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Quantitation of Venous Clot Lysis With D-Dimer Assay During Catheter-Directed Thrombolysis for Lower Extremity Deep Venous Thrombosis

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This study evaluated whether D-dimer (DD) concentration analysis is a useful approach for noninvasive monitoring of clot lysis during catheter-directed thrombolysis (CDT) for deep vein thrombosis (DVT). DD levels have been found to be elevated during fibrinolytic therapy for DVT. Therefore, measuring the level of DD is a potential alternative method to assess the effect of fibrinolytic therapy. From January 2013 to March 2014, 32 patients with symptomatic acute DVT involving the iliac or femoral veins were treated using CDT. Urokinase was the thrombolytic agent. Demographics, procedural details, DD concentration, and thrombus score were recorded before and after the thrombolytic therapy. The peak DD concentration was 35.35 ± 11.18 μg/mL during CDT therapy, and the time-integrated DD concentration was 157.95 ± 69.46 μg·d/mL. The peak DD concentrations were higher in patients with substantial lysis compared with those in patients with minimal or no lysis (40 ± 0 versus 30.7 ± 14.57 μg/mL; $P = 0.016$). The time-integrated DD concentrations were also higher in patients with substantial lysis compared with those in patients with minimal or no lysis (194.14 ± 37.57 units versus 121.75 ± 75.93 units, $P = 0.002$). There was a moderate correlation ($r = 0.57$) between the peak DD level and the lysed clot volume. There was also a correlation between the time-integrated DD and clot lysis ($r = 0.65$). DD concentration analysis offers an alternative approach to noninvasive monitoring of venous clot lysis during CDT for DVT.

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Catheter-directed thrombolysis (CDT) has been widely used for the treatment of lower extremity deep venous thrombosis (DVT). Previous studies have demonstrated that CDT significantly improves the quality-of-life (QOL) in patients with DVT compared with anticoagulative therapy alone.[1–3] To accurately assess the therapeutic response to CDT, however, patients usually have to undergo repeated venography, which is invasive and is also associated with a high cost and radiation exposure. D-dimer (DD) is a specific fibrin clot degradation product that results from the action of thrombin, activated factor XIII, and plasmin.[4] Therefore, measuring the soluble products of fibrin lysis, such as DD, is a potential alternative method to assess the effect of fibrinolytic therapy. In the present study, we evaluated whether DD concentration analysis is a useful approach to noninvasively monitor clot lysis during CDT for DVT.

Methods

Patients

From January 2013 to March 2014, 32 patients with symptomatic acute DVT involving the iliac or femoral veins in 32 limbs (2 right, 30 left) were treated with CDT. Patients who had pulmonary emboli or other comorbidity, which were contraindicated to the use of anticoagulation, contrast media, or thrombolytic agents, were excluded. The data were retrospectively reviewed following institutional review board approval.

Procedures

DVT of the lower limb was verified using routine ultrasound. In all patients, anticoagulation therapy was started using subcutaneous low molecular weight heparin (LMWH), either with dalteparin (Fragmin, Pfizer, New York, New York) or enoxaparin (Klexane, Sanofi, Paris, France). The ipsilateral popliteal vein was accessed under anterograde venography or ultrasonographic guidance. A 6-French sheath was commonly inserted, through which all subsequent catheter and wire exchanges were performed. After baseline phlebography, the thrombosed segment was traversed using a 0.035-inch guidewire. CDT was performed by inserting a multi-side hole catheter (Uni*Fuse Infusion Catheter, AngioDynamics, Latham, New York) for intrathrombus infusion. Urokinase was the thrombolytic agent in all cases. After a bolus of 200,000 IU urokinase, 20,000 to 40,000 IU per hour, was infused through the multi-side hole catheter, unfractionated heparin (UFH) was continuously infused through the sheath for anticoagulation. The lysis procedure was terminated when maximal benefit from the procedure was obtained, as determined by the operator. Following lysis, a balloon catheter was used as needed (more than 50% stenosis) to dilate the stenosis, and stenting was performed to ensure unobstructed venous drainage from the common femoral vein into the vena cava.

Data collection

Clot burden at the start and end of CDT was assessed using venography and graded using a modification of the technique described by Marder *et al*,[5] in which a thrombus score was calculated for 7 venous segments: the inferior vena cava (IVC), the common iliac vein, the external iliac vein, the common femoral vein, the proximal portion of the femoral vein, the distal portion of the femoral vein, and the proximal portion of the popliteal vein. Each of these deep veins was assigned a relative value reflecting the calculated volume of the segment (Table 1). The total thrombus score before and after lysis was then calculated by adding the scores of the 7 venous segments. The maximum possible score for involvement of the deep veins of the leg and pelvis was 35. The difference between the pre- and postlysis thrombus scores was defined as the thrombolysis score. The clot resolutions were scored by Yuanyong Jiao and Jun Jiang to ensure less variability.

