Systemic thrombolysis in the upper extremity deep vein thrombosis

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Abstract

Almost 4% of all patients with venous thrombosis have upper extremity deep vein thrombosis (UEDVT) and the incidence of UEDVT increases over time. The frequency of post-thrombotic syndrome (PTS) after UEDVT is not low and upper extremity PTS is a potentially major morbidity that adversely affects quality of life, particularly if the dominant arm is involved. We discuss briefly the role of thrombolytic therapy in the treatment of upper extremity deep vein thrombosis and also the role of systemic thrombolysis in selected patients.

Keywords: Venous Thrombosis, Post-thrombotic Syndrome, Upper Extremity Deep Vein Thrombosis, Paget-Schroetter Syndrome, Effort Induced Upper Extremity Deep Vein Thrombosis, Central Venous Catheter Thrombosis, Thoracic Outlet Syndrome, Axillary Vein, Subclavian Vein.

ARYA Atherosclerosis 2011; 7(1): 40-46.

Date of submission: 3 Mar 2011, ***Date of acceptance:*** 3 May 2011

Introduction

A previously healthy, 24-year-old man was referred to our hospital with a five-day history of right upper-extremity pain and swelling. He was a national volleyball player and right-handed. He initially complained of arm pain and minimal numbness during exercise training in the camp. He later developed swelling of the right arm. He denied any recent trauma, use of IV drugs and indwelling catheters, or history of thromboembolism. Physical examination on admission was notable for edema involving the right upper arm and shoulder. The circumference of the right upper arm was 4.5 cm more than that of the left arm. Abduction of the right arm was painful. Jugular venous pressure was not elevated. No dilated superficial or collateral veins were seen on the anterior chest wall or shoulder. Arterial pulses were intact, and there was no evidence for sensory deficit. Duplex ultrasound of the right upper extremity revealed acute occlusive thrombus in a dilated axillary and brachial vein and also in the distal end of the subclavian vein. Clotting studies, hematocrit, chest radiograph and the computed tomography scan of the chest were normal.

We had not access to the catheter-directed thrombolysis and the patient was symptomatic despite heparin administration during previous five days. The patient was a volleyball player and had a low risk for bleeding. We decided to use systemic thrombolysis. The patient received infusion of 100 units IV t-PA followed by IV heparin. The patient's symptoms and venous congestion diminished significantly within 120 minutes of treatment. Thirty hours later the patient was asymptomatic and a CT venography showed near-complete resolution of the thrombus. He experienced no bleeding complications and soon was discharged on warfarin. Warfarin was administered for 4 months. At one-year follow-up, the patient was asymptomatic with no restriction of his activity.

Almost 4% of all patients with venous thrombosis have upper extremity deep vein thrombosis (UEDVT).[1,2] UEDVT occurs in 0.15% of in-patients.[3] Thrombosis of the arm is rare and has not been investigated as extensively as deep venous thrombosis of the leg.[4] The incidence of deep vein thrombosis in the upper limb is very lower than that of the lower extremity. The explanation for this discrepancy is multifactorial and may involve more than one of the following factors: 1) there is no analog in the upper limb to the soleal network of the calf; these veins are probably the site of thrombus formation for most lower extremity deep vein thrombosis; 2) there are fewer and smaller valves in the veins of the upper limb; these valves may be the site of thrombus formation for most venous thrombi; 3) immobilization of the upper limb is less likely even in patients with complete bed rest; 4) hydrostatic pressure in the arms is less than that of the legs; 5) increased fibrinolytic activity is present in the venous circulation of the upper limb.[5]

However, the incidence of UEDVT increases over time.[6-9] The cause is the increasing use of central

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venous catheters (CVCs), which combined with cancer, is the most important cause of UEDVT.[10,11] Besides foreign bodies such as CVCs and pacemaker leads, the main reason of upper limb thrombosis is a hypercoagulable condition, as induced by stasis in veins, coagulation abnormalities, or cancer. The stasis can be caused by a variety of conditions such as trauma of the arm, effort-related compression of the veins or compression caused by the thoracic outlet syndrome.[1,6,10,12–15]

UEDVT are divided into two groups: primary (includes unprovoked with or without thrombophilia, effort related, and thoracic outlet syndrome) and secondary (provoked by central venous catheters, pacemakers, or cancer); secondary UEDVT accounts for 75 to 80% of all cases.[16-18]

