

Ultrasound-accelerated Thrombolysis for the Treatment of Deep Vein Thrombosis: Initial Clinical Experience

Sanjiv Parikh, MD, Amir Motarjeme, MD, Thomas McNamara, MD, Rodney Raabe, MD, Klaus Hagspiel, MD, James F. Benenati, MD, Keith Sterling, MD, and Anthony Comerota, MD

PURPOSE: To evaluate the success of lysis and clinical outcomes in patients treated with ultrasound (US)-accelerated thrombolysis for deep vein thrombosis (DVT).

MATERIALS AND METHODS: Forty-seven patients with 53 cases of DVT were treated with US-accelerated thrombolysis at eight centers in the United States. Sixty percent of the occlusions were in the lower extremity, 36% were in the upper extremity, and 4% were hepatic. The clot was acute (≤ 14 days) in 47% of cases, subacute (15–28 d) in 8%, chronic (> 28 d) in 17%, acute-on-chronic in 17%, and not specified in 11%. Patients were treated with urokinase (UK), tissue plasminogen activator (tPA), recombinant plasminogen activator (rPA), or tenecteplase.

RESULTS: Complete lysis ($\geq 90\%$) was seen in 37 of 53 cases (70%) and overall lysis (complete plus partial) was seen in 48 (91%). No lysis occurred in five cases (9%), four of which were chronic. The median thrombolysis infusion time was 22.0 hours. Major complications (hematoma at site of earlier surgery) occurred in only two patients (3.8%), with no incidence of intracranial or retroperitoneal hemorrhage. US-accelerated thrombolysis exhibited comparable or better lysis with a lower average drug dose and shorter median treatment times than reported in the National Venous Registry and a more recently published study of standard catheter-directed thrombolysis.

CONCLUSIONS: US-accelerated thrombolysis was shown to be a safe and efficacious treatment for DVT in this multicenter experience. The addition of US reduces total infusion time and provides a greater incidence of complete lysis with a reduction in bleeding rates.

J Vasc Interv Radiol 2008; 19:521–528

Abbreviations: DVT = deep vein thrombosis, PTA = percutaneous transluminal angioplasty, PTS = postthrombotic syndrome, rPA = recombinant plasminogen activator, tPA = tissue plasminogen activator, UK = urokinase

AFFECTING more than 250,000 individuals in the United States each year, deep vein thrombosis (DVT) is associated with potentially life-threatening

complications including pulmonary embolism and long-term sequelae of postthrombotic syndrome (PTS) (1,2). Pulmonary embolism, the most seri-

ous acute complication of DVT, results in as many as 100,000 deaths annually. It has been reported in 5% of treated and as many as 67% of untreated patients with lower-extremity DVT (3), and in 8%–36% of patients with upper-extremity DVT (4,5).

PTS, a chronic condition that develops in 30%–75% of patients with DVT as a result of ambulatory venous hypertension caused by valvular incompetence and venous obstruction (1,2,6,7), is a common cause of long-term morbidity and disability (4,8). Symptoms include edema, heaviness, pain, varicosities, hyperpigmentation, and in severe cases, ulcerations of the limb. Because of its prevalence and chronic nature, PTS is a costly condition, ac-

From the Department of Interventional Radiology (S.P.), Swedish Medical Center–Cherry Hill Campus, Seattle; Inland Imaging (R.R.), Spokane, Washington; Department of Radiology (A.M.), Advocate Good Samaritan Hospital, Downers Grove, Illinois; Interventional Radiology Section (T.M.), University of California Los Angeles Medical Center, Los Angeles, California; Department of Radiology (K.H.), University of Virginia Medical Center, Charlottesville; Department of Cardiovascular and Interventional Radiology (K.S.), INOVA Alexandria Hospital, Alexandria, Virginia; Department of Interventional Radiology (J.F.B.), Baptist Cardiac and Vascular Institute, Miami, Florida; and Jobst Vas-

lar Center (A.C.), Toledo, Ohio. Received July 13, 2007; final revision received and accepted November 27, 2007. **Address correspondence to** S.P., Department of Interventional Radiology, Swedish Medical Center–Cherry Hill Campus, 500 17th Ave., Seattle, WA 98122; E-mail: sparikh@radiax.com

S.P., A.M., T.M., R.R., and J.F.B. are consultants for EKOS Corporation, Bothell, WA. None of the other authors have identified a conflict of interest.

© SIR, 2008

DOI: 10.1016/j.jvir.2007.11.023

counting for more than 40% of the total health care costs for DVT treatment, in addition to the socioeconomic impact of work disability and quality of life impairment (9). Reports in the literature have emphasized the importance of rapid and complete thrombolysis to prevent or alleviate the symptoms of PTS (10,11).

