Predicting Pulmonary Embolism in Total Joint Arthroplasty Patients

A Pilot Study

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Abstract

Postoperative venous thromboembolism (VTE) is a common and costly complication following total joint arthroplasty (TJA). Development of a refined thrombophilic screening panel will better equip clinicians to identify patients at highest risk for developing VTEs. In this pilot study, 62 high-risk TJA recipients who had developed pulmonary emboli (PE) within 90-days of surgery were eligible to participate. Of these patients, 14 were enrolled and subsequently administered a pre-determined panel of 18 hematologic tests with the aim of identifying markers that are consistently elevated or deficient in patients developing PE. A separate cohort of seven high-risk TJA recipients who did not report a symptomatic VTE within 90-days of surgery were then enrolled and Factor VIII and lipoprotein(a) levels were assessed. The most common aberrance was noted in 10 patients (71.4%) who had elevated levels of Factor VIII followed by five patients (35.7%) who had elevated levels of lipoprotein(a). Factor VIII was significantly prevalent ($p < 0.001$) while lipoprotein(a) failed to achieve statistical significance ($p = 0.0708$). Of the patients who were within normal limits of Factor VIII, three-fourths were "high-normal" with Factor VIII levels within 5% of the upper limit of normal. This study demonstrates the potential utility of this hematologic panel as part of a perioperative screening protocol aimed at identifying patients at risk for developing VTEs. However, future larger scale studies assessing the capabilities and limitations of our findings are warranted.

Symptomatic pulmonary emboli (PE) or deep venous thromboemboli (DVT), both examples of venous thromboembolism (VTE), are relatively common and costly complications of total joint arthroplasty (TJA).[1-5] Symptomatic PEs have been reported in between 0.4% to 1.1% and 0.61% to 3.5% of patients following primary total hip arthroplasty (THA) and total knee arthroplasty (TKA), respectively.[1,3,6-10] Although our ability to detect DVTs and PEs has largely improved thanks to the advent of advanced radiographic technologies, the mortality rate due to PEs has remained constant, with fatal PEs reported to be the second most common non-cardiac cause of death following TJA occurring at a rate of 0.02% to 0.5%.[6,10] This is particularly concerning as the demand for TJA continues to increase at greater than 10% a year and is projected to reach four million procedures by 2030.[11]

Thromboprophylaxis is not benign and has been associated with an increased risk for postoperative bleeding, hematoma development, infection, and increased wound drainage.[12-14] Thus, given the risks associated with use and misuse of thromboprophylaxis, it seems prudent that orthopedic surgeons risk stratify their patient population prior to determining the appropriate thromboprophylaxis regimen. By having a standardized hematologic screening panel, orthopedic surgeons may be better equipped to identify high-risk surgical candidates for VTE disease, potentially avoiding significant morbidity and mortality while reducing

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unnecessary exposure to potent thromboprophylactic agents.

In order to achieve this goal, it is important to evaluate the elements that play a role in the development of VTE.[15] Virchow's triad describes three major factors that contribute to VTE: endothelial damage, hypercoagulable state, and stasis of blood flow.[5,16] These three factors are often influenced by the patient's preexisting conditions. Several comorbidities—including obesity, chronic obstructive pulmonary disorder (COPD), congestive heart failure (CHF), tobacco use, active cancer treatment, and atrial fibrillation—are recognized to increase the risk for VTEs and have been used to determine a patient's preoperative VTE risk profile.[6,16-19] Moreover, other studies have attempted to isolate phenotypic and genomic variations predisposing TJA candidates to the development of VTEs; however, these studies have largely been limited by their design and scope.[16,20-24] Given the paucity of literature evaluating the pathophysiologic mechanism responsible for VTEs, there is no hematologic screening protocol endorsed by the American Association of Orthopedic Surgeons (AAOS) or American College of Chest Physicians (ACCP) for identifying high-risk TJA candidates.[15,19]

The purpose of this study was to refine an accurate and cost-effective thrombophilic screening panel for PE that will allow us to preoperatively risk stratify TJA candidates. Through such an approach, orthopedic surgeons will be better able to predict which patients require additional thromboprophylactic interventions, thereby reducing unnecessary prophylactic exposure in low to moderate risk patients while allowing for more aggressive therapy in high-risk patients. We hypothesized that this study would identify markers common in patients who develop PE.

