The Art and Science of Infusion Nursing

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Does Prophylactic Anticoagulation Prevent PICC-Related Upper Extremity Venous Thrombosis? A Case-Control Study

ABSTRACT

The evidence regarding the value of prophylactic anticoagulation to prevent peripherally inserted central catheter-related upper extremity venous thrombosis (PRUEVT) is inconsistent. The authors reviewed 3 years of data, identifying all cases of PRUEVT at a facility in Texas, and individually matched each for risk factors with 2 controls. Not being on any form of anticoagulant or antiplatelet agent was associated with a modestly increased risk of PRUEVT (odds ratio 1.93, $P = .036$, 95% confidence interval, 1.025-3.602). Each approach to thrombosis prevention showed a trend toward a protective effect, but none reached statistical significance individually.

Key words: anticoagulation, PICC, thrombosis

Peripherally inserted central catheters (PICCs) are commonly encountered in many health care settings. PICCs allow access to the central circulation with the perceived advantages over traditional central venous catheters (CVCs) of lower cost, possibly lower infection rates, low risk of pneumothorax, and insertion by nurses. It has been suggested that the perceived advantages may be overrated.[1]

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An indwelling central catheter has been shown to be a major risk factor for upper extremity thrombosis.[2-4] Possible reasons for this are the disruption of the endothelium during insertion and interference with normal blood flow.[5,6] The risk has been found to be greater with PICCs than with CVCs.[7-10] Possible reasons for this increased risk are that PICCs usually are placed in narrower veins, and the catheters typically are longer.[5]

Symptomatic PICC-related upper extremity venous thrombosis (PRUEVT) has been reported to have an incidence of 1.9% to 15%.[2,3,10-17] When surveillance imaging has been used to evaluate asymptomatic patients with PICCs, the incidence has been found to be much higher: 23% to 58%.[5-7,16,18,19] The incidence may be lower in children. A study of pediatric patients found an incidence of 1.9%.[20]

Historically, upper extremity venous thrombosis was considered a rarity of little clinical significance. However, it is increasingly being recognized that it carries a substantial risk of pulmonary embolus and postthrombotic syndrome.[21] The percentage of patients with symptomatic PRUEVT who develop pulmonary embolism has been reported from 3.8% to 15%.[13,22] In patients with PRUEVT, length of hospital stay is longer, and costs are increased.[22,23] Damage to veins in the arm may create difficulties for patients who subsequently require dialysis.[24] Twenty-five percent of patients in 1 study had persistent arm pain on follow-up.[2] The degree of risk presented by asymptomatic PRUEVT is not clear.

Because of the high incidence of PRUEVT, several authors have suggested there is a need for research into prophylaxis for patients with PICCs.[2,4,10,12,16] Intuitively, it seems an anticoagulant or antiplatelet agent should decrease the incidence of PRUEVT. In fact, the evidence is inconsistent.

A Cochrane review[25] failed to find a benefit of anticoagulation in prevention of catheter-related thrombosis in cancer patients with CVCs. In 1 review, 97% of patients (38 of 39) who developed PRUEVT had received either anticoagulant or antiplatelet agents.[22]

Case-control studies have failed to find a significant protective effect with prophylactic doses of warfarin,[10,22] low-molecular-weight heparin,[23] unfractionated heparin,[23] and antiplatelet agents.[23] Others found results that suggested anticoagulation was associated with increased risk for PRUEVT but attributed it to confounders.[13,15]

There is also evidence supporting the use of prophylactic anticoagulation to prevent PRUEVT. Meta-analysis has shown that heparin reduced thrombosis in CVCs and pulmonary artery catheters.[26] A prospective cohort study using routine surveillance ultrasound on all patients with PICCs found that prophylactic doses of anticoagulant were associated with a dramatic decrease in the incidence of PRUEVT (61.9% vs 22.9%).[6] The odds ratio (OR) for PRUEVT has been found to be decreased with antiplatelet agents in 1 case-control study.[16] It has been observed that therapeutic anticoagulation has been very effective in preventing a second thrombus in patients who suffered 1 PRUEVT.[13] A recent randomized controlled trial found a benefit for cancer patients with CVCs.[27]

The American Academy of Chest Physicians recommends against the routine use of low-molecular-weight heparin or prophylactic doses of warfarin to prevent catheter-related thrombosis in cancer patients with CVCs. Their analysis includes studies of CVCs as well as PICCs and both inpatient and outpatient management. Although their discussion explains that the evidence is mixed, they reach a conclusion that there is no net benefit in this population.[28] International guidelines also do not recommend routine use of prophylactic anticoagulation to prevent catheter-related thrombosis in cancer patients.[29]

Because of the conflicting nature of the evidence, the authors conducted a case-control study to evaluate whether anticoagulant and antiplatelet agents were associated with a lower risk of PRUEVT. Approval to conduct the study was obtained from the institutional review board.