Although the current standard of care, anticoagulation therapy with unfractionated or low molecular weight heparin, prevents thrombus propagation, it does not resolve existing thrombus. Catheter-directed thrombolysis has demonstrated efficacy in the treatment of DVT with the potential for rapid and complete resolution of thrombus resulting in venous recanalization, preservation of valvular function, prevention of pulmonary embolism, increase in long-term patency rates, and improvement of quality of life (6,12,13,14). Successful thrombolysis of iliofemoral DVT has been shown to significantly improve quality of life compared with failed thrombolysis or treatment with anticoagulation alone (14). Several thrombolytic drugs are currently used in catheter-directed thrombolysis for the treatment of DVT. Urokinase (UK) was historically the most widely used thrombolytic agent, but upon temporary removal of UK from the United States market in 1999, second-generation plasminogen activators such as tissue plasminogen activator (tPA; alteplase) and recombinant plasminogen activator (rPA; reteplase) became more commonly used. A recent retrospective study (15) compared the efficacy and safety of UK, tPA, and rPA used in catheter-directed thrombolysis for the treatment of symptomatic DVT. All three thrombolytic drugs demonstrated similar success and complication rates, with complete thrombolysis ranging from 50.0% to 71.1% of cases and major complication rates ranging from 3.1% to 8.3%. More recently, tenecteplase, a third-generation genetically engineered thrombolytic agent, was developed with greater fibrin specificity than tPA. In a single-center pilot study (16), tenecteplase used in standard thrombolysis for the treatment of DVT was reported to achieve significant or complete lysis in 83.3% of cases. Despite its effectiveness, widespread use of thrombolysis in the treatment of upper- and lower-

extremity DVT is limited by long thrombolytic infusion times, prolonged intensive care unit stay, high drug costs, and risks of hemorrhagic complications associated with large doses of thrombolytic drugs (6,12).

Because of these limitations, adjunctive endovascular techniques for the treatment of DVT have been developed to reduce therapy time, decrease thrombolytic drug exposure, and improve efficacy compared with standard thrombolysis. One of these techniques is ultrasound (US)-accelerated thrombolysis, which involves simultaneous delivery of low-intensity US and thrombolytic agent into a thrombosed vessel. US-accelerated thrombolysis has been shown *in vitro* to accelerate clot lysis by increasing clot permeability and penetration of the thrombolytic agent into the thrombus (17). The technique also has been demonstrated to be safe and effective clinically in the treatment of peripheral arterial occlusion and embolic stroke (18–21). The present multicenter retrospective study reports the initial clinical experience of eight centers in the United States with US-accelerated thrombolysis in the treatment of proximal DVT of the upper and lower extremity.

MATERIALS AND METHODS

Patient Population

All patients who presented with DVT and were treated with US-accelerated thrombolysis for primary thrombolysis between September 2004 and March 2006 were included in this retrospective study. Forty-seven patients (26 male and 21 female patients; mean age, 50.8 years \pm 20.1; age range, 15–90 y) with 53 venous occlusions underwent US-accelerated thrombolysis in eight medical centers in the United States (Table 1). Patients were treated with UK (ImaRx Therapeutics, Tucson, AZ), tPA (Activase; Genentech, South San Francisco, CA), rPA (Retavase; PDL BioPharma, Fremont, CA), or tenecteplase (TNKase; Genentech). Each participating medical center received institutional review board approval or gained an exemption by collecting data without patient identification.

According to the classification system for symptom duration published

in the Society of Interventional Radiology reporting standards for endovascular treatment of lower-extremity DVT (22–24), symptom duration was defined as acute (\leq 14 days), subacute (15–28 d), chronic ($>$ 28 d) and acute-on-chronic (containing chronic and acute components). Twenty-five occlusions (47.2%) were acute, four (7.5%) were subacute, nine (17.0%) were chronic, and nine (17.0%) were acute-on-chronic (Table 1). Symptom duration was not reported in one case (7.1%) treated with UK, four cases (18.2%) treated with rPA, and one case (12.5%) treated with tenecteplase.

Thirty-two occlusions (60.4%) were located in the lower extremity, with 19 iliofemoral and 13 femoropopliteal occlusions. Nineteen occlusions (35.8%) occurred in the upper extremity with two brachiocephalic/jugular, 15 axillosubclavian, and two brachial occlusions. Two occlusions (3.8%) occurred in the hepatic vein.

US-accelerated Thrombolysis Procedure

Venous access was obtained based on the standard practice of each investigator, typically in the vein distal to the occlusion (ie, basilic or brachial vein in the upper extremity and posterior tibial or popliteal vein in the lower extremity) or with use of a contralateral femoral approach. Subtherapeutic doses of heparin were administered in most cases through a peripheral catheter or vascular sheath.