Paget in England and von Schrötter in Germany described effort vein thrombosis many years ago. Effort-induced thrombosis occurs most frequently in young men younger than 45 years. Compression of the subclavian vein usually develops in young athletes with hypertrophied anterior scalene muscle who do heavy lifting or abduct their arms. Cervical ribs, long transverse processes of the cervical spine, musculofascial bands, and clavicular or first rib abnormalities are found in these patients.[19] It is probably the microtrauma to the venous wall that activates the coagulation cascade. Also, repetitive venous compression can induce fibrous tissue formation and constriction in the vein.[20]

Central venous catheter is the most common risk factor for UEDVT.[3,17,21] Among 208 intensive care needed patients with CVCs, 33% showed catheter associated UEDVT.[22] Several factors can be important in the thrombus formation; these include catheter size, catheter material, multilumen catheters, duration of catheterization, composition of infusate, and final position of the catheter tip. In one series, all catheter related thromboses of the upper limb were associated with large-size catheters.[23] Catheter composition is important; for example, silicone elastomer catheters are less thrombogenic than polyvinyl chloride catheters.[24,25] The agents being infused, including amino acids, osmolality, and PH and proper placement of the catheter in the superior vena cava, to provide sufficient dilution of the infusate, may contribute to the development of a catheter induced thrombus. Horattas et al. found that 65% of catheter-induced thromboses were left sided.[26] Also, among one hundred patients with CVCs for dialysis, Schillinger et al. found 42% subclavian vein stenoses and only 10% jugular veins stenoses.[27] So, the right internal jugular vein should be the primary site for CVCs because the risk of stenosis and thrombosis is lower.

In one study, in one fourth of patients with idiopathic UEDVT, malignancies (most commonly lung carcinoma or lymphoma) were discovered during the follow-up period. Most of these cancers were diagnosed during the first week of evaluation for the venous thrombosis.[28]

There are limited data about the prevalence of prothrombotic abnormalities in patients with UEDVT, but studies in patients with lower-extremity DVT showed an overall rate of thrombotic disorders ranging from 30% to 40%.[29] The prevalence of coagulation abnormalities in patients with primary UEDVT in recent reports has been more than hat in previous reports.[14,15,18,30]

Clinical Manifestations

Symptoms can be intermittent, or can develop during up to one week.[31] UEDVT may involve the subclavian, axillary or brachial veins. Physical examination may show low-grade fever due to thrombus formation. Higher fevers are seen with septic thrombophlebitis or in patients with associated malignancy. SVC syndrome decreases venous return to the heart and may cause sinus tachycardia. Patients with UEDVT may have mild cyanosis of the same extremity, a palpable tender cord, limb edema, supraclavicular fullness, jugular venous distension, and dilated cutaneous collateral veins over the chest or upper arm.[13,32] If there is a central venous catheter, one or multiple ports may be occluded.[33]

The disease may lead to complications, including pulmonary embolism (PE), recurrent UEDVT and post-thrombotic syndrome (PTS) of the arm and also, loss of vascular access.

The frequency of PE in patients with UEDVT ranges from 0 to 36% but it is up to 50% in the proximal lower extremity deep vein thromboses.[16,18,34,35] Fatal PE in the UEDVT is rare.[13] Catheter withdrawn is a risk factor for PE. As catheters are removed, fibrin sheaths may peel off the catheter, separate from the vessel wall, and induce PE.[33]

Upper-extremity PTS can be a disabling condition especially if the dominant arm is involved.[36] The risk of PTS after UEDVT varies from 7-46% (weighted average 15%). Residual thrombosis and axillosubclavian vein thrombosis probably increase and catheter associated UEDVT may decrease the risk of PTS.[37]At present, there is no standardized score to assess upper extremity PTS. The modified Villalta score is a clinical PTS scale and the patients are asked to rate the severity of each of five symptoms (pain, pruritus, cramp, heaviness, and paresthesia) and a doctor then will evaluate the

severity of each of five signs (prominent veins, hyperpigmentation, edema, induration, and redness). Each symptom and sign was given a value from 0 (absent) to 3 (severe). A total score of 5 or higher was classified as the presence of PTS, and a score of 15 or higher was classified as severe PTS.[38]

DVT recurs less frequently in the upper-extremities than in the lower extremities.[6,39] In a study, female sex (adjusted HR [HRadj], 1.8; 95% CI, 0.9 to 3.9), a first non-subclavian vein thrombosis (HRadj, 2.0; 95% CI, 0.8 to 2.7), and body mass index (BMI)≥25 kg/m^2 (BMI 25 to 29 kg/m^2: HRadj, 1.6; 95% CI, 0.7 to 3.8; BMI ≥30 kg/m^2: HRadj, 2.7; 95% CI, 1 to 7.3) were associated with a higher risk of a recurrent thrombosis. A CVC at the time of first thrombosis was associated with a reduced risk of recurrence (HRadj, 0.2; 95% CI, 0.1 to 1).[20] Clearly, recurrence rate of the venous thrombosis in the lower limbs is higher among men than women.[40-44] First events in the subclavian vein were showed less recurrence than thromboses in other veins of the upper extremity. The cause may be the removal of the CVC because most CVCs are inserted in the subclavian vein.[20]

Patients with an UEDVT have an increased risk of death compared with the general population that is mainly related to cancer.[9,20,45]

Diagnosis

Venography is the standard method of diagnosis, but ultrasonography remains the most available and noninvasive test used.