Blood samples

Venous blood samples from DVT patients were obtained before and every 24 hours after starting CDT. DD testing was performed using the CA7000 coagulation analyzer (Sysmex Corporation, Kobe, Japan) with the Innovance DD Kit (Siemens, Erlangen, Germany). Fibrinogen was determined by the Clauss method[6] using the CA7000 coagulation analyzer.

Statistical analysis

DD levels are presented as the median ± SD. The integrated DD, the area under the curve connecting the DD concentrations, was calculated using Origin-

Table 1 Venographic thrombosis quantitation

Deep vein	Thrombotic score (units)
Inferior vena cava	10
Common iliac vein	3
External iliac vein	3
Common femoral vein	4
Proximal portion of the superficial femoral vein	5
Distal portion of the superficial femoral vein	5
Proximal portion of the popliteal vein	5

Pro 8 software (OriginLab Corporation, Northampton, Massachusetts). The Student *t* test and linear regression analysis were performed using a standard computer software package (SPSS 17 for Windows, SPSS Inc, Chicago, Illinois). Statistical significance was assumed for a P value < 0.05.

Results

Thirty-two patients with symptomatic acute DVT involving the iliac or femoral vein underwent CDT. The mean age of the patients was 50.4 ± 16.6 years and 21 patients (65.6%) were female. The mean duration of symptoms was 6.9 ± 7.7 days. The left limb was more frequently involved (30/32, 93.8%). To reduce the risk of bleeding, we used a thrombolytic strategy involving a low daily dose for a long duration. The duration of CDT was 6.8 ± 1.2 days, and the total amount of urokinase was 4.25 ± 1.64 million units.

The pretreatment DD concentration was 6.68 ± 6.17 μg/mL. After initiation of urokinase therapy, DD levels rose rapidly to 17.12 ± 11.79 μg/mL after 24 hours, reached a peak of 30.1 ± 13.34 μg/mL on day 4, and then declined slowly despite continuous thrombolytic drug infusion. The pretreatment fibrinogen (FIB) concentration was 3.38 ± 0.88 g/L. The FIB levels declined slowly during the CDT.

Peak DD concentration observed during CDT therapy was 35.35 ± 11.18 μg/mL. To adjust for different durations of therapy, an integrated DD was calculated as the area under the curve connecting the DD concentrations that were measured from pretreatment to the end of CDT. The time-integrated DD concentration was 157.95 ± 69.46 μg·d/mL.

After therapy, repeat venograms showed thrombolysis of 14.16 ± 7.68 units (range, 0–25 units). A substantial response to CDT was achieved in 16 patients in whom 14 to 25 units of clot were lysed, and a minimal response or no lysis was observed in 16 patients (0–13 units). Peak and integrated DD levels were compared in patients with substantial and minimal or no clot lysis. The peak DD concentrations were higher in patients with substantial lysis compared with those in patients with minimal or no lysis (40 ± 0 versus 30.7 ± 14.57 μg/mL; $P = 0.016$). The time-integrated DD levels were also higher in patients with substantial lysis, and the mean values were significantly different (121.75 ± 75.93 versus 194.14 ± 37.57 units; $P = 0.002$). The lowest FIB levels were compared in patients with substantial and minimal or no clot lysis. There was no significant difference between the 2 groups (1.59 ± 0.50 versus 1.89 ± 0.73 g/L; $P = 0.19$) (Table 2).

Table 2 Analysis of peak DD, integrated DD, and FIB in 2 groups (substantial response group versus minimal or no lysis group)

	Substantial response group (n = 16)	Minimal or no lysis group (n = 16)	*P* value
Peak DD (μg/mL)	30.7 ± 14.57	40 ± 0	0.016
Integrated DD (units)	194.14 ± 37.57	121.75 ± 75.93	0.002
FIB (g/L)	1.59 ± 0.50	1.89 ± 0.73	0.19

There was a moderate correlation ($r = 0.57$) between the peak DD value and the volume of lysed clot, and also between the measured time-integrated DD and clot lysis ($r = 0.65$). There was a negative correlation ($r = –0.51$) between the lowest FIB value and peak DD.

Discussion

This study shows that both the peak DD concentrations and the time-integrated DD levels were higher in patients with substantial lysis compared with patients with minimal or no lysis. There was also a correlation between the amount of venous thrombus lysed during thrombolytic treatment and both the peak DD and the time-integrated DD.

DVT is a major health problem with 2.5% to 5% of the population affected at some time in their lives. Anticoagulation is the standard treatment, and it is aimed mainly at preventing pulmonary embolism (PE) and recurrent DVT. Despite treatment, over 50% of patients may have postthrombotic symptoms (PTS) in the long term, which manifests as some degree of pain, swelling, skin pigmentation, or venous ulceration on the affected leg.[7] PTS is associated with reduced individual health-related QOL and a substantially increased economic burden.[8,9] Thrombolysis increases the patency of veins and reduces the incidence of PTS after proximal DVT by one third.[10]

However, systemic thrombolysis treatment was associated with an increased risk of bleeding.[10,11]

Percutaneous mechanical thrombectomy (PMT) devices can quickly remove a thrombus from a vein and restore patency; however, risks of venous wall and valve injury are high given the mechanical forces exerted by some of the equipment. Pharmacomechanical thrombolysis devices combine a mechanical thrombus-maceration component with a thrombolytic agent in the same catheter to shorten treatment time. However, the device has some limitations: the 8-French sheath may be too large for infrapopliteal DVT treatment; the small caliber aspiration lumen evacuates the slurry but not older clot chunks; and occluding balloons expand only to $\leq$16 mm, so they cannot fully occlude in the IVC.[11] In addition, these catheters are not currently widely used in clinical practice.