METHODS

PICCs in the authors' hospital system are started under sonographic guidance by the PICC team's specially trained registered nurses. All PICCs used are Bard polyurethane catheters. The nurse inserting the PICC selects the vein and the size of catheter after evaluating the patient. Tip position is confirmed by a chest x-ray read by a physician. After insertion, site monitoring is the responsibility of the floor nursing staff and the physician, although the PICC team will reevaluate a line on request. Surveillance imaging of asymptomatic patients is not routinely performed. A log is kept by the team of all PICCs and complications.

All patients with PRUEVT between June 2009 and June 2012 were identified from the log. PRUEVT was defined as a description of thrombosis in a radiology report of an upper extremity in which there had been a PICC during the preceding 48 hours. Imaging was only performed on patients in whom the treating physician had clinical concern for PRUEVT. The medical records were reviewed to determine age, gender, body mass index (BMI), past history of deep vein thrombosis (DVT), current active cancer, size and location of the PICC, and whether the patient had been receiving antiplatelet and/or anticoagulant medications for the entire 48 hours before the PRUEVT was identified by imaging. Exclusion criteria were documented: coagulopathy, age under 18, pregnancy, and incarceration. In cases in which 1 matching datum was unknown, the patient was enrolled; if more than 1 item was unknown, the patient was excluded.

For each case of PRUEVT, 2 controls were individually matched from patients who had a PICC but did not develop a PRUEVT. These controls were matched for age (± 10 years), gender, BMI (± 5), presence or absence of active cancer or previous DVT, and same size and location of PICC. Controls could be matched to a case with 1 unknown item if all other information matched. Exclusion criteria were the same as for cases. After the potential control had been enrolled, the medical record was reviewed to determine whether the control had received antiplatelet and/or anticoagulant medication for at least 48 consecutive hours while the PICC was in place.

After controls and cases were identified and it had been determined whether they had received antiplatelet and/or anticoagulant medications, the authors compared the groups to determine whether prophylaxis was associated with PRUEVT.

RESULTS

During the study period, a total of 4227 PICCs were started. There were 69 documented PRUEVTs, giving a rate of 1.6%. Eight of the cases (11.6%) had a diagnosis of an active cancer, and 3 (4.3%) had a history of DVT. No patient with a PRUEVT met exclusion criteria. We were able to identify 2 appropriate controls for each case. Of the cases, 36/69 (52%) were not receiving any pharmacologic prophylaxis. Of the controls, 50/138 (36.7%) were not receiving pharmacologic prophylaxis (Table 1). Of the cases not receiving pharmacologic prophylaxis, 18/36 (50%) had a clear contraindication. Of the controls not receiving pharmacologic prophylaxis, 9/50 (18%) had a clear contraindication.

Several approaches were found to have been used for prevention of thrombosis. These included prophylactically dosed anticoagulants, therapeutically dosed

TABLE 1

Comparison of Cases and Controls

	Cases	Controls
Male	34 (49.3%)	68 (49.3%)
Female	35 (50.7%)	70 (50.7%)
Total	69	138
Mean age	64.32 (SD 16.78)	64.20 (SD 15.61)
Mean BMI	29.15 (SD 8.82)	28.51 (7.63)
PICC size		
4 Fr	2 (2.9%)	4 (2.9%)
5 Fr	47 (68.1%)	95 (68.3%)
6 Fr	19 (27.5%)	39 (28.1%)
Unknown	1 (1.4%)	
Vein		
Cephalic	4 (5.8%)	6 (4.3%)
Basilic	45 (65.2%)	93 (66.9%)
Brachial	9 (13%)	24 (17.3%)
Unknown	11 (15.4%)	16 (11.5%)
Active cancer diagnosis	8 (11.6%)	16 (11.5%)
History of deep vein thrombosis	3 (4.3%)	6 (4.3%)

Abbreviation: BMI, body mass index.

anticoagulants, antiplatelet agents, and combinations of anticoagulants and antiplatelet agents. The most commonly used prophylactically dosed agent was enoxoparin. A small number of controls were on unfractioned heparin or fondiparinux at prophylactic doses. No patient was on prophylactic "microdose" warfarin. Antiplatelet agents included aspirin and clopidigrel, used either individually or in combination. Anticoagulant agents found to have been used in therapeutic doses included enoxoparin and warfarin.

