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The Risk Factors and Clinical Outcomes of Upper Extremity Deep Vein Thrombosis

Jung-Ah Lee, PhD, RN[1], Brenda K. Zierler, PhD, RN, RVT[2,3], and R. Eugene Zierler, MD[3,4,5,6]

Abstract

The prevalence of upper extremity deep vein thrombosis (UEDVT) has shown a dramatic increase with the use of central venous catheters (CVCs) for patient care. The objective of this study was to identify risk factors and clinical outcomes in patients diagnosed with UEDVT at an academic medical center over a 1-year period. Medical records of 373 consecutive patients who underwent upper extremity venous duplex ultrasound (VDU) examination were retrospectively reviewed. A quarter of the patients screened by VDU (94 of 373) had acute UEDVT; 63% presented with arm swelling or arm pain; 48% had cancer; and 93% had indwelling CVCs. Cancer patients with CVCs were more likely to develop UEDVT (48%). Of the 94 UEDVTs, 16% had concurrent lower extremity DVT. The incidence of objectively confirmed pulmonary embolism (PE) was 9% (8 of 94 patients), and the 1-month mortality rate was 6.4%. The majority of patients (80%) with UEDVT received anticoagulation therapy and 20% were not treated. The most common risk factors for UEDVT were indwelling CVCs and a diagnosis of cancer. The incidence rate of PE and mortality rate from UEDVT were not insignificant at 9% and 6%, respectively. There were no institutional screening protocols for patients at risk of UEDVT associated with CVCs. Future research should focus on risk assessment and management protocols for patients at risk of UEDVT. In addition, a comparison of clinical outcomes associated with the type, size, and duration of catheter placement should be conducted in patients at risk of or diagnosed with UEDVT.

Keywords

upper extremity deep vein thrombosis, venous thromboembolism, pulmonary embolism, mortality, prophylaxis, risk factors, outcomes

Introduction

Upper extremity deep vein thrombosis (UEDVT) has traditionally been considered a rare condition, partly because of a relatively lower rate of complications (eg, pulmonary embolism [PE], postthrombotic syndrome [PTS], and mortality) when compared to lower extremity deep vein thrombosis (LEDVT).[1-3] With an increase in the use of central venous catheters (CVCs) for acute and long-term care, UEDVT has become a more common clinical problem in the last few decades.[4] Moreover, higher morbidity and mortality rates associated with UEDVT compared to LEDVT have been reported,[1] suggesting that a diagnosis of UEDVT may be a predictor of morbidity and mortality. Although UEDVT accounts for <4% of all episodes of DVT, this rate is believed to be underestimated and may only reflect symptomatic and objectively documented UEDVT.[5,6] With the increase in utilization of CVCs, especially peripherally inserted central catheters (PICCs), the risk of UEDVT is even greater.[7-9] Due to their low cost and ease of placement, the use of PICCs for central venous access has markedly increased over the last decade. Indications for placement of CVCs vary but predominantly include access for chemotherapeutic agents, parenteral nutrition, and antibiotic therapy.[10,11] The purpose of this study was to identify risk factors associated with acute UEDVT and to describe the clinical outcomes in patients who were objectively diagnosed with acute UEDVT over a 1-year study period.

Methods

The design of this study was descriptive using retrospective chart reviews of consecutive patients who underwent upper

[1] Program in Nursing Science, University of California Irvine, Irvine, California
[2] Department of Biobehavioral Nursing and Health System, School of Nursing, University of Washington, Seattle, WA, USA
[3] Department of Surgery, University of Washington School of Medicine, Seattle, WA, USA
[4] D. E. Strandness Jr. Vascular Laboratory, University of Washington School of Medicine, Seattle, WA, USA
[5] University of Washington Medical Center, University of Washington School of Medicine, Seattle, WA, USA
[6] Harborview Medical Center, University of Washington School of Medicine, Seattle, WA, USA

Corresponding Author:
Jung-Ah Lee, Program in Nursing Science, University of California Irvine, 100A Berk Hall, Irvine, CA 92697, USA
Email: jungahl@uci.edu

