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JAMA INTERNAL MEDICINE

Nonleg Venous Thrombosis in Critically Ill Adults: A Nested Prospective Cohort Study

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IMPORTANCE Critically ill patients are at risk of venous thrombosis, and therefore guidelines recommend daily thromboprophylaxis. Deep vein thrombosis (DVT) commonly occurs in the lower extremities but can occur in other sites including the head and neck, trunk, and upper extremities. The risk of nonleg deep venous thromboses (NLDVTs), predisposing factors, and the association between NLDVTs and pulmonary embolism (PE) or death are unclear.

OBJECTIVE To describe the frequency, anatomical location, risk factors, management, and consequences of NLDVTs in a large cohort of medical-surgical critically ill adults.

DESIGN, SETTING, AND PARTICIPANTS A nested prospective cohort study in the setting of secondary and tertiary care intensive care units (ICUs). The study population comprised 3746 patients, who were expected to remain in the ICU for at least 3 days and were enrolled in a randomized clinical trial of dalteparin vs standard heparin for thromboprophylaxis.

MAIN OUTCOMES AND MEASURES The proportion of patients who had NLDVTs, the mean number per patient, and the anatomical location. We characterized NLDVTs as prevalent or incident (identified within 72 hours of ICU admission or thereafter) and whether they were catheter related or not. We used multivariable regression models to evaluate risk factors for NLDVT and to examine subsequent anticoagulant therapy, associated PE, and death.

RESULTS Of 3746 trial patients, 84 (2.2%) developed 1 or more non–leg vein thromboses (superficial or deep, proximal or distal). Thromboses were more commonly incident (n = 75 [2.0%]) than prevalent (n = 9 [0.2%]) ($P < .001$) and more often deep (n = 67 [1.8%]) than superficial (n = 31 [0.8%]) ($P < .001$). Cancer was the only independent predictor of incident NLDVT (hazard ratio [HR], 2.22; 95% CI, 1.06-4.65). After adjusting for Acute Physiology and Chronic Health Evaluation (APACHE) II scores, personal or family history of venous thromboembolism, body mass index, vasopressor use, type of thromboprophylaxis, and presence of leg DVT, NLDVTs were associated with an increased risk of PE (HR, 11.83; 95% CI, 4.80-29.18). Nonleg DVTs were not associated with ICU mortality (HR, 1.09; 95% CI, 0.62-1.92) in a model adjusting for age, APACHE II, vasopressor use, mechanical ventilation, renal replacement therapy, and platelet count below 50 × 109/L.

CONCLUSIONS AND RELEVANCE Despite universal heparin thromboprophylaxis, nonleg thromboses are found in 2.2% of medical-surgical critically ill patients, primarily in deep veins and proximal veins. Patients who have a malignant condition may have a significantly higher risk of developing NLDVT, and patients with NLDVT, compared with those without, appeared to be at higher risk of PE but not higher risk of death.

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Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) of the lower extremity and pulmonary embolism (PE) and is the third most common cardiovascular disease after acute myocardial infarction and stroke, affecting up to 5% of the population during their lifetime.[1] The epidemiology of thrombosis at other sites, including upper extremity veins, intra-abdominal veins, and cerebral veins, is less well defined, and the reported frequency depends on the data source.[2] The optimal treatment for nonleg deep vein thrombosis (NLDVT) is unclear because there are no prospective management studies and current recommendations are based on expert opinion and extrapolation from proximal leg DVT studies.

Of NLDVTs, upper extremity DVT (UEDVT) is the most common, accounting for approximately 10% of all DVT.[3] The incidence of UEDVT is increasing, paralleling an increase in central line and cardiac device usage.[3] Upper extremity DVT involves the brachial, axillary, subclavian, and more proximal veins, with proximal events defined as occurring in or proximal to the axillary vein. Unprovoked or primary events are effort related or may be caused by costoclavicular junction anatomic abnormalities. Secondary UEDVT is more common than primary UEDVT and may be caused by central venous catheters, cardiac pacemakers and defibrillators, and malignancies.[4] Complications of UEDVT include PE, postthrombotic syndrome, and, in those related to central venous catheters,

loss of catheter function. Secondary complications of UEDVT are less common than they are in lower extremity DVT (LEDVT).[3]

