CLINICAL RESEARCH STUDY

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Periprocedural Anticoagulation Management of Patients with Thrombophilia

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ABSTRACT

BACKGROUND: Appropriate periprocedural management of the chronically anticoagulated patient with an inherited or acquired thrombophilia is uncertain. The objective of this study was to test "thrombophilia" as a potential predictor of the 3-month cumulative incidence of thromboembolism and major bleeding among chronically anticoagulated patients undergoing an invasive procedure.

METHODS: In a prospective cohort study, consecutive chronically anticoagulated patients referred to the Mayo Thrombophilia Center for standardized periprocedural anticoagulation management who had venous thromboembolism and complete thrombophilia testing were categorized as "severe," "non-severe," or "no identifiable" thrombophilia. The 3-month cumulative incidence rates of thromboembolism, bleeding, and death were estimated using the Kaplan-Meier product limit method.

RESULTS: Among 362 patients with complete thrombophilia testing, 165 (46%) had a defined thrombophilia; 76 patients had severe thrombophilia, mainly due to antiphospholipid syndrome (66%). Half of the patients in each of the 3 groups received pre- and postprocedure heparin. During follow-up, there were no thromboembolic events, rare major bleeding events (1% for each group), and 4 deaths. Due to the very low event rates for each of these outcomes, Cox proportional hazard modeling could not be performed.

CONCLUSIONS: Periprocedural event rates were low irrespective of thrombophilia status. Inherited or acquired thrombophilia was not a predictor of thromboembolism, major bleeding, or mortality after temporary interruption of chronic anticoagulation for an invasive procedure.

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Approximately 6 million patients in the US receive chronic anticoagulant therapy.[1] Each year an estimated 10% of these individuals will require temporary interruption of their anticoagulant therapy to undergo an invasive procedure.[2] Current guidelines recommend the use of bridging heparin for patients with either inherited or acquired "severe" thrombophilia, defined as deficiency of antithrombin, protein C, or protein S; antiphospholipid antibody syndrome; homozygous factor V Leiden or prothrombin G20210A genotypes or combined heterozygous genotypes.[2] "Non-severe" thrombophilia, defined as either heterozygous factor V Leiden or prothrombin G20210A genotypes, have been deemed "intermediate risk." However, data on periprocedural management outcomes are lacking and recommendations about periprocedural anticoagulation management of severe and nonsevere thrombophilia are based solely on expert opinion.[2]

To address this gap in knowledge, consecutive patients with prior venous thromboembolism who were referred to the Mayo Clinic Thrombophilia Center for periprocedural anticoagulation management over the 10-year period (1997-2007) were followed forward in time to estimate the

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3-month cumulative incidence of thromboembolism, bleeding, and all-cause mortality. We tested thrombophilia category, adjusted for heparin bridging, as a predictor of thromboembolism, major bleeding, and death.

METHODS

Study Population, Design, and Setting

Consecutive patients anticoagulated for venous thromboembolism who were referred to the Mayo Clinic Thrombophilia Center for periprocedural anticoagulation management over the 10-year period (January 1, 1997 to December 31, 2007) were eligible for inclusion; 97% consented to participate. The methods included in this study have been previously described.[3] All patients were followed forward in time for 3 months from the date of the Thrombophilia Center consultation. Patients (or family members of deceased patients) who did not return for a clinic visit were mailed a questionnaire or contacted by telephone for any symptoms or signs of thromboembolism or bleeding in the 3 months after the Thrombophilia Center consultation, and for vital status. The local medical records of patients reporting thromboembolism or bleeding, and death certificates and autopsy reports for deceased patients were obtained and reviewed by the study endpoint adjudication committee. Two experienced study nurse abstractors reviewed the complete inpatient and outpatient medical records for each patient. The study was approved by the Mayo Clinic Institutional Review Board, and all research conduct was performed according to the ethical principles of the Declaration of Helsinki.

For this analysis, only patients with a complete thrombophilia assessment performed at the Mayo Clinic Special Coagulation and DNA Diagnostic Laboratories were included. Patients were divided into 3 groups based on their confirmed thrombophilia status. These groups included "severe thrombophilia," "non-severe thrombophilia," and "negative/normal" test results. Severe thrombophilias included those patients with deficiencies of protein C, protein S, or antithrombin; homozygous Factor V Leiden or prothrombin G20210A genotypes or compound heterozygous genotypes; or antiphospholipid antibody syndrome. Criteria for the antiphospholipid antibody syndrome included lupus anticoagulant assessed by clot-based assays (dilute Russell viper venom time, activated partial thromboplastin time with platelet neutralization procedure, Sta-Clot LA [Diagnostica Stago, Inc, Parsippany, NJ]) with or without enzyme-linked immunosorbent assay-based antiphospholipid antibody testing (immunoglobulin [Ig]G and IgM isotypes at $\geq$40 units/mL) repeated at 12-week intervals to document persistence. During the time frame of this study, anti-β_2 glycoprotein 1 antibody testing was not yet included in our testing repertoire. Nonsevere thrombophilias included patients with heterozygous Factor V Leiden or prothrombin G20210A genotypes.

CLINICAL SIGNIFICANCE

- Among venous thrombosis patients with complete thrombophilia testing, nearly half had a defined thrombophilia. Of these, nearly half had a severe thrombophilia, mainly antiphospholipid syndrome.
- Inherited or acquired thrombophilia was not a predictor of thromboembolism, major bleeding, or mortality after temporary interruption of chronic anticoagulation for an invasive procedure.

Periprocedural Anticoagulation Management

Patients were seen in the Thrombophilia Center between 4 and 7 days prior to the anticipated procedure and assessed for patient-specific risk of thromboembolism and procedure-specific risk of major bleeding according to published guidelines and as previously described.[2-5] For patients requiring outpatient dental or other minor procedures associated with either a low risk of bleeding or easy access for physical hemostasis, the intensity of warfarin anticoagulation was reduced to the lower limit of the therapeutic range. For patients undergoing a nonminor procedure who were at low risk of a thromboembolic event, warfarin was stopped 5 days prior to surgery and resumed as soon as possible after surgery, starting with the patient's usual daily warfarin dose. For nonminor procedures in patients at moderate to high risk for thromboembolism, warfarin was stopped 5 days prior to surgery and the patient was "bridged" with low-molecular-weight heparin (LMWH) started when the international normalized ratio (INR) was anticipated to fall below the lower limit of the therapeutic range (typically INR $<$2.0). The last LMWH injection was given 24 hours prior to the procedure at 50% of the weight-adjusted daily dose. For all high-risk patients requiring postoperative therapeutic-dose LMWH, the first dose was delayed 48 hours. Warfarin and LMWH therapy were overlapped until the INR exceeded the lower limit of the therapeutic range for at least 24 hours. Over the 10-year study period, 3 successive LMWHs (ardeparin, dalteparin, and enoxaparin) were on the Mayo Clinic formulary and were used for periprocedural anticoagulation therapy. All patients received guideline-endorsed venous thromboembolism prophylaxis relative to patient risk, procedural risk, and bleeding risk factors.[6-8]

Laboratory Testing

All assays were performed in the Mayo Clinic Special Coagulation and DNA Diagnostic Laboratories and ordered as a test panel rather than as individual assays as previously described.[9] The thrombophilia test panel included assessment for deficiencies of protein C,[10] protein S,[11,12] or antithrombin,[13] dysfibrinogenemia, intravascular coagulation and fibrinolysis, activated protein C resistance[14]