US-accelerated thrombolysis was performed with use of the EKOS EndoWave system (Fig 1; EKOS, Bothell, WA). EndoWave 5.2-F multilumen drug delivery catheters and matching US coaxial core wires (EKOS) with available treatment lengths ranging from 6 cm to 50 cm were used based on the length of the occlusion. The drug delivery catheter was navigated over a 0.035-inch guide wire so that the treatment zone traversed the entire clot and the tip exited the thrombus. After final positioning, the guide wire was exchanged for a matching US core wire containing a series of US transducer elements (2.2 MHz, 0.45 W) distributed approximately 1.0 cm apart along its leading tip to evenly deliver US energy radially along the coaxial infusion zone.

After priming the drug lumens of

Table 1
Patient Demographics

Characteristic	Thrombolytic Drug			
	UK (n = 10)	tPA (n = 9)	rPA (n = 21)	Tenecteplase (n = 7)
Sex				
Male	3 (30)	7 (77.8)	12 (57.1)	4 (57.1)
Female	7 (70)	2 (22.2)	9 (42.9)	3 (42.9)
Mean age ± SD (y)	61.3 ± 21.8	54.6 ± 18.7	42.4 ± 19.9	56.3 ± 10.7
Cases of DVT	14	9	22	8
Location				
Upper extremity	2 (14.3)	3 (33.3)	13 (59.1)	1 (12.5)
Lower extremity	12 (85.7)	6 (66.7)	9 (40.9)	5 (62.5)
Other	–	–	–	2 (25.0)
Reported symptom duration				
Acute (≤14 d)	4 (30.8)	8 (88.9)	12 (66.7)	1 (14.3)
Subacute (15–28 d)	1 (7.7)	1 (11.1)	1 (5.6)	1 (14.3)
Chronic (>28 d)	6 (46.2)	0 (0.0)	1 (5.6)	2 (28.6)
Acute-on-chronic	2 (15.4)	0 (0.0)	4 (22.2)	3 (42.9)

*Symptom duration was not reported in one case treated with UK, four cases treated with rPA, and one case treated with tenecteplase.

Note.—Values in parentheses are percentages.



Figure 1. The EKOS EndoWave System consists of a multiple-lumen infusion catheter with removable, coaxial US core and a control unit that delivers low-energy US with concomitant thrombolytic drug infusion into the thrombus.

the catheter with subtherapeutic heparin (1,000 U/mL), continuous infusion of thrombolytic agent was initiated through the side-hole delivery infusion catheter. UK was infused most commonly at a rate of 100,000 U/h or 120,000 U/h (range, 80,000–140,000 U/hr). tPA was infused typically at a rate of 1.0 mg/h (range, 0.25–2.0 mg/h) and rPA was infused at 0.25 U/h or 0.5 U/h (range, 0.25–0.50 U/h). One patient received a 2-U bolus of rPA on initiation of infusion. Tenecteplase was typically infused at 0.2 mg/h or 0.5 mg/h (range, 0.20–0.50 mg/h). Normal or heparinized saline solution was also continuously infused through the central lumen of the catheter at a rate of 35–70 mL/h for the purpose of dissipating any small amount of heat generated by the US energy.

US energy was delivered via the core wire with simultaneous infusion of thrombolytic drug. The EndoWave system control unit, which monitors temperature and power in the infusion zone via a series of thermocouples in the catheter, automatically adjusted power to optimize lysis of the treated occlusion.

Follow-up venography was performed on all patients at the discretion of the interventional radiologist, with the first check ranging from 2 to 29 hours after initiation of treatment. The

study reflected the standard clinical practice of each investigator; therefore, variables such as thrombolytic drug and venographic follow-up checks were not standardized. Treatment was terminated if complete lysis was achieved; otherwise, US-accelerated thrombolysis was continued until complete lysis was achieved or there was no progression of thrombolysis between venography studies. After the thrombus was cleared, adjunctive procedures and/or surgical therapies including percutaneous transluminal angioplasty (PTA) and stent placement were performed to treat any underlying lesion.

Patients received thrombolytic therapy in the intensive care unit or an intermediate care unit and remained hospitalized until their condition was stabilized with anticoagulant therapy. After discharge, patients were followed per site standard practice. Post-procedural outcomes were not collected.

Definitions

Hourly infused dose, total thrombolytic drug dose, and infusion times were recorded. Complete lysis was assessed by the physician in the treated vessel at final venography before adjunct intervention and defined as at least 90% lysis. Partial lysis was de-

defined as perceptible lysis less than 90%. Major complications were those that required significant therapy including any unplanned increase in level of care, permanent adverse sequelae, prolonged hospitalization, or death. Major bleeding complications were those that required significant therapy such as blood transfusions and surgery.