Materials and Methods

Study Design

In this pilot study, we examined a subgroup of patients who are part of a larger retrospective study group (Fig. 1). This study was approved by our Institutional Review Board (IRB) and informed consent was obtained from each subject prior to data collection and analysis.

All patients who had TJA from January 2012 to October 2016 were identified through review of our institution's electronic medical record and were cross-matched with a list of patients who were diagnosed with a PE over the same time period. Those who were found to have developed the PE within 90 days of TJA were included in the final screening list to be contacted. All data collected for this study was entered into a secure database that was password protected to ensure only designated study personnel could

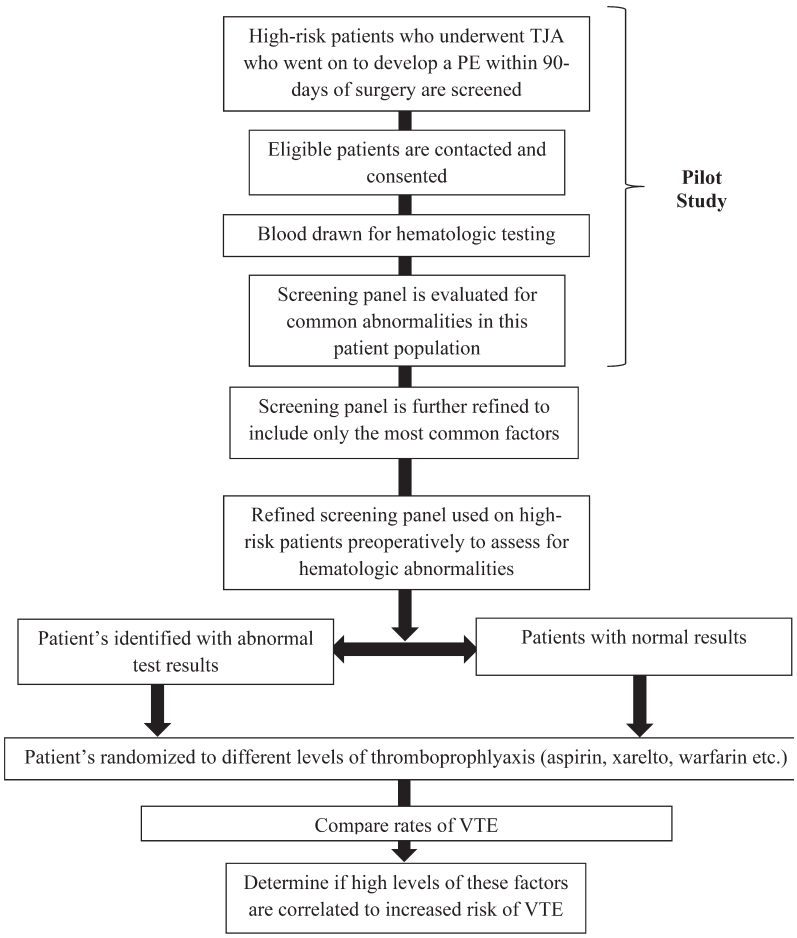

Figure 1 Study flowchart.

