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Regular Article

A shortened activated partial thromboplastin time predicts the risk of catheter-associated venous thrombosis in cancer patients ☆

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ABSTRACT

Introduction: Hypercoagulability due to high coagulation factor levels resulting from host inflammatory response to cancer contributes to an increased risk of venous thromboembolism (VTE) in cancer patients. Central venous catheters (CVCs) further heighten this risk. Activated partial thromboplastin time (aPTT) can be used to broadly screen for elevated levels of relevant coagulation factors. Our objective was to determine if a shortened aPTT ratio (coagulation time of test- to- reference plasma) was a predictor of CVC-associated VTE in cancer patients.
Materials and Methods: We performed a retrospective case–control study on cancer patients undergoing tunneled CVC insertion at our center from 1999 to 2006 and identified 40 patients who had CVC-associated VTE. VTE was confirmed with color duplex ultrasonography or computed tomography scan. For each case, we obtained 5 controls that had the same cancer diagnosis and were matched on the following factors: age, chemotherapy, hormone therapy (if applicable), tobacco use, TNM staging and year of diagnosis. All patients had aPTT testing within 30 days prior to surgery. We compared aPTT and aPTT ratio between cases and controls using Wilcoxon two sample test.
Results: aPTT ratio was significantly shorter in patients with CVC-related VTE as compared to controls [0.86 (95% confidence interval (CI) 0.78, 0.94) vs. 0.98 (0.94, 1.01), $p = 0.0003$]. Mean aPTT was also significantly shorter. [25.6 seconds (95% CI 23.2, 27.9) vs. 28.1 (26.9, 29.3), $p = 0.001$] aPTT ratios of the controls tended to spread across larger aPTT ratio values whereas those of cases tended to clustered around the mean.
Conclusions: Cancer patients undergoing catheter placement who develop CVC-associated VTE have a shorter aPTT and aPTT ratio than those who do not develop VTE. aPTT, a simple and inexpensive test might be useful as a predictor of CVC-associated VTE risk in cancer patients.

Introduction

Patients with cancer are at 4- to 6-fold increased risk of developing venous thromembolism (VTE) [1]. This risk varies with cancer type, stage, host responses, chemotherapy, hormonal therapy, surgery and use of central venous catheters (CVCs) [2–5]. The exact mechanism of hypercoagulability in cancer is not completely understood. Host inflammatory reaction to cancer seems to play an important role. Tumor infiltrating macrophages, key mediators of anti-tumor response produce a number of cytokines which in turn increase the synthesis and release of acute phase proteins like fibrinogen and Factor VIII (FVIII) tilting the hemostatic balance in favor of a prothrombotic state [6]. In addition, elevated levels of coagulation factors particularly FVIII and fibrinogen have recently emerged as independent risk factors for VTE [7–9]. These 'acute phase reactant' coagulation factors (FVIII and fibrinogen) can be cumulatively assessed by activated partial thromboplastin time (aPTT), a common laboratory test performed prior to surgical interventions. We reasoned that elevated levels of one or more of the relevant coagulation factors would shorten aPTT and a short aPTT ratio (coagulation time of test-to-reference plasma) can be used as a surrogate marker for elevated levels of these factors in the 'intrinsic' coagulation pathway and thereby, predict the risk of postoperative CVC-associated VTE in cancer patients. Our primary predictor of interest was aPTT as aPTT would be shortened by increased levels of both FVIII and fibrinogen, both acute phase reactants and known risk factors for VTE. The spread of normal aPTT values is also sufficiently wide to allow for accurate determination of aPTT shortening. To test our hypothesis we conducted

Abbreviations: VTE, Venous thromboembolism; CVCs, Central venous catheters; aPTT, Activated partial thromboplastin time; CT, Computed tomography; CI, Confidence interval; (F1.2), Prothrombin fragment 1.2; (TAT), Thrombin-antithrombin; FVIII: C, FVIII coagulant activity; LETS, Leiden Thrombophilia Study; CRP, C-reactive protein.

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a retrospective case–control study in cancer patients undergoing tunneled catheter insertion who have had CVC-associated VTE in the post operative period in order to determine if a short aPTT at preoperative screening in this high risk population is a risk factor for the same.

Materials and methods

Study design

Approval for the study was obtained from the Institutional Review Board at City of Hope. We carried out a retrospective case–control study on cancer patients undergoing CVC placement at our center from 1999 to 2006 and developed an episode of post-operative CVC-associated VTE within 30 days after surgery. For the purpose of this study CVC refers to an implantable catheter that have a subcutaneous tunnel such as Hickmans or Port- A- Caths. Peripherally inserted central catheters or percutaneous directly centrally placed catheters (femoral or subclavian lines) were excluded. Patients were identified using available electronic databases with ICD-9 codes for VTE. From these cases, we manually reviewed the charts of eligible patients with CVC-associated VTEs. VTE was diagnosed by color duplex ultrasonography or computed tomography (CT) scan. Cases were defined as patients with aPTT testing performed within 30 days prior to surgery and identified through the medical services system as having had a VTE after catheter placement (excluding VTE 30 days after removal of catheter). Patients who were pre-treated with anticoagulants or those who had major surgeries up to a year prior of the CVC placement were excluded. Among the cases (N = 40), there were 3 patients who had major surgeries prior to CVC placement. One patient had gastro-esophagectomy (4.5 years prior to catheter placement), another patient had nephrectomy with lymph node dissection (3 years prior), and the third patient had sigmoid resection (2 years prior); these are not counting patients with incisional biopsies. The predictors of interest for the study were aPTT and aPTT ratio prior to CVC placement. As a comparator group to the cases, we queried our cancer registry for subjects in the same time frame and similar diagnoses. Among the 8487 eligible controls, we excluded patients who did not have aPTT testing done prior to surgery and those who were pre-treated with anticoagulants.