Table 1. Baseline Characteristics of Patients With UEDVT

Characteristic	N (%)
Mean age (SD, range): year	51(13.6, 19-80)
Sex (female)	43 (56%)
Race (Caucasian)	74 (79%)
Patient status (inpatient)	78 (83%)
Mean length of hospital stay (SD, range), day	26 (23, 1−121)
Malignancy	46 (49%)
Signs and symptoms	
Pain and/or swelling in upper extremity	58 (61.7%)
Pain and/or swelling in neck and/or face	6 (6.4%)
PE symptoms (dyspnea, chest pain, and fever)	11 (11.7%)
Asymptomatic	24 (25.5%)

Abbreviations: UEDVT, upper extremity deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation.

extremity venous duplex scanning from January 1 to December 31, 2001. During this period, 373 patients were evaluated with upper extremity venous duplex scans to rule out UEDVT in a vascular laboratory accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories at an academic medical center. Twenty-five percent (94) of the patients were diagnosed with one or more thrombi in at least one or more upper extremity deep veins. Venous duplex scans were utilized as the standard objective test for diagnosing an UEDVT. Venography was only performed for the purpose of finding an appropriate vein to insert additional CVCs when existing catheters were occluded, or to confirm the catheter location, but not for the primary diagnosis of acute UEDVT.[3]

The medical records of the 94 patients diagnosed with UEDVT by venous duplex scans were reviewed in detail to identify patient demographic information, risk factors for UEDVT, sites of thrombi, physician management patterns for UEDVT, and clinical outcomes, such as concurrent LEDVT, PE, and mortality at 1 month.

Data were analyzed using SPSS version 16 for Windows. Descriptive statistics (frequencies and percentage) were performed. The University of Washington Human Subjects Committee approved this study.

Results

Patients

During the 1-year study period, 373 patients at risk of UEDVT with or without typical symptoms and signs were screened by venous duplex ultrasound (VDU). Of the 373 patients scanned, 94 patients (25%) were diagnosed with acute UEDVT.

Table 1 presents the characteristics of the presenting signs and symptoms of patients diagnosed with UEDVT. The mean age was 51years ($\pm$14, range 19-80 years); 56% were females and 79% were Caucasian. Eighty-three percent (78 of 94) of patients who were diagnosed with UEDVT were inpatients and 14% (13 of 94) of patients were referred from the hospital outpatient clinics but had recently been hospitalized. The mean length of stay for hospitalized patients with UEDVT was 25.5 days (range 1-121 days, median: 25 days). Approximately one half of patients with UEDVT had a clinical diagnosis of cancer (49%, 46 of 94). The remaining patients with UEDVT had a clinical diagnosis of cardiac, infectious, hepatic, gastrointestinal, pulmonary, renal, hematologic, or endocrine diseases. The most common signs and symptoms for UEDVT were pain and swelling in an upper extremity (62%, 58 of 94). Six percent of patients with UEDVT presented with pain and edema in the neck or/and face. Symptoms of PE, including dyspnea, chest pain, or fever, were present in 12% of patients with UEDVT. A quarter of patients who were diagnosed with UEDVT were asymptomatic; however, they had more than 1 risk factor for DVT.

Table 2. Anatomic Sites of UEDVT

Venous Sites Involved	Multiple Site UEDVT N (%)	Single Site UEDVT, %
Subclavian vein	58 (62)	13
Internal jugular vein	42 (45)	11
Axillary vein	42 (45)	2
Brachial vein	27 (29)	7
Innominate vein	24 (26)	2
Radical vein	1 (1)	1

Abbreviation: UEDVT, upper extremity deep vein thrombosis.

The sites of UEDVT are listed in Table 2. In 62% (58 of 94) of patients, thrombi were present in more than 1 deep vein of the upper extremities, including, the subclavian, internal jugular, auxillary, brachial, and innominate veins. Isolated UEDVT was not common but occurred more often in the subclavian vein (13%), the internal jugular vein (11%), and the brachial vein (7%).

Risk Factors for UEDVT and Clinical Outcomes

Table 3 describes the risk factors and clinical outcomes associated with UEDVT, including PE and the 1-month mortality rate. The risk factors identified in this study for UEDVT were indwelling CVCs, immobilization, cancer, previous UEDVT, cardiac diseases, recent surgery, hypercoagulable states, age ($\geq$ 75), and hormone replacement therapy. The most common risk factor was indwelling CVCs (93%, 87 of 94). The types of catheters associated with UEDVT were PICCs, which accounted for 40% (38 of 94), followed by implanted port-a-catheters (18%), and nontunneled Hickman catheters (15%). The majority of the cancer patients with UEDVT had indwelling CVCs (89%, 41 of 46). Fifty-nine percent (27 of 46) of cancer patients with UEDVT concurrently underwent chemotherapy and 26% (12 of 46) were undergoing radiation therapy.