Table 1 Hematologic Thrombophilia Screening Panel and Legend

Legend	Screening Panel Item	Reasoning
A	Prothrombin Time	The purpose of the PT test in the thrombophilia profile is to rule out Coumadin therapy or vitamin K deficiency, which would result in reduced levels of Protein C and Protein S.
B	INR	The INR is a calculated value used to standardize the PT from one laboratory to another.
C	Thrombin Time	The Thrombin Time is performed to rule out the presence of heparin or a DTI (direct thrombin inhibitor) that might negatively affect the accuracy of certain tests in this profile. Additionally, the Thrombin Time is a screening test for dysfibrinogenemia, which can be associated with thrombosis.
D	PTT Normalized Ratio	The PTT-LA Normalized Ratio is an integrated test for which screen and confirm tests are to always performed, the results of which are used to calculate the PTT-LA Sensitive Normalized Ratio. The interpretation of these tests is based only on the Normalized Ratio. A normal ratio indicates the absence of a lupus anticoagulant.
E	DRVVT Ratio	The DRVVT Normalized Ratio is calculated from the screen and confirm tests. A normal ratio indicates the absence of a lupus anticoagulant.
F	Factor 8 Activity	Factor 8 is a major component of the blood coagulation cascade and increased levels of Factor 8 are thought to elevate risk of VTE.
G	Antithrombin III activity	It is a SERPIN (serine protease inhibitor) that acts as an anticoagulant. A deficiency is associated with an increased risk for thrombosis.
H	Activated Protein C resistance	The Activated Protein C Resistance test is a screening tool for the presence of the Factor V Mutation (FVM). A ratio < 2.1 suggests the presence of the FVM, which should be confirmed by molecular testing.
I	Free Protein S Antigen	Protein S deficiency can result in excessive or inappropriate blood clot.
J	Protein C Activity	Protein C deficiency can result in excessive or inappropriate blood clot.
K	Prothrombin G20210A Mutation	The Prothrombin G20210A Mutation is a mutation in the prothrombin gene that has been shown to be a risk factor for the development of thrombosis factor, and a mutation in this factor can lead to an increased risk of blood clots.
L	Total Cholesterol Level	Cholesterol is typically used as a measure of cardiovascular health and is used to estimate the risk of artherosclerosis, but there is evidence that cholesterol levels are elevated in HKA patients who sustain VTE.
M	Lipoprotein(a) Assay	Lipoprotein(a) is typically used as a measure of cardiovascular or cerebrovascular health and is used to estimate the risk of heart attack or stroke, but there is evidence that Lipoprotein(a) levels are elevated in TJA patients who sustain VTE and it may interfere with the thrombolytic process by competing with prothrombin.
N	Homocysteine Assay	Elevated homocysteine levels have been implicated in atherosclerosis and blood thrombus.
O	Beta 2 Glycoprotein 1 IgG	The persistent presence of IgG and/or IgM beta 2 glycoprotein I (B2GPI) antibodies (>99th percentile) is a laboratory criterion for the diagnosis of antiphospholipid syndrome (APS), which is a hypercoagulation disorder.
P	Beta 2 Glycoprotein 1 IgM	The persistent presence of IgG and/or IgM beta 2 glycoprotein I (B2GPI) antibodies (> 99th percentile) is a laboratory criterion for the diagnosis of antiphospholipid syndrome (APS), which is a hypercoagulation disorder.
Q	Cardiolipin Antibody IgG	Part of the laboratory criteria for the diagnosis of anti-phospholipid syndrome.
R	Cardiolipin Antibody IgM	Part of the laboratory criteria for the diagnosis of anti-phospholipid syndrome.

access it. Study participants from the final screening list were contacted by a designated member of the study team and interested subjects were asked to report to our institution's outpatient laboratory to provide consent and hematologic samples. During the initial visit, informed consent was obtained and 29.4 mL of blood was drawn using the appropriate aseptic technique. This blood was used for a pre-determined hematologic thrombophilia screening panel that was designed specifically for this study (Table 1). Upon enrollment, subjects were assigned a unique study ID, after which all patient identifiers were discarded to ensure patient privacy.

We included a cohort of high-risk patients who were 18 years of age or older and who underwent TJA (including primary, revision, unilateral, and bilateral) at our institution. Patients currently participating in clinical pharmacologic or

device trials or who were unable to give informed consent or adhere to follow-up as per the protocol were excluded.

To be enrolled, each subject had to have a diagnosis that would categorize them as a high-risk patient preoperatively. High-risk patients were defined as those with a history of or active cerebrovascular disease [such as prior stroke, transient ischemic attack (TIA) or carotid artery disease with more than 70% stenosis], COPD, coronary artery disease, peripheral vascular disease, venous thromboembolism or arterial thromboembolism, cancer, active smoker or stopped smoking less than 30 days prior to consent, and a body mass index (BMI) greater than 30 kg/m^2. All patients within the PE cohort developed a PE within 90 days of TJA. Symptomatic PE was defined as clinical and radiographic findings consistent with a PE.