RESULTS

Thrombolytic Drugs and Infusion Times

US-accelerated thrombolysis was performed in 53 cases of symptomatic upper-extremity, lower-extremity, and hepatic DVT. Median hourly infused doses were 10.6×10^4 U UK, 0.85 mg tPA, 0.29 U rPA, and 0.28 mg tenecteplase. Median total doses of each thrombolytic drug were 2.0 million U UK, 14.0 mg tPA, 6.9 U rPA, and 9.5 mg tenecteplase. The median infusion time for all patients was 22.0 hours. Median hourly infusion thrombolytic drug doses, total thrombolytic drug doses, and infusion times are shown and compared with the findings of a recently published study of standard catheter-directed thrombolysis (15) in **Table 2**. Infusion times in the current study were based on standard practice patterns; therefore, lysis may have occurred before venographic assessment. Median total thrombolytic drug dose for US-accelerated thrombolysis

Table 2
Comparison of Thrombolytic Drug Dose and Infusion Times for US-accelerated Thrombolysis versus Standard Catheter-directed Thrombolysis (15)

Thrombolysis Drug and Method	Median Hourly Infused Dose	Median Total Drug Dose	Median Infusion Time (h)
UK			
US-accelerated (<i>n</i> = 14)	10.6 × 10 ⁴ U	2.0 × 10 ⁶ U	19.3
Standard (15) (<i>n</i> = 38)	11.3 × 10 ⁴ U	4.4 × 10 ⁶ U	40.6
tPA			
US-accelerated (<i>n</i> = 9)	0.85 mg	14.0 mg	18.0
Standard (15) (<i>n</i> = 32)	0.57 mg	21.6 mg	30.8
rPA			
US-accelerated (<i>n</i> = 22)	0.29 U	6.9 U	24.0
Standard (15) (<i>n</i> = 12)	0.74 U	21.4 U	24.3
Tenecteplase			
US-accelerated (<i>n</i> = 8)	0.28 mg	9.5 mg	24.3

Table 3
Resolution of Thrombus by Duration of Symptoms*

Symptom Duration	Complete Lysis (≥90%)	Overall Lysis†
All occlusions (<i>n</i> = 53)	37 (69.8)	48 (90.6)
Acute (<i>n</i> = 25)	18 (72.0)	24 (96.0)
Subacute (<i>n</i> = 4)	3 (75.0)	4 (100.0)
Chronic (<i>n</i> = 9)	7 (77.8)	7 (77.8)
Acute-on-chronic (<i>n</i> = 9)	6 (66.7)	7 (77.8)

Note.—Values in parentheses are percentages.

* Symptom duration was not reported in six cases.

† Cases with complete or partial lysis.

Table 4
Resolution of Thrombus by Thrombolytic Drug

Thrombolytic Drug	Complete Lysis (≥90%)	Overall Lysis*
UK (<i>n</i> = 14)	12 (85.7)	13 (92.9)
tPA (<i>n</i> = 9)	5 (55.6)	9 (100.0)
rPA (<i>n</i> = 22)	13 (59.1)	18 (81.8)
Tenecteplase (<i>n</i> = 8)	7 (87.5)	8 (100.0)

Note.—Values in parentheses are percentages.

* Cases with complete or partial lysis.

demonstrated an advantage compared with standard thrombolysis, with the total dose of UK decreased by 54%, that of tPA by 35%, and that of rPA by 68%. In addition, median infusion times were reduced compared with those of standard thrombolysis by 52% for patients treated with UK and by 41% for patients treated with tPA, and were similar for patients treated with rPA. Mean hourly infusion rates and durations of infusion were similar between US-accelerated thrombolysis and catheter-directed thrombolysis for patients treated with tenecteplase (16).

Resolution of Thrombus

Overall lysis (ie, sum of partial and complete thrombolysis) as confirmed through venographic assessment was achieved in 90.6% of DVT occlusions with a median infusion time of 22.0 hours (range, 6–69 h). Complete lysis was achieved in 37 occlusions (69.8%) and partial lysis in an additional 11 occlusions (20.8%) (Fig 2). Complete or partial lysis was achieved in 96.6% of occlusions that were classified as acute or subacute (Table 3). Of the five occlusions that were not lysed, four

involved chronic thrombus that did not respond to thrombolysis. One acute occlusion with recorded symptom duration of 3 days did not respond to treatment. Complete and overall lysis rates for each thrombolytic agent were similar among all groups (Table 4). As a result of the small number of cases in each group, statistical analysis comparing results with each drug was not performed.

Safety

A very low incidence of major complications was reported. Despite the fact that at least five patients were at an increased risk of bleeding as a result of relative contraindications to thrombolytic treatment, bleeding complications occurred in only two patients (3.8%), with no incidence of intracranial or retroperitoneal hemorrhage. These patients had undergone surgery and were at increased risk of bleeding. Nevertheless, the treatment team determined that the benefit of the lytic procedure outweighed the increased bleeding risk, and US-accelerated thrombolysis was initiated in both cases. The treatment successfully cleared the thrombosis, but a hematoma developed at the site of surgery. Both patients had surgical evacuation of the hematoma and blood transfusion (2 U packed red blood cells), and the complications resolved successfully with no permanent sequelae.