Cervical spine and chest plain films are necessary to evaluate thoracic outlet syndrome. If thoracic outlet syndrome is suspected, the examiner should palpate the supraclavicular fossa for brachial plexus tenderness, see the hand and arm for atrophy, and do some maneuvers (Table 1).[13] To perform the Adson test, the examiner extends the patient's arm on the affected side while the patient extends the neck and rotates the head towards the same side. Decreasing the radial pulse with deep inspiration suggests compression of the subclavian artery. Wright's maneuver determines the reproduction of symptoms and weakening of the radial impulse when the patient's shoulder is abducted and the humerus is turned outside.[19]

Coagulation tests (lupus anticoagulant, anticardiolipin antibodies, antiphospholipid units for IgG and IgM, plasma homocysteine, activated protein C resistance, protein S and C deficiencies, antithrombin III deficiency, and prothrombin gene mutation G20210A) were done at least 2 months after the thrombotic event because of possible abnormal results due to consumption of natural inhibitors or acute phase reaction of thrombosis. Protein C and protein S plasma levels were evaluated after termination of anticoagulation treatment.

Management

There are five methods for the initial treatment of DVT: (1) subcutaneous low-molecular weight heparin (LMWH), without monitoring; (2) intravenous unfractionated heparin (UFH), with monitoring; (3) subcutaneous UFH, with monitoring (4); weight-based subcutaneous UFH, without monitoring; and (5) subcutaneous fondaparinux, without monitoring. The current recommended approach is to start both heparin and vitamin K antagonists, and to stop heparin after 5 days if the international normalized ratio (INR) is >2.0 for at least 24 h.[46] Warfarin can usually be started at a dose of 10 mg in younger (< 60 years), otherwise healthy outpatients, and at a dose of 5 mg in older or hospitalized patients. Warfarin doses should be adjusted to achieve the target INR (range 2.0 to 3.0).[47,48]

In more than 50% of patients, anticoagulation results in symptomatic improvement. However, anticoagulation can not remove existent thrombus and may not prevent PTS. The clinical improvement with anticoagulant treatments may be related more to development of collateral veins than resolution of thrombus.[49]

For most patients with acute UEDVT, the routine use of systemic or catheter-directed thrombolysis is not recommended (Grade 1C). In selected patients with acute UEDVT who are low risk of bleeding with severe symptoms of recent onset, the catheter-directed thrombolysis (CDT) may be used for initial treatment if appropriate expertise and resources are available (Grade 2C).[46]

Also, in selected patients with acute UEDVT and failure of anticoagulant or thrombolytic treatment who have severe persistent symptoms, other methods (catheter extraction, surgical thrombectomy, transluminal angioplasty, or a staged approach of lysis followed by a vascular interventional or surgical procedure) can be used if appropriate expertise and resources are available (Grade 2C).[46]

In selected patients with acute UEDVT and contraindication for anticoagulation with evidence of DVT progression or significant PE, filter placement in the superior vena cava is recommended (Grade 2C).[46]

For most patients with catheter induced UEDVT, catheter removal is not recommended if it is functional and necessary (Grade 2C).[46] New-site catheter insertion has a high rate of new thrombus formation. [50]

For patients who have UEDVT in association with a central venous catheter that is removed, the duration of long-term anticoagulant treatment should not be shortened to less than three months (Grade 2C).[46]

No randomized controlled studies have evaluated the thrombolytic therapy for the initial treatment of patients with UEDVT. But, some studies report good results for thrombolytic therapy in terms of early and late venous patency.[51-53] However, for important clinical end points such as PE, recurrent VTE, bleeding, and PTS, there is not enough data to see whether thrombolytic approach is better than anticoagulation or not.