In order to better assess the clinical significance associated with the elevated hematologic markers (e.g., lipoprotein(a) and Factor VIII) a separate control cohort of high-risk TJA candidates with a similar comorbidity profile who had not sustained a symptomatic PE within 90 days of surgery were enrolled into the study. Patient demographic information was obtained retrospectively via chart review and hematologic labs (e.g., lipoprotein(a) and Factor VIII) through prospective blood draws.

Baseline Patient Characteristics and Outcomes

Baseline characteristics were assessed in our patients for a variety of variables including patient age, sex, ethnicity, BMI, procedure performed, date of procedure, time to PE diagnosis, diagnosis of high-risk factor, and a measure of comorbidity American Society of Anesthesiologists (ASA) score. The primary aim of our study was to validate a thrombophilia screening panel that can identify high-risk VTE patients in the preoperative period. The individual markers and their significance are discussed in Table 1.

Statistical Analysis

Sample Size Determination

For the retrospective group, given that no prior data exists to ascertain the specificity and sensitivity of these tests, a feasible sample size was estimated. Our institution currently performs an average of 4,000 TJA procedures annually. Our preliminary screening for this pilot study identified 62 patients who developed a PE after TJA in roughly 4 years indicating a PE rate of less than 1%. This subject size of 14 patients represents greater than 20% of all PEs after TJA in the past 4 years.

Statistical Method

Descriptive statistics were used to quantify patient demographics, baseline characteristics, and interventions implemented. In order to determine whether biomarker levels were significantly different from established normal values, a Wilcoxon signed rank test was performed. As the reference range for "normal" FVIII levels is set at 50% to 149%, we used 100% as the mean for comparison with our population. For the lipoprotein(a) group, as the "normal" levels were less than or equal to 29 mg/dL, we set the mean normal value as 14.5 mg/dL. Statistical significance was set at a p-value of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Baseline Characteristics of the Pulmonary Embolism Cohort

A total of 62 patients who had TJA at our institution from January 2012 to October 2016 were found to have developed a PE within 90 days of their procedure. Forty-five patients were excluded for the following reasons: no significant inclusion risk factor (nine), non-English speakers (10), did not consent to study or were unable to contact (25), lab draw appointment postponed indefinitely (three), deceased (one). The remaining 14 patients from this cohort were enrolled, of which eight were female and six were male.

Their baseline characteristics are described in Table 2. Briefly, the mean age of the subjects was 68.1 years with a mean preoperative BMI of 31.2 kg/m^2. On average, female patients were younger (mean age: 66.9 vs. 69.7 years) and had lower BMIs (30.8 kg/m^2 vs. 31.5 kg/m^2) than their male counterparts did. The average ASA score was 2.5 preoperatively. None of the patients were smokers at the time of their procedure or during the blood test, but eight patients were former smokers.

All subjects denied having active cancer during their procedure, but three patients had a history of cancer. Additionally, following surgery all patients were administered a chemoprophylactic agent. Eight patients were administered 325 mg aspirin, two received 81 mg aspirin, and four received 30 mg enoxaparin injection (30 mg twice per day as inpatients and later switched to 40 mg daily upon discharge). The mean time to the PE event was 2 days after their procedure, with nine knee procedures (seven primary TKAs and two bilateral TKAs) and five primary THAs as the index surgery.

Thrombophilia Panel

All but one subject (patient 4) had values outside the normal range for at least one hematologic marker. Blood specimens were obtained at a mean of 19.7 months from the date of surgery (range: 3 to 31 months). On average, each subject had 1.9 (range: 0 to 4) abnormalities. Of the 18 panel items tested for, the most common aberration was noted in Factor VIII (FVIII); in fact, 10 of 14 patients (71.4%) had increased FVIII levels with three out of the four remaining subjects in the "high-normal" range (within 5% of the upper limit of normal) including one patient who had previously had an elevated FVIII level (Fig. 2A). Factor VIII values among this patient population were significantly different from our established normal for this biomarker of 100% (mean: 187.6%; SD: 41.06; $p < 0.001$). Lipoprotein(a) was elevated