CDT is a widely used modality in which a catheter is introduced into the affected vein and advanced through the thrombotic segment. Multiple side holes enable delivery of a thrombolytic agent directly into the clots, and reduced doses of thrombolytic agents are used. Venographic assessment of the therapeutic response in patients with DVT treated with CDT is accurate and quantitative, but its invasive nature makes it unsuitable for routine follow-up. Noninvasive approaches rely on clinical observation or evaluation of venous flow using plethysmography or Doppler ultrasound, but they may be inaccurate. Clinical changes such as symptomatic improvement or reduction in leg swelling are nonspecific. Recently, greater elevations in DD levels have been found during systemic fibrinolytic therapy for myocardial infarction,[12] DVT,[13,14] or PE.[15] Despite the consistent increase during lytic therapy, no correlation between the degree of thrombolysis and the elevation in DD levels has been found during DVT treatment. A potential explanation that has been proposed for the lack of correlation is the presence of multiple sources of fibrin, which may degrade during therapy. For example, patients with DVT may also have clinically unsuspected pulmonary emboli. No matter what the extraneous source of fibrin is, it has been of sufficient quantity to obscure the specific detection of thrombus-derived DD, thereby limiting the application of this assay for noninvasive quantitation of therapeutic thrombolysis. Brenner *et al*[16] have suggested that a major source of cross-linked fibrin-degradation products during fibrinolytic therapy is soluble plasma fibrin. Electrophoretic analyses in normal subjects indicated that approximately 0.8% of total fibrinogen is present as cross-linked fibrin dimer. The elevation in DD during fibrinolytic therapy results from degradation of soluble fibrin and from lysis of thrombi. Adjusting the plasma DD concentration to account for the contribution from soluble fibrin degradation offers an approach to noninvasive monitoring of venous clot lysis during fibrinolytic therapy.[16] However, DD detection from degradation of soluble fibrin is not suitable for clinic application.

In this study, the significant correlation between the degree of thrombolysis and the elevation in DD levels seems to contradict the results of the above-mentioned studies, which showed no correlation between these factors.[14,16] There are several potential explanations for the difference. In the present study, a thrombolytic agent was injected into the thrombus through the side holes of the thrombolysis catheter, which resulted in a higher local concentration of drug inside the thrombus compared with that outside. Therefore, the elevation in DD during CDT was mainly from lysis of thrombi, and the proportion from degradation of soluble fibrin and other sources was relatively small. Moreover, numerous studies suggest that additional CDT may provide highly effective clot lysis.[2,17] These published results are consistent with the results of our study. The peak DD concentration was 35.35 $\pm$ 11.18 μg/mL, which was about 3-fold higher than the DD of systemic thrombolytic treatment reported by Brenner *et al* (10.33 $\pm$ 1.0 μg/mL).[16] The high DD level from thrombolysis reduced the proportion from degradation of other sources. Therefore, the significant correlation between the amount of venous thrombus lysed and both the peak DD and time-integrated DD was almost unchanged.

If DD levels measured during therapy do not increase significantly, our analysis suggests that little or no lysis is occurring. Conversely, if concentrations do increase, the degree of elevation should correlate with the amount of clot lysis. Potentially, the course of therapy over time could be followed by measuring serial DD values and predicting continued clot lysis if the DD level remained high and if concentrations returned to a low level after being elevated; our analysis suggests that this is the time to end thrombolytic therapy. Venography remains the gold standard for assessing the amount of clot lysis, but DD levels measured during CDT offer a noninvasive method for monitoring lytic therapy, thereby reducing repeated venography and guiding the treatment process.

The FIB levels were also assessed in the present study. The FIB levels declined slowly during CDT

because the thrombolytic drug (urokinase) degraded both fibrin and FIB. There was a negative correlation between the lowest FIB value and the peak DD. Therefore, a lower FIB level suggested a higher efficiency for the thrombolytic agent.

Our study has some limitations. First, it is a retrospective study with a small sample size. The majority of the patients underwent venography only twice, including pre- and postlysis, rather than repeated venography during CDT to monitor the thrombus clearance. Second, because the upper limit of the DD test in the present study was 40 μg/mL, the DD levels may be underestimated.

In conclusion, DD concentration analysis is a potential alternative approach to noninvasive monitoring of venous clot lysis during the CDT for DVT, and this possibility requires further assessment in a prospective study.

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