In addition, cardiac diseases were identified as common risk factors for UEDVT (29%, 27 of 94). Twenty-seven patients (29%) with UEDVT had a history of DVT (UEDVT in 17%, LEDVT in 4.3%, and both upper and lower extremity DVT in 7.4%). Twenty-seven percent of patients (25 of 94) with UEDVT had undergone major surgery within 30 days prior

Table 3. Risk Factors and Clinical Outcomes of UEDVT

Risk Factors	N (%)	1-Month Mortality (N = 6)
Central venous catheter placement	87 (93)	6
Prolonged bed rest (more than 3 days)	67 (71)	5
Malignancy	46 (49)	6
Previous UEDVT	27 (29)	0
Cardiac diseases	27 (29)	2
Recent surgery (within 30 days)	25 (27)	1
Hypercoagulable state	9 (10)	1
Age $\geq$ 75	5 (5)	0
Hormone therapy	2 (2)	0
No apparent cause of UEDVT	1 (1)	0
Concomitant LEDVT	15 (16)	0
Concomitant PE	8 (9)	0
Anticoagulation	75 (80)	3
No anticoagulation	19 (20)	3

Abbreviations: UEDVT, upper extremity deep vein thrombosis; LEDVT, lower extremity deep vein thrombosis; PE, pulmonary embolism.

to the diagnosis of their UEDVT. Nine patients with UEDVT were screened for a hypercoagulable condition and 4 (4%, 4 of 94) had positive results (including antithrombin III, protein C and S, factor V and VIII, lupus anticoagulant, cardiolipin antibody, homocysteine, and von Willebrand antibody). Five patients over age 75 were diagnosed with UEDVT. Two patients with hormone replacement therapy were diagnosed with UEDVT. No patients with a family history of secondary DVT or exercise-induced (effort thrombosis or primary) DVT were identified within the time period of this study.

Among the patients with UEDVT, 16% (15 of 94) had concomitant LEDVT and 9% (8 of 94) had concurrent PE. Three of the 8 patients with PE also had LEDVT. Six patients (6.4%) died within 1 month after being diagnosed with UEDVT. Their underlying disease was cancer and they had indwelling CVCs placed for their intensive treatment.

Six patients with UEDVT had received prophylactic anticoagulation. Eighty percent (75 of 94) of patients with UEDVT were treated with various combinations of anticoagulants including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and/or warfarin. Twenty percent (19 of 94) of patients with UEDVT were not treated with any anticoagulation therapy. The CVCs of 8 patients who were not treated with anticoagulation were removed following the diagnosis of acute UEDVT.

Discussion

Upper extremity DVT has been increasingly recognized in clinical settings with the increase in utilization of CVCs and the increase in the use of VDU to screen for UEDVT.[12] We observed that a quarter of those who were referred to the vascular laboratory at an academic medical center were diagnosed with UEDVT (25%, 94 of 375). The most common risk factors associated with UEDVT found in this study population were indwelling CVCs (93%), immobilization for more than 3 days (71%), and cancer (49%), which is consistent with previous studies.[11,13,14]

Risk Factors for UEDVT

Upper extremity DVT is classified as either primary or secondary on the basis of its pathogenesis. Primary UEDVT is a rare disease referring to either effort thrombosis (Paget-Schroetter syndrome) or idiopathic UEDVT. In this study, only 2 patients (19 and 39 years) presented with arm swelling after exercise, and they were not diagnosed with UEDVT. Secondary UEDVT develops in those who have CVCs, pacemakers/defibrillators, or cancer.[3,15] In this study, 93% of patients with UEDVT had CVCs and a diagnosis of cancer. The risk factors for UEDVT in those without CVCs (7.5%, 7 of 93) were cancer, previous UEDVT, recent surgery, cardiac disease, hormone therapy, hypercoagulable state, and/or immobilization.