Table 2 Baseline Patient Characteristics

Variable	PE Cohort (N = 14)	Control Cohort (N = 7)	P-Value
Age at surgery (mean ± SD, range)	68.1 ± 8.6 (56-85)	69 ± 7.0 (58-80)	0.81
Sex, n (%)			
Female	8 (57.1)	3 (42.9)	0.66
Male	6 (42.9)	4 (57.1)	
Ethnicity, n (%)			
White	11 (76.6)	5 (71.4)	NA
Black	2 (14.3)	1 (14.3)	
Hispanic	1 (7.1)	0	
Asian	0	1 (14.3)	
BMI (kg/m^2) (mean ± SD, range)	31.2 ± 6.8 (20.6-45.4)	31.1 ± 7.1 (25.6-46.1)	0.98
Procedure Type, n (%)			
Primary Hip	5 (35.7)	3 (42.9)	
Primary Knee	7 (50)	4 (57.1)	
Bilateral Knee	2 (14.3)	0	
Revision Knee	0	0	
High Risk Category, n (%)			NA
COPD	3 (21.4)	0	
CAD	3 (21.4)	2 (28.6)	
Obesity	9 (64.3)	3 (35.7)	
Current Smoker	0	2 (28.6)	
Active Cancer	0	1 (14.3)	
CVA/TIA	1 (7.1)	2 (28.6)	
History of VTE	0	0	
Diabetes	4 (28.6)	2 (28.6)	
A-fib	1 (7.1)	0	
ASA Class, n (%)			
2	8 (57.1)	3 (42.9)	NA
3	5 (35.7)	4 (57.1)	
4	1 (7.1)	0	
(mean ± SD, range)	2.50 ± 0.63 (2-4)	2.6 ± 0.5 (2-3)	0.72
PE Diagnosed on POD	2.00 ± 1.3 (1-6)	NA	NA
Thromboprophylaxis			
Aspirin 81 mg BID	2 (14.3)	1 (14.3)	1.0
Aspirin 325 mg BID	8 (57.1)	4 (57.1)	
Enoxaparin 30 mg	4 (28.6)	2 (28.6)	

A-fib: atrial fibrillation; ASA: American Society of Anesthesiologists; BID: two times per day; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CVA: cerebrovascular accident; PE: pulmonary embolism; POD; postoperative day; TIA: transient ischemic attack; VTE: venous thromboembolism; NA: not applicable.

in five of 14 patients (35.7%; Fig. 2B). These values differed from our established mean normal value for this biomarker of 14.5 mg/dL (mean: 31.0 mg/dL; SD: 25.75; p = 0.07). None of the subjects had abnormal results for cardiolipin IgG Ab, cardiolipin IgM Ab, PTT-LA normalized ratio, DRVVT normalized ratio, or prothrombin G20210A mutation. Four patients had PT values were minimally decreased (values 10.0 to 10.3). However, since these tests were used to rule out Coumadin therapy or vitamin K deficiency (which could result in reduced protein C and S levels) and not as a true