Adjunct Procedures

Adjunct procedures including PTA, stent placement, mechanical thrombectomy, and surgery were performed to improve venous flow after thrombolytic treatment in 40 cases (75.5%; Table 5). Chronic total occlusions and high-grade venous stenoses were treated with PTA (49.1%) and/or stent placement (24.5%). In two patients (3.8%), a surgical arteriovenous fistula was created to enhance flow through the treated stenotic and occlusive iliac venous segments.

DISCUSSION

Developed to overcome the limitations posed by long treatment times and high drug doses in catheter-directed thrombolysis, US-accelerated thrombolysis enhances drug permeation through thrombus by disaggre-

Table 5
Adjunct Procedures

Procedures	Cases
Total adjunct procedures*	40 (75.5)
PTA	26 (49.1)
Stent placement	13 (24.5)
Mechanical thrombectomy	12 (22.6)
Surgery (AV fistula)	2 (3.8)

Note.—AV = arteriovenous. Values in parentheses are percentages.

* Multiple adjunct interventions were performed in 13 cases.

gating the fibrin matrix, exposing additional plasminogen receptor sites to the thrombolytic agent (17). The US energy affects thrombus in the entire venous segment, including the space behind the valves, increasing the probability of complete thrombus clearing (Fig 3). Improved long-term patency rates in limbs with complete thrombolysis versus limbs with partial lysis has been demonstrated in previous studies of standard thrombolysis (13). For this reason, the ability of this technique to penetrate and resolve the entire thrombus may potentially lead to increased long-term patency rates and better long-term outcomes.

The present multicenter study demonstrates a considerable improvement versus previous studies of catheter-directed thrombolysis alone for the treatment of DVT, with fewer complications, reduced drug doses, and shorter infusion times. In a National Venous Registry of 287 patients with DVT treated with catheter-directed thrombolysis across 63 centers, 83% of patients exhibited some degree of lysis, but only 31% exhibited complete thrombolysis. By comparison, the overall lysis rate in the present study was 90.6% and the complete lysis rate was 69.8% (13). A single-center pilot study (16) on the use of tenecteplase in standard thrombolysis for the treatment of DVT reported significant lysis observed in 83% of cases and a complete lysis rate of 50%. In a more recent single-center retrospective study of thrombolysis in 74 patients with 82 treated DVT occlusions in the upper and lower extremities, Grunwald and Hofmann (15) compared three different thrombolytic agents—UK, tPA, and rPA—and reported similar thrombolysis rates regardless of the drug

used. The rates of thrombolysis reported in their study, ranging from 50% to 71% for complete lysis and from 96.9% to 100% for overall lysis, are similar to the US-accelerated thrombolysis results presented herein, with a comparable percentage of patients receiving corrective adjunct procedures such as PTA and stent placement (80.5% vs 75.5%, respectively). However, it is important to note that the final venograms in the current study were obtained on termination of US-accelerated thrombolysis before the performance of any adjunct procedures, whereas the study of Grunwald and Hofmann (15) reflected success rates achieved after adjunct interventional procedures. Because adjunctive therapies improve venographic appearance of the treated veins, final venographic interpretations after adjunctive procedures can be expected to indicate better outcomes than final venographic interpretations after lysis but before adjunctive procedures, as in this study. Therefore, the thrombus resolution reported in the current study may be artificially lower than those in the comparative data.

Efficacy rates reported for standard catheter-directed thrombolysis in the treatment of DVT have focused on treatment of acute thrombus. For example, a recent study used for comparison (15) reported high efficacy rates of standard catheter-directed thrombolysis; however, only 9.7% of limbs involved subacute or chronic occlusions. In addition, several studies (9,13,25) investigating endovascular interventions in the treatment of DVT have demonstrated efficacy in acute thrombus, but with lower success rates in subacute and chronic cases. Historically, the ability of endovascular interventions to clear chronic organized thrombus has been limited. In the current study, almost half of treated limbs (47%) involved subacute, chronic, or acute-on-chronic occlusions, with remarkably high rates of thrombus clearing. US-accelerated thrombolysis was shown to accomplish complete or partial lysis in 96.0% of documented acute DVT occlusions, 100% of subacute DVT occlusions, 77.8% of cases of chronic thrombus, and 77.8% of acute-on-chronic occlusions.