The most frequent risk factor associated with UEDVT was the presence of CVCs (93%). Almost half of the patients with CVCs had PICC placements (44%, 38 of 87). The use of PICCs has markedly increased for in-hospital use and home therapy due to its relatively low cost, ease of placement, and good tolerance by patients.[8] Currently, more than 400 PICCs per month are inserted by skilled nurses in this medical center. The PICCs were found in 37% of the inpatients (29 of 78) and 69% of the outpatients (9 of 13) diagnosed with acute UEDVT in this study. The actual incidence of UEDVT in all patients with PICC placements was not available in this study due to the study design, but Allen et al reported an overall thrombosis rate associated with PICCs of 38% when all upper extremity veins and subsequent PICCs were included.[8]

Unlike the relatively high rate of venous thrombosis from PICCs in the study by Allen et al, lower rates of thrombosis associated with PICC were reported in other studies (2.5% to 7%).[7,16-18] Recently Evans et al conducted a prospective observational study of PICC insertions at an academic medical center with a level I trauma center over a 1-year period and reported that 3.0% of symptomatic patients with PICC lines developed UEDVT, and the most common risk factors were prior DVT and surgery lasting > 1 hour.[18] They emphasized that the size of CVCs was significantly associated with increasing risk of PICC-associated DVT. Similarly, Grove and Pevec[7] reported a significant and linear relationship between catheter diameter and rates of UEDVT in a retrospective review of 678 patients with 813 PICCs inserted for hemodialysis access. They reported an overall thrombosis rate of 3.9% with increasing rates associated with an increase in catheter diameter (1% for 4F catheters, 6.6% for 5F, and 9.8% for 6F). In contrast, Gonsalves et al[16] found a 7% risk of developing central vein stenosis or occlusion in 154 patients who had a PICC placement with a normal venogram and showed no relationship between catheter size and catheter abnormalities. Their study also identified that catheter dwell times were significantly longer in patients with central vein abnormalities due to catheter stenosis or occlusion.[16] However, there was no significant difference in the rates of thrombosis by the diameter of PICCs in

the study by Allen et al.[8] The different results (catheter diameter, dwell time, and thrombosis rates) among those studies may be due to differences in the study populations (underlying risk factors, clinical diagnoses, and/or small sample size of patients who developed thromboses).

Patients with cancer may be in a prothrombotic state because cancer cells themselves activate the coagulation system. Moreover, patients with cancer usually have more than 1 risk factor for UEDVT due to anticancer therapy including chemotherapy, hormone therapy, radiotherapy, surgery, indwelling CVC placement, and bed rest (immobility).[3,19] In this study, all patients with cancer had one or more types of CVCs placed for therapeutic or nutritional reasons. However, there were no institution-wide standardized protocols for those patients with cancer to prevent and manage CVC-related UEDVT.

Clinical Outcomes of UEDVT

The low mortality and morbidity rates related to UEDVT have been documented previously[3]; however, a 5-year study by Hingorani et al showed a 1-month mortality rate of 16% and 3-month mortality rate[20] of 34%. In a recent report by Ascher et al in 2005, high mortality rates were associated with UEDVT at 1, 3, and 12 months (13%-23%, 31%-44%, and 40%-59% in 3 groups of upper extremity veins, respectively).[21] In the current study, an overall mortality rate of 9.6% and a 1-month mortality rate of 6.4% were found. All patients who died within 1 month after an UEDVT was diagnosed had cancer and a CVC (see Table 3).

Major complications from UEDVT are PE and PTS. The incidence of PE after UEDVT in this study was 9% which is similar to that in other studies.[1,12,21] Long-term follow-up of patients with UEDVT to document recurrent thrombosis and PTS is not common when compared to patients with LEDVT.[22,23] No data on long-term outcome including PTS were available in this study due to the nature of the study design (descriptive study using retrospective review of medical records that did not contain follow-up data on all patients with UEDVT).

Sixteen percent of the patients in this study had concurrent UEDVT and LEDVT. A higher mortality has been documented in the literature in patients with both UEDVT and LEDVT compared to those with UEDVT alone.[24] However, the results from this descriptive study did not support those findings and the differences may be attributed to the relatively small sample size and short follow-up period ($n = 94$ and study period of 1 year).