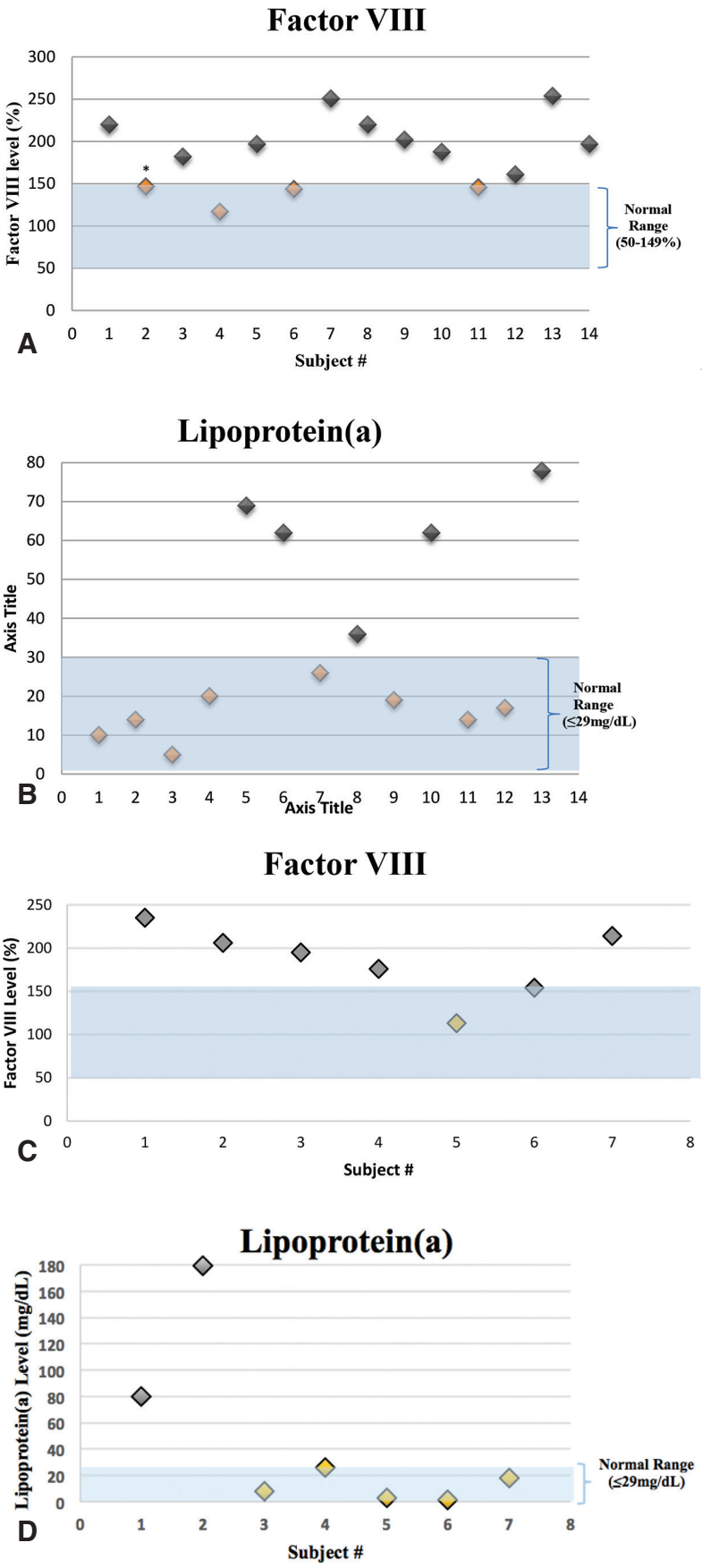

Figure 2 Factor VIII and lipoprotein (**A**) levels for all subjects who sustained a pulmonary embolism (**A** and **B**) and high-risk controls who did not sustan a pulmonary embolism (**C** and **D**). *Patient had a positive test result previously (FVIII: 152%).

Table 3 Summary of Patient Test Results

Subject	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
1-PE						●												
2-PE										●		●						
3-PE						●									●	●		●
4-PE																		
5-PE						●				●		●	●					
6-PE													●					
7-PE						●												
8-PE						●						●	●					
9-PE						●												
10-PE						●							●					
11-PE			●															
12-PE						●								●				
13-PE						●				●			●					
14-PE						●												
1-C	-	-	-	-	-	●	-	-	-	-	-	-	●	-	-	-	-	-
2-C	-	-	-	-	-	●	-	-	-	-	-	-	●	-	-	-	-	-
3-C	-	-	-	-	-	●	-	-	-	-	-	-		-	-	-	-	-
4-C	-	-	-	-	-	●	-	-	-	-	-	-		-	-	-	-	-
5-C	-	-	-	-	-		-	-	-	-	-	-		-	-	-	-	-
6-C	-	-	-	-	-	●	-	-	-	-	-	-		-	-	-	-	-
7-C	-	-	-	-	-	●	-	-	-	-	-	-		-	-	-	-	-

● Represents an abnormal test result. C: Control; PE: Pulmonary embolism.

part of the screening panel, these small abnormalities were ignored. The comprehensive results for the entire hematologic panel are presented in Table 3.

Cholesterol levels were elevated in three patients, but nine patients were on a lipid lowering medication at the time their blood was drawn, including two of the three patients with elevated cholesterol levels. Patient 5 had an activated protein C ratio (APCR) of 1.81, which is consistent with heterozygosity for a factor V mutation. Patients 10 and 13 had APCRs of 2.09, which are just below the cut-off of 2.10. This test should be repeated and molecular studies should be done for confirmation. Patient 3 was noted to have a significantly elevated anti-Beta 2 glycoprotein 1 IgM as well as a slightly elevated anti-cardiolipin IgM that are suggestive of possible diagnosis of anti-phospholipid syndrome. Further testing is needed to confirm this diagnosis as well.