In the National Venous Registry (13), the mean total dose of UK used to

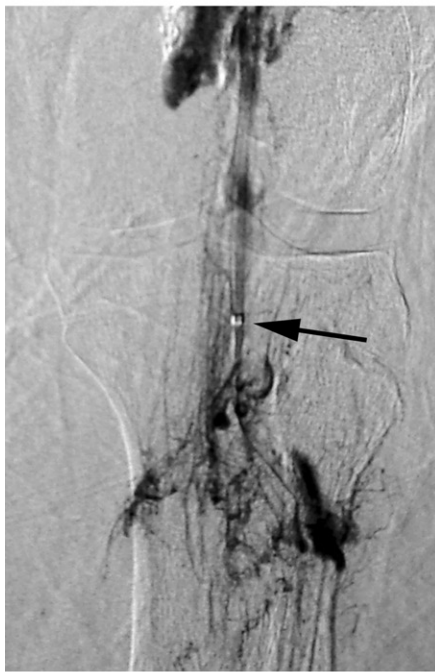
achieve complete lysis was 7.8 million U, with a mean infusion time of 53.4 hours. This total drug dose is 3.4 times higher than those in our study of US-accelerated thrombolysis with UK, with an infusion duration more than twice as long. Our results also trended toward a better outcome than seen in the study of Grunwald and Hofmann (15), which reported median total drug doses of 4.361 million U for UK, 21.6 mg for tPA, and 21.4 U for rPA. US-accelerated therapy demonstrated a considerable advantage in terms of decreased doses of UK (by 54%), tPA (by 35%), and rPA (by 68%). Median infusion times were similar between US-accelerated and catheter-directed thrombolysis for patients treated with rPA; however, US-accelerated thrombolysis infusion times were reduced versus standard thrombolysis by 52% for patients treated with UK and by 41% for patients treated with tPA.

High drug doses and long infusion times are associated with major bleeding complications, as seen in the 11% major bleeding complication rate reported for catheter-directed thrombolysis in the National Venous Registry (13). The major bleeding complication rate reported more recently by Grunwald and Hoffman (15) across all drug groups was 4.9%. Standard DVT treatment with low molecular weight heparin or long-term anticoagulation therapy is associated with relatively low major bleeding rates, ranging from 0.8% to 2.4% and from 2% to 3%, respectively (26–31). Only two major complications (3.8%) occurred in this multicenter US-accelerated thrombolysis experience. In addition, the two major bleeding complications reported in this study occurred in post-surgical patients and did not involve intracranial or retroperitoneal hemorrhage. US-accelerated thrombolysis offers similar low major bleeding rates as anticoagulation therapy, with the added benefit of complete clearing of thrombus even behind venous valves, thereby potentially preventing late complications associated with the development of PTS. Reduction in the duration and dose of thrombolytic infusion potentially decreases the rate of major hemorrhagic complications because less thrombolytic drug is administered.

Investigators report that, with US-accelerated thrombolysis, they are



a.



b.



c.



d.

Figure 2. (a) Left lower extremity with massive swelling and pain consistent with phlegmasia in a 70-year-old woman in a hypercoagulable state with lung cancer. Failed access into thrombosed deep left popliteal and posterior tibial vein. (b) Successful placement of infusion catheter from right internal jugular venous approach to left popliteal vein. (c) At 12-hour follow-up, catheter-directed thrombolysis with 0.5 U/h rPA resulted in no significant improvement. An EKOS EndoWave 5-F infusion catheter with 40 cm treatment length was placed via left posterior tibial vein access (d). Overnight US-accelerated thrombolysis with 0.25 U/h rPA resulted in resolution of thrombus in left femoral and popliteal veins.

willing to expand the use of thrombolysis. "Borderline" cases in which thrombolysis would not have been used are being treated based on observed results and the simplicity of a

single system, regardless of occlusion location within the upper and lower extremities, with very little additional effort or time. The procedure uses the same simple catheter positioning tech-

nique as standard thrombolysis, and no additional manipulations are required after the catheter is in place, requiring very little time in the interventional radiology suite. The authors