The routine use of elastic compression or venoactive medications for PTS prevention after UEDVT is not recommended. In patients with persistent edema and pain, elastic compression to reduce symptoms of PTS is recommended (Grade 2C).[46]

Systemic Thrombolytic Therapy for Acute DVT

The best candidates for thrombolytic therapy are young, healthy patients with primary UEDVT, patients with symptomatic SVC syndrome, and those who require preservation of a central venous catheter.[34] Some trials demonstrated that systemic thrombolytic therapy provided a better lysis with reduction in post-thrombotic syndrome.[54-61]

There are two recommendations: 1-Some patients with extensive proximal DVT (*e.g.*, symptoms for less than 14 days, good functional status, life expectancy of more than 1 year, and low risk of bleeding) may benefit from the systemic thrombolytic therapy to reduce acute symptoms and post-thrombotic morbidity if CDT is not available (Grade 2C).[46]

2-In patients with acute PE, the thrombolytic agent is administered via a peripheral vein rather than placing a pulmonary artery catheter (Grade 1B).[46]

And, we want to think about systemic thrombolytic therapy in selected patients with UEDVT; those patients who are low risk for bleeding and high risk for PTS.

Surgical Therapy versus Stenting

The standardized protocol for treatment includes CDT, a short period of anticoagulation, and selective surgical decompression for patients with persistent symptoms. Some believe that there is no role for stenting of the subclavian vein in the region of the thoracic outlet before operative decompression because the persistent mechanical forces likely lead to stent malfunction and making the situation worse.

The young age (<28 years old) and the use of stent during initial treatment increase the recurrent rate of thrombosis. Thus, younger patients are probably suitable for early surgical decompression, and the use of stents without thoracic outlet decompression is not recommended. Patients who respond to warfarin therapy and demonstrate complete resolution of symptoms can be offered a non-operative approach with acceptable long-term results. Younger patients who are potentially more active and might engage more rapidly in strenuous activities probably should be offered surgical decompression. There are not persistent venographic findings that necessitate surgical intervention.[62]

There are different strategies from immediate first-rib resection during the hospitalization to some delayed surgery, 3 months later to no surgery at all. Indications for the surgery early after thrombolysis and the trial of outpatient anticoagulation include (1) the persistence or recurrence of venous hypertensive symptoms,(2) any evidence for recurrent or new thrombus, (3) obstruction of perivenous collaterals with abduction/external rotation in the face of subclavian vein occlusion, and (4) evidence of persistent or recurrent vein damage, as demonstrated by significant wall thickening.[62]

The potential benefit of conservative approach versus thoracic outlet decompression is to avoid the surgical complications, such as brachial plexopathies, phrenic nerve paresis, subclavian arterial injuries, and lymphatic leaks, with incidences ranging from 15% to 20%.[63]

Table 1. Provocative Physical Tests [64]

Diagnostic Test	Maneuver	Positive Test
Adson (scalene)	The patient inspires maximally and hold his or her breath while the neck is fully extended and the head is turned toward the affected side.	The loss or decrease of radial pulse or the reproduction of neurologic symptoms means a positive test.
Halsted (costoclavicular)	The patient places his or her shoulders in a military position (drawn backward and downward).	The loss or decrease of radial pulse or the reproduction of neurologic symptoms means a positive test.
Wright (hyperabduction)	The patient's arm is hyperabducted 180°.	The loss or decrease of radial pulse or the reproduction of neurologic symptoms means a positive test.

Conclusions

The optimal management of effort-related primary upper extremity vein thrombosis is not determined because outcomes after different treatment strategies are based on isolated case reports and small retrospective series. Thus, decision should be individualized.

The patients are often young people and otherwise healthy. Major disability can develop in these patients if PTS is occurred.

Anticoagulant therapy did not achieve complete resolution of the thrombus over months of follow-up. Other treatments, including thrombolytic therapy and surgical intervention might be indicated in patients whose symptoms do not decrease significantly after conservative therapy.

The catheter-directed thrombolysis provides higher clot resolution rates and less systemic side effects from systemic thrombolysis. However, it is possible to use systemic thrombolytic therapy for selected cases with UEDVT. It may be similar to the use of systemic thrombolysis in the pulmonary emboli or extensive proximal DVT.

Footnote (page 1 or 2): If benefits clearly do or do not outweigh harms, burden, and costs, it makes a strong Grade 1 recommendation. If there are less certainty about the magnitude of the benefits and risks, burden, and costs, it makes a weaker Grade 2 recommendation.

For grading the methodologic quality, randomized controlled trials (RCTs) are high-quality evidence (designated by "A"), but quality can decrease to moderate ("B"), or low ("C") because of poor design and conduct of RCTs, imprecision, inconsistency of results, or a high suspicious for reporting bias. Observational studies are as low quality of evidence (C) but can improve their quality with very large treatment effects.

Conflict of Interests

Authors have no conflict of interests.

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