Statistical methods

Our matching algorithm was based on the Mahalanobis distance between cases and controls on the following clinical and demographic factors: age, disease site, chemotherapy, hormone therapy (if applicable), tobacco use, TNM stages and year of diagnosis. In the case of treatment types and disease staging, these factors were matched within each disease site so that the staging and treatments were appropriate for each specific site. For Mahalanobis distance and matching implementation, we used the *optmatch* package [10]. From the Mahalanobis distances and resulting confusion matrix, each eligible control was scored with each case. Controls were only used once for matching; subjects matched once were not reused. For each case, we obtained 5 controls. Final data set contained 40 cases and 157 matched controls.

Our statistical analysis tested the hypothesis that aPTT values and aPTT ratio are shorter in subjects who developed CVC-associated VTE within 30 days of catheter insertion. We compared cases versus controls with respect to these two outcomes using the Wilcoxon two sample test. Barplots were relative frequency charts rounded to the nearest tenth for both aPTT and aPTT ratio.

Results

Patient characteristics

Table 1 shows the baseline characteristics of the 40 cases and 157 matched controls. Due to the matching algorithm, the cases and controls were balanced across clinical factors. However, there was a significant difference between cases and controls for the number of days from when aPTT testing was obtained and when the catheter was inserted (p = 0.021).

Table 1
Demographics of the cases of catheter-related venous thromboembolism and matched cases.

	Cases (N = 40)		Controls (N = 157)	
Age at Dx Mean ± SE	43 ± 1.5		48 ± 2.4	
Days between PT labs & catheter insertion Mean ± SE	8.4 ± 1.3		5.5 ± 0.6*	
Gender				
Female	17	(44)	69	(44)
Tobacco Use				
No	22	(55)	83	(53)
Yes	5	(13)	15	(10)
Former smokers	9	(22)	32	(20)
Unknown	4	(10)	27	(17)
Site				
Blood/Bone Marrow	17	(43)	72	(46)
Breast	3	(7)	12	(8)
Kidney/Prostate/Bladder	2	(5)	10	(6)
Skin	1	(3)	3	(2)
Colon/Rectum/Anus	2	(5)	6	(4)
Esophagus	1	(3)	3	(2)
Lymph nodes	10	(25)	36	(23)
Ovary	1	(3)	2	(1)
Other**	3	(7)	13	(8)

Coagulation studies

Fig. 1 Panel A demonstrates barplots comparing aPTT between cases with CVC-related VTE and their matched controls. The Wilcoxon test for this means comparison was statistically significant (p = 0.001). We performed an ANOVA analysis to adjust for the difference in days between aPTT testing and catheter insertion. The difference in days was not a significant factor (p = 0.42) however, the difference between cases and controls remained significant (p = 0.03). The mean aPTT was 25.6 seconds (s) (95% confidence interval (CI) 23.2 – 27.9 s) for cases and 28.1 s (95% CI 26.9 – 29.3 s) for controls respectively. Levene test for variance homogeneity was not significant. (p = 0.27).

Fig. 1 Panel B demonstrates barplots comparing aPTT ratio between the cases and controls. Consistent with the aPTT results, there were statistically significant differences between the aPTT ratios of cases as compared to controls (p = 0.0003). As with aPTT, an ANCOVA analysis to adjust for the difference in days between coagulation lab testing and catheter insertion was performed. The difference in days was not a significant factor (p = 0.91) however, the difference between cases and controls remained significant (p = 0.0084). The mean aPTT ratio was 0.86 (95% CI 0.78-0.94) for cases and 0.98 (95% CI 0.94-1.01) for controls respectively. From the barplots, there appears to be variance heterogeneity between the aPTT ratios. Specifically, the aPTT ratios of the controls tended to be spread across larger aPTT ratio values whereas the cases tended to be clustered around the mean (Fig. 2). Levene's test for variance homogeneity was significant (p = 0.039), which may indicate that VTE cases with shorter aPTT ratios are distributed around a mean at or below 1.0. None of the VTE cases were noted to have aPTT ratio of 1.2 or greater. Among the cases, 6/40 (15%) had aPTT ratio of 1.0 or 1.1. In contrast, 17/157 (11%) of the control cases had aPTT ratio of 1.2 or greater, and 70/157 (45%) of the controls had aPTT ratio of 1.0 or greater. Two cases and zero controls had aPTT ratio of 0.6.

Discussion

Our results show that a shortened aPTT ratio prior to CVC insertion in cancer patients is a strong predictor for risk of CVC-associated VTE in the

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