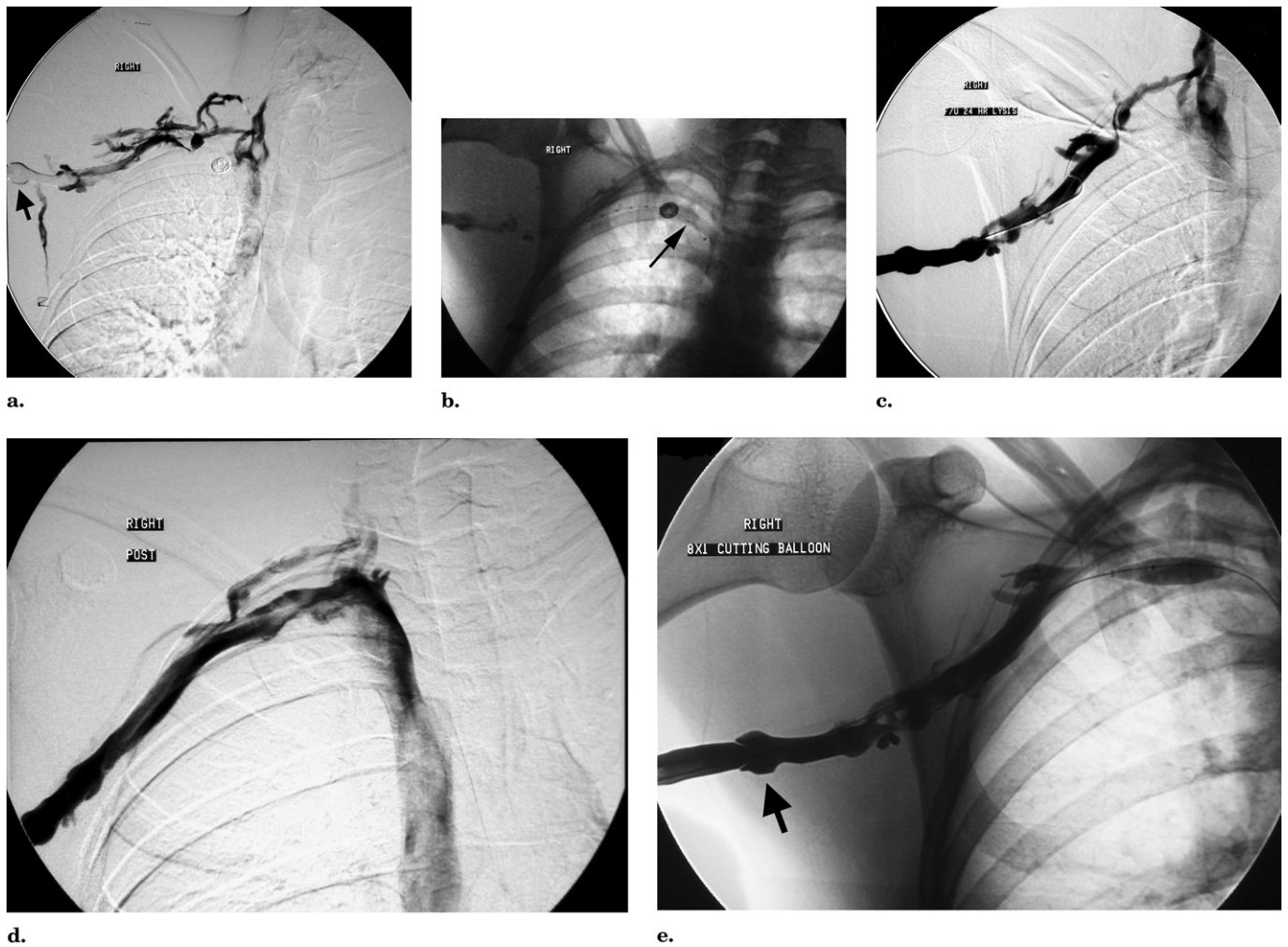


Figure 3. (a) Images from a 19-year-old male baseball pitcher who presented with acutely thrombosed right axillary and subclavian veins with immature collateral vessels caused by effort vein thrombosis. (b) EKOS catheter was placed into the thrombus. (c) Follow-up venogram at 24 hours after US-accelerated thrombolysis with 0.25 U/h rPA demonstrates near-complete resolution of thrombus. (d) Balloon angioplasty of right subclavian vein at costoclavicular space results in reestablishment of patency and flow. (e) Thrombus behind the valves was completely cleared (arrows).

of this study have also had encouraging results in treatment of thrombosis involving large veins, including the inferior and superior vena cava, saddle pulmonary embolism, and portal vein thrombosis. US-accelerated thrombolysis has also been shown to be effective in the treatment of peripheral arterial occlusions and acute ischemic stroke (18–21).

Although a cost analysis has not been performed as part of this investigation, reduced total drug doses and reduced intensive care unit stay, as well as the potential for decreased length of hospital stay, fewer lytic checks, and shorter infusion times suggest the potential for reduced costs compared with catheter-

directed thrombolysis infusion therapy alone.

The current multicenter experience was retrospective and nonrandomized, and was limited by the small number of patients. In addition, infusion time was more indicative of each investigator's practice patterns rather than actual time to achieve clot lysis, likely resulting in an underestimation of the ability of US-accelerated thrombolysis to accelerate clot dissolution. However, the high degree of complete and partial lysis coupled with reduced dosage, shorter infusion times, and low bleeding complication rate suggest that US-accelerated thrombolysis may play a significant role in catheter-

directed treatment of DVT. With future enhancements to the technology, there is potential for further benefit in these areas.