Prophylaxis and Treatment of UEDVT

There has been a change in the recommendations for using prophylaxis to prevent UEDVT in cancer patients over the last 10 years. According to the Sixth American College of Chest Physicians (ACCP) Consensus Conference on antithrombotic therapy[25] in 2001, prophylactic therapy with low-dose heparin or low-dose warfarin was recommended for patients with long-term CVCs, and LMWH was an alternative to warfarin for UEDVT prophylaxis in cancer patients with CVCs. Interestingly, the guidelines from the seventh ACCP conference on antithrombotic therapy[26] in 2004 offered a different recommendation based on available data which was that "clinicians should not routinely use prophylaxis to try to prevent thrombosis related to long-term indwelling CVCs in cancer patients."[26] Such recommendations were based on the evidence from recent randomized clinical trials.[27,28] In 2005, a study by Verso et al[29] supported the recommendation that efforts to use prophylactic heparin or warfarin to reduce catheter-related UEDVT were not warranted. The most recent ACCP guidelines (8th edition)[30] from 2008 on prevention of venous thromboembolism(VTE) continued to recommended no prophylaxis to prevent catheter-related thrombosis in cancer patients (LMWH, Grade 1B or minidose warfarin, Grade 1B).[30]

Only 5 patients with CVCs received prophylaxis (6%) and 3 patients with cancer with CVCs received prophylactic anticoagulation therapy (7%) in this study during 2001 when the use of low-dose warfarin (1 mg/d) or low-dose heparin was recommended by the ACCP for the prevention of catheter-related DVT. With respect to critically ill patients, the seventh and eighth ACCP guidelines[26,30] recommended that thromboprophylaxis should be administered according to the assessment for risk of VTE in medical patients in acute care settings. Moreover, clinical trials[31,32] have shown a lower risk of VTE for hospitalized acutely ill medical patients receiving heparin (UFH or LMWH) as thromboprophylaxis versus those receiving no thromboprophylaxis, unless patients were at high risk of bleeding.

There were multiple disciplines involved in the care of patients who were diagnosed with or at high risk of UEDVT. This study identified that the management of patients with UEDVT varied widely and ranged from immediate administration of anticoagulants to removing the catheter identified as the source of UEDVT, without any subsequent treatment or systematic follow-up. Twenty percent (19 of 94) of patients diagnosed with UEDVT were not treated with anticoagulants. Some patients had supportive care including elevation of their affected upper extremity with or without removal of CVC line or only follow-up duplex evaluation. Others were likely to be at high risk of bleeding such as those diagnosed with end-stage liver disease. No standards of care for patients with UEDVT were identified in this study. The management of each individual patient with UEDVT was left up to the referring or treating physician.

There are several limitations related to the design of this study, which is a descriptive study using retrospective chart reviews. Incomplete charting by providers or lack of information about subsequent treatment was evident. Treating physicians' decisions to manage patients was ascertained by the discharge summary notes, which were sometimes incomplete and did not always have information about catheter type, size, duration, or placement location. The UEDVT study population consisted of very sick individuals with multiple disciplines involved in the management of their care. It was difficult to distinguish between providers and to determine who was making

the treatment decisions. A patient might be referred to the vascular laboratory by 1 physician, and if the study was positive for acute DVT, another physician might prescribe anticoagulation therapy or remove the catheter.

Another limitation of this study involves the generalizability of the results because the present study reported a small sample size (94 or 379) and the individuals were selected from only 1 institution. In addition, this tertiary medical center treats very sick patients and has a large population of patients with cancer, so the results would not be generalizable to medical centers with different populations. Finally, catheter-related risk factors for UEDVT, such as dwell time, location and size of catheter, side of placement, or catheter materials were not known. Therefore, it was difficult to assess for individual contributions of catheter versus patient-related risk factors in this population.

Conclusions

The most common risk factors for UEDVT in this study were indwelling CVCs and cancer. The incidence rate of PE and mortality rate from UEDVT were not low. Prophylaxis was rarely used. There was no screening protocol or systematic documentation for patients at risk of UEDVT associated with CVCs. Upper extremity deep vein thrombosis is frequently asymptomatic until its complications occur, and thus it is important to assess risk factors for UEDVT to prevent VTE. Little is still known about the clinical outcomes of catheter-related UEDVT. Also the effectiveness of prophylaxis for the prevention of UEDVT is still controversial with a large gap between recommendations from nationwide consensus conference panels and individual practice. Therefore, future research should focus on such issues to improve patient safety in UEDVT care.

Declaration of Conflicting Interests

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