should be broadened to include follow-up outcome variables that were related with CDT, such as PTS and quality of life. Furthermore, regimen of CDT varied among these patients, which might influence the reliability of conclusion.

**Conclusions**

Anticoagulation therapy using low molecular-weight heparin during CDT for DVT is effective and safe. In comparison with sub-therapeutic-dose anticoagulation, therapeutic-dose anticoagulation did not improve the thrombolytic effect or increase risks of bleeding.

**Declarations**
Ethics approval and consent to participate: This retrospective study was approved by the Institutional Review Board and was performed in the Department of Cardiovascular Surgery, the Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Consent for publication: Not applicable

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests: None.

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Authors' contributions: Yonghui Li and Junwei Wang: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Rongzhou He: (1) acquisition of data, analysis and interpretation of data, (2) revise the article critically, (3) final approval of the version to be submitted.

Junmeng Zheng: (1) acquisition and analysis of data, (2) revise the article critically, (3) final approval of the version to be submitted.

Zhibo Chen: (1) acquisition of data, (2) revise the article critically, (3) final approval of the version to be submitted.

Chen Yao and Kai Huang: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) revising it critically for important intellectual content, (3) final approval of the version to be submitted and funding.

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