CONCLUSION

US-accelerated thrombolysis appears to be a safe and efficacious treatment for DVT in this small retrospective study. Lower than expected total thrombolytic drug doses and shorter infusion times may be possible with the addition of US. A larger, prospective study with long-term follow-up is necessary to further define the potential role of this treatment in DVT and to assess prevention of PTS.

Acknowledgments: The authors thank Shirley Carrillo, RN, BSN, and Robin Carlson for their contributions in collecting and analyzing the case data.

References

1. Augustinos P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. *Circulation* 2004; 110:127–134.
2. Bulger CM, Jacobs C, Patel NH. Epidemiology of acute deep vein thrombosis. *Tech Vasc Interv Radiol* 2004; 7:50–54.
3. Markel A. Origin and natural history of deep vein thrombosis of the legs. *Semin Vasc Med* 2005; 5:65–74.
4. Kommareddy A, Zaroukian MH, Hassouna HI. Upper extremity deep vein thrombosis. *Semin Thromb Hemost* 2002; 28:89–99.
5. Malhotra S, Punia VPS. Upper extremity deep vein thrombosis. *J Assoc Physicians India* 2004; 52:237–241.
6. Semba CP, Razavi MK, Kee ST, et al. Thrombolysis for lower extremity deep venous thrombosis. *Tech Vasc Interv Radiol* 2004; 7:68–78.
7. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med* 2004; 164:17–26.
8. Sharafuddin MJ, Shilian S, Hoballah JJ, Youness FM, Sharp WJ, Roh B. Endovascular management of venous thrombotic and occlusive diseases of the lower extremities. *J Vasc Interv Radiol* 2003; 14:405–423.
9. Jackson LS, Wang XJ, Dudrick SJ, Gersten GD. Catheter-directed thrombolysis and/or thrombectomy with selective endovascular stenting as alternatives to systemic anticoagulation for treatment of acute deep vein thrombosis. *Am J Surg* 2005; 190:864–868.
10. Killewich LA, Bedford GR, Beach KW, et al. Spontaneous lysis of deep venous thrombi: rate and outcome. *J Vasc Surg* 1989; 9:89–97.
11. Meissner MH, Manzo RA, Bergelin RO et al. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg* 1993; 18:596–605.
12. Blum A, Roche E. Endovascular management of acute deep vein thrombosis. *Am J Med* 2005; 118(suppl):315–365.
13. Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis of lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology* 1999; 211:39–49.
14. 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; 32:130–137.
15. Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. *J Vasc Interv Radiol* 2004; 15:347–352.
16. Razavi MK, Wong H, Kee ST, Sze DY, Semba CP, Dake MD. Initial clinical results of tenecteplase (TNK) in catheter-directed thrombolytic therapy. *J Endovasc Ther* 2002; 9:593–598.
17. Braaten JV, Goss RA, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. *Thromb Haemost* 1997; 78:1063–1068.
18. Parikh SR. Ultrasound accelerated thrombolysis of peripheral arterial occlusions (PAO) [abstract]. *J Vasc Interv Radiol* 2005; 16(suppl):SS18.
19. Chamsuddin A, Nazzal L, Kang B, et al. Catheter-directed thrombolysis with the endowave system in the treatment of acute massive pulmonary embolism: a retrospective multicenter case series. *J Vasc Interv Radiol* 2008; 19:372–376.
20. Motarjeme A. Ultrasound-enhanced thrombolysis. *J Endovasc Ther* 2007; 14:251–256.
21. The IMS II Trial Investigators, The Inter-ventional Management of Stroke (IMS) II Study. *Stroke* 2007; 38:2127–2135.
22. Vedantham S, Grassi CJ, Ferral H, et al. treatment of lower extremity deep vein thrombosis. *J Vasc Interv Radiol* 2006; 17:417–434.
23. Vedantham S, Thorpe PE, Cardella JF, et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol* 2006; 17:435–447.
24. Vedantham S, Millward SF, Cardella JF, et al. Society of Interventional Radiology position statement: treatment of acute iliofemoral deep vein thrombosis with use of adjunctive catheter-directed intrathrombus thrombolysis. *J Vasc Interv Radiol* 2006; 17:613–616.
25. Sillesen H, Just S, Jorgensen 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; 30:556–562.
26. Gouin-Thibault I, Pautas E, Siguret V. Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Saf* 2005; 28:333–349.
27. Couturaud F, Kearon C. Treatment of deep vein thrombosis. *Semin Vasc Med* 2001; 1:43–54.
28. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; 340:901–907.
29. Schulman S, Granqvist S, Holmström M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997; 336:393–398.
30. Palaretti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; 348:423–428.
31. Kearon C. Long-term management of patients after venous thromboembolism. *Circulation* 2004; 110:I-10–I-18.