Central venous catheters are an important cause of UEDVT, accounting for more than 50% of all UEDVTs. Risk factors for catheter-related thrombosis include catheter position, history of VTE, number of catheter lumens, technical difficulties at time of insertion, and central venous catheter infection.[3] The effectiveness of primary prophylaxis to prevent catheter-related thrombosis is not known. A recent meta-analysis of 7 randomized clinical trials of thromboprophylaxis for prevention of catheter-related thrombosis among patients with malignancy failed to demonstrate a significant reduction in catheter-related thrombosis.[5] The use of thromboprophylaxis for the prevention of catheter-related UEDVT is not endorsed by clinical practice guidelines.[4]

In the May 2014 issue of *JAMA Internal Medicine*, Lamontagne and colleagues[6] reported findings from a prospective nested cohort of general medical and surgical intensive care unit patients with venous thrombosis that were not LEDVT. This study was a secondary analysis of a larger international randomized clinical trial (Prophylaxis for Thromboembolism in Critical Care Trial [PROTECT]), which compared dalteparin with unfractionated heparin thromboprophylaxis for prevention of LEDVT.[7] In contrast to the primary study, thrombotic events were not ascertained with routine screening, but based on symptoms and clinical suspicion. Descriptive information was presented about 84 patients (2.2% of the 3746 patient population of PROTECT) who experienced nonleg venous thrombosis. These thrombotic events were classified as being proximal, distal, superficial, or deep vein distributions in any venous system other than the lower limb. Of patients with thrombotic events in PROTECT, only 47 (1.3%) had incident DVT events involving a true anatomical deep vein (defined as NLDVT) diagnosed while in an intensive care unit. Seven patients (0.2%) were diagnosed with axial (nonextremity) DVTs of the abdominal or cerebral veins or the vena cava. The only independent predictor of NLDVT was cancer.

Most of the PROTECT patients had a central venous catheter present (3218 patients, >80%), and 34 (1.1%) of them had a catheter-related proximal DVT. This observed incidence of approximately 1% for symptomatic catheter-related thrombosis in patients receiving thromboprophylaxis is similar to that previously reported.[5]

Patients with NLDVT were more likely to develop PE (14.9% vs 1.9%, $P < .001$) than patients without NLDVT. However, the diagnosis of PE in the study by Lamontagne et al[6] was "definite" in only 4 of 67 patients, with the remaining classified as "probable or possible." The true incidence of PE in this population may in fact be closer to 6%. Because 6 of the 10 reported PEs occurred prior to or on the same day as the UEDVT diagnosis, it is not clear that UEDVT caused PE.

In PROTECT, 67 patients received treatment after being diagnosed with NLDVT. Of these, only 9 (13.4%) received therapeutic anticoagulation within 3 days of the diagnosis. It is not clear why some patients were not treated. It is also not known if the untreated thrombotic events were clinically significant. Frequently, catheter-associated DVTs that are small in size may not be clinically important and may be observed by serial imaging to monitor for proximal extension instead of pursuing anticoagulation therapy. Physicians participating in the multicenter PROTECT may have chosen not to treat these events for similar reasons. Current clinical practice guidelines recommend a minimum of 3 months of anticoagulation for proximal UEDVT (axillary vein or more proximal) (Grade 1B).[4] This evidence was derived from small observational studies or assumptions made from studies of LEDVT treatment. No randomized clinical trials have evaluated UEDVT treatment.[4] A pilot study evaluating therapeutic anticoagulation for catheter-related thrombosis in patients with malignancy demonstrated good efficacy with no reports of thrombus extension or PE, and all the catheters remained patent and functional.[8] The rate of true PE observed in PROTECT patients experiencing NLDVT appeared to range from 6% to 14.9%. Because of diagnostic uncertainty and unclear clinical relevance of the thrombotic events observed, recommendations regarding therapeutic anticoagulation cannot be derived from this study. Furthermore, Lamontagne and colleagues[6] report 2 of 10 PEs in their cohort were diagnosed prior to NLDVT diagnosis and 4 PEs were diagnosed on the same day as NLDVT, suggesting therapeutic anticoagulation would not have prevented these events.

Among intensive care unit patients receiving thromboprophylaxis, the incidence of NLDVT was low (<2%). The clinical consequences of these events are unclear because PROTECT was not designed to assess these outcomes. Thrombotic events occurred despite use of thromboprophylaxis, and further well-designed prospective studies are needed to evaluate clinical importance and management of NLDVT.

ARTICLE INFORMATION

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