DISCUSSION

The authors found that not being on any anticoagulant or antiplatelet agent was modestly associated with symptomatic PRUEVT (OR = 1.92; P = .036; 95% confidence interval, 1.025-3.602). Several approaches to anticoagulation were found to have been used. The protective effect from pharmacologic prophylaxis reached statistical significance only when all approaches were evaluated collectively. Although each approach showed a tendency toward a protective effect, none reached statistical significance.

This study differs from earlier case-control studies because the only factor the authors evaluated was pharmacologic anticoagulation. This allowed them to match their cases with controls on both patient-related factors and catheter-related factors that had been suggested as risk factors (Table 2). It was hoped that more rigorous matching would provide information not evident from case-control studies in which numerous risk factors were evaluated.

It is recognized that the study has limitations. As a retrospective, nonrandomized study, it may have been subject to confounding. Only inpatients were studied and the percentage of cancer patients was relatively low, so generalizing the study's results to other populations may be difficult. The only outcome studied was PRUEVT, so morbidity resulting from anticoagulation is not reflected.

The study's overall rate of PRUEVT (1.6%) was lower than has been reported in many other studies. The reason is unclear.

Among the patients not receiving anticoagulant or antiplatelet agents, 50% of cases had a documented

TABLE 2

Approaches to Anticoagulation Used

	Cases	Controls	Odds Ratio	*P* Value (Fisher Exact Test)	95% Confidence Interval
No APA or ACM	36 (52%)	50 (36.7%)	1.92	.036	1.025-3.602
Total with any APA or ACM	33 (47.8%)	88 (63.8%)	0.521	.036	0.2898-0.9359
Any ACM	29 (42%)	74 (53.6%)	0.637	.142	0.335-1.170
Any APA	12 (17.4%)	35 (20.7%)	0.626	.223	0.279-1.357
APA and ACM	8 (11.6%)	21 (30.4%)	0.737	.533	0.278-1.868
Therapeutic ACM	4 (5.8%)	10 (5.9%)	0.790	.776	0.193-2.787

Abbreviations: APA, antiplatelet agent (aspirin and/or clopidigrel); ACM, anticoagulant medication (enoxoparin, warfarin, heparin, fondiparinux).

contraindication, while only 18% of controls did. The reason for this is not apparent. Possibly this represents a higher level of overall morbidity among cases. Alternatively, clinicians may be more diligent in explaining their reasons for not ordering anticoagulants in patients who have had thromboses.

Pharmacologic prophylaxis may be of value in the prevention of PRUEVT, but as a result of the study, the researchers are unable to recommend any specific approach. Further research in this area is needed. The presence of a PICC may be a factor that clinicians should consider when evaluating the benefits and risks of ordering anticoagulation to a patient, but each decision must remain an individual one.

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APPENDIX

Risk Factors for PRUEVT

The risk factors for lower extremity DVT are well known, but the risk factors for PRUEVT may be different. Several investigators have identified a number of risk factors for PRUEVT; their findings have often been in conflict.

Patient-related factors that have been reported to increase risk include female gender,[7] male gender,[22] young age,[13] older age,[30] active cancer or chemotherapy,[2,11,30,31] and past history of DVT,[4,13,14] which failed to reach statistical significance in a large study.[23] Additional suggested patient-related risk factors include use of erythrocyte-stimulating agents,[16] amphotericin-B,[13] antibiotics (particularly vancomycin),[23] parenteral nutrition,[23] hospitalization,[16] infection of line,[1] smoking,[30] chronic obstructive pulmonary disease,[31] and diabetes.[30]

Other investigators have found that smoking and diabetes do not affect PRUEVT risk.[18] Catheter-related risk factors that have been suggested have included larger PICC size.[14,15,19,24,30] Others did not find catheter size to be a risk factor.[5,24,31] Different investigators have reported different catheter locations to increase risk; basilic placement,[23] cephalic placement,[5] left-sided placement,[23] left-sided basilic placement,[7] and noncentral PICC tip location[3] have all been reported to be risk factors. Location[18,31] and laterality[32] of the catheter have been reported not to be risk factors.