Baseline Characteristics and Lipoprotein(a) and Factor VIII Analysis of the Control Cohort

The control cohort included seven TJA recipients who had undergone surgery at our institution between March 2014 and February 2016. Their baseline characteristics are presented in Table 2 and demonstrate no statistically significant difference for any baseline characteristic when compared to the PE cohort.

Total joint arthroplasty recipients within the control cohort were only administered the Factor VIII and lipoprotein(a) hematologic tests. Patient 1C and 2C had elevated lipoprotein(a) and Factor VIII and lipoprotein(a) levels, respectively. Additionally, during the index hospitalization (after TJA) patient 6C had symptoms consistent with a PE, however, computed tomography and ultrasound were used to rule out PE and DVT. Interestingly, patient 1C was diagnosed with a PE approximately 16 months after the index orthopedic procedure. The patient was a current smoker with a complicated surgical history that included at least seven spine procedures, one total shoulder arthroplasty, and bilateral hip arthroplasties.

Sub-Analysis of Lipoprotein(a) and Factor VIII

Comparative analysis of lipoprotein(a) and Factor VIII levels between the PE and control cohorts demonstrated little sta-

tistical significance (mean: 187.6%, SD: 41.06 vs. 184.7%, SD: 41.05; p = 0.868) and (mean: 31.0 mg/dL, SD: 25.75 vs. mean: 45 mg/dL, SD: 64.99; p = 0.483), respectively.

Discussion

Venous thromboembolism is a devastating complication following TJA.[5] With the projected rise in demand for TJA, the medical optimization and risk stratification of arthroplasty candidates is crucial if value-based principles are to be implemented, and this is particularly true among high-risk patients.[11] A series of meta-analyses demonstrated that, even when thromboprophylactic protocols are implemented, the risk of DVT ranges from 17.7% to 31.1% after THA and 31.3% to 81.6% after TKA.[25,26] Additionally, PEs have been reported to occur at a rate of 0.4% to 3.5% following primary TJA.[1,6,7,9,10] Many have hypothesized that the relatively high rate of VTE diagnosis is at least in part due to the robust diagnostic capabilities available to health care providers. Yet, it is well recognized that, although diagnostic capabilities have improved, the incidence of fatal PEs following TJA has remained constant.

Many studies have previously attempted to identify a relationship between hematologic markers and a patient's actual risk of VTE following arthroplasty. A study by Nowak-Gottl et al.[27] demonstrated that lipoprotein(a) was associated with an increased risk of VTE in childhood, however, the study did not evaluate VTE risk in adults. Mont et al.[20] retrospectively evaluated patients who sustained VTE following TKA and found that aberrations in plasminogen activator inhibitor activity, dilute Russell's vipor venom time (DRVVT), PT, and cholesterol levels were highly sensitive and specific for the development of PEs. In addition, Ringwald et al.[21] suggested that the presence of a single thrombophilic polymorphism may not increase the risk of symptomatic DVTs after THA, but rather several distinct mutations may have an additive effect. Conversely, many studies looking at Factor V Leiden and polymorphisms in the angiotensin-converting enzyme gene suggest these factors have not been shown to correlate with an increased prevalence of VTEs following TJA.[22-24]

Pertinent to our results, elevated levels of FVIII have been shown to be a significant and independent risk factor for the development of Pes.[28,29] The normal value of FVIII ranges from 500 to 1,500 IU/L, which represents 50% to 150% of the "normal" concentration of 1,000 IU/L. While not specific to arthroplasty patients, a population-based study by Koster et al.[30] presented results on 301 consecutive patients diagnosed with DVTs and 301 healthy controls matched for age and sex. In this study, they reported a prevalence of subjects containing a FVIII concentration greater than 1 500 IU/L was 25% versus 11% in VTE patients compared to matched controls. Furthermore, they reported that patients with elevated FVIII (greater than 1,500 IU/L) were six times as likely to develop VTEs. Recurrence rates of VTE have also been shown to steadily increase at higher FVIII levels with patients in the highest category of having a recurrence, three-fold greater than patients in the lowest subgroup.[31]

Interestingly, our results demonstrate that patients with a previous history of PE shortly after TJA were significantly more likely to have elevated FVIII (72%). Although our results support the findings of Koster et al.,[30] the correlation between elevated FVIII and VTE may be stronger than previously described. This suggests a more significant relation between elevated FVIII levels and the incidence of VTEs, particularly among high-risk TJA candidates. It may be true that higher levels of FVIII are necessary to create the risk environment necessary to predispose these patients to PE as opposed to DVTs.

In this pilot study, we were able to elucidate markers found most commonly in high-risk patients who developed a pulmonary embolism within 90 days of TJA. Increased levels of FVIII were found in nearly 72% of study participants. Interestingly, of the patients who were within normal limits, 75% were "high-normal" with Factor VIII levels within 5% of the upper limit of normal. As such, if the upper limit of normal for this screening test were adjusted by 5%, the number of patients with FVIII abnormalities would increase from 72% to 93% (Fig. 2A). Moreover, the mean FVIII level was significantly greater than the "normal" FVIII level set at 100% ($p < 0.001$). When we compared FVIII levels among the PE cohort with high-risk TJA recipients who had not suffered a PE, FVIII levels were similarly elevated with six of seven patients reporting FVIII levels greater than the normal threshold. However, lipoprotein(a) levels appeared more promising with elevated levels reported in two patients resulting in a median lipoprotein(a) level of 18 mg/dL substantially lower than the average of 45 mg/dL. Although this study is only a preliminary analysis, our results demonstrate FVIII may be an inflammatory marker elevated in patients at high-risk for VTEs during surgery, additionally lipoprotein(a) may be a promising biomarker that may help identify surgical candidates at highest risk for developing PEs. Patient 1C supports this hypothesis. With these results, we hope to optimize the hematologic panel with the aim of developing a sensitive instrument to prospectively screen high-risk TJA candidates. Patients who have elevated coagulation biomarkers can then be easily identified and appropriately managed prior to surgery.

Limitations

Our study is not without limitations. This is a pilot study assessing a unique cohort of patients, therefore, only a small subset of patients met the eligibility criteria. Second, due to the study's retrospective nature, we cannot assume that the correlation among the various hematologic markers and the development of a PE are due to causality. Additionally, in an effort to minimize study costs, no comparative control cohort was utilized. Despite the limitations, our study evaluates hematologic markers within a very select patient population and suggests an association between elevated

FVIII and clinically significant PEs. Given our results, future multi-center studies assessing surgical candidates for hematologic markers and their relationship with postoperative VTEs is warranted.

Future Research

To our knowledge, this is the first study assessing the relationship between PEs and elevated FVIII, however, we recommend that future investigators examining the occurrence of VTEs in TJA consider the following: 1. include patients with symptomatic DVTs, 2. increase study power, and 3. rigorously explore baseline patient comorbidities. Such an approach will provide a comprehensive biochemical perspective into why VTEs occur at an increased rate within the TJA population while also allowing for the development of a robust screening instrument targeting high-risk surgical candidates. Once such an instrument is developed, it may be prospectively applied in high-risk TJA candidates, thus allowing clinicians to optimize thromboprohylactic regimens with their VTE risk profile. For the first time, the tailored delivery of thromboprophylactic agents will enable physicians to minimize the complications (e.g., prolonged wound drainage, hematoma, seroma, increased bleeding) and readmissions often associated with chemoprophylaxis.

Conclusion

This study is only a necessary first step aimed at curbing the prevalence of VTE following TJA. We hope to isolate specific hematologic markers associated with the development of VTEs in order to allow clinicians to identify and aggressively manage high-risk surgical candidates. Our study suggests that the combination of FVIII and lipoprotein(a) may correlate with the development of PEs in high-risk TJA candidates. Although our study makes several noteworthy observations, we cannot explain the mechanisms responsible for these elevated hematologic markers. Moreover, there is currently no anti-thrombotic agent available that specifically targets FVIII. For this reason, future research evaluating the comprehensive clinical application of elevated FVIII and lipoprotein(a) are needed. Additionally, a better understanding of the biochemical and genomic relationships associated with elevated FVIII and lipoprotein(a) will enable scientists and health care providers to safely and reliably manage these high-risk patients.

Disclosure Statement

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