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Incidence of symptomatic venous thromboembolism in patients with hemophilia undergoing joint replacement surgery: A retrospective study

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is a recognized complication after joint replacement surgery, and prophylaxis is routinely used in patients without bleeding disorders. However, for patients with hemophilia, pharmacologic prophylaxis is highly variable and controversial because of the inherent bleeding risk.
Aim: To review our institutional experience with outcomes of total knee or hip arthroplasty with regard to symptomatic VTE and use of VTE prophylaxis in patients with hemophilia and without inhibitors.
Methods: We reviewed records of 42 consecutive patients with hemophilia A or B who underwent 71 hip or knee replacements over a 39-year period. We also reviewed the literature to estimate the incidence of VTE after arthroplasty in the hemophilia population.
Results: All patients used compression stockings for up to 6 weeks after surgery; additionally, 6 cases (10.5%; 57 with available data) used sequential intermittent compression devices and 2 (2.8%) postoperatively received low-molecular-weight heparin. One patient (1.4%) who received low-molecular-weight heparin had a symptomatic, lower-extremity, deep venous thrombosis 10 days after hip replacement for traumatic fracture. None of the other 70 surgical cases had symptomatic VTE within 3 months after the procedure. Analysis of pooled data from published series of hemophilia patients undergoing arthroplasty showed an estimated incidence of symptomatic VTE of 0.5%.
Conclusion: Our study suggests that in patients with hemophilia, joint replacement surgery can be performed safely without routine pharmacologic VTE prophylaxis and without increasing risk of thromboembolic events. Pharmacologic VTE prophylaxis may be considered in select patients with known additional risk factors for VTE.

Introduction

Deep venous thrombosis (DVT) and pulmonary embolism (venous thromboembolism [VTE]) are well-recognized complications after major surgery, particularly orthopedic procedures such as total knee arthroplasty (TKA) and total hip arthroplasty (THA). In the general population, the cumulative rate of symptomatic VTE up to 35 days after major orthopedic surgery has been estimated to be 4.3% without prophylaxis and 1.8% with the use of postoperative low-molecular-weight heparin (LMWH) corresponding to a risk reduction greater than 50%. The rates of asymptomatic, radiologically (Doppler and/or venography) detected VTE are much higher. Thus, providing thromboprophylaxis (pharmacologic, nonpharmacologic, or both) is the standard of care [1].

In patients with hemophilia, recurrent hemarthroses result in hemophilic arthropathy and eventual need for TKA or THA [2,3]; these procedures increasingly are being performed, given improved surgical techniques and availability of coagulation factor concentrates [4]. However, correction of the hemostatic defect through perioperative use of coagulation factor concentrates theoretically increases their risk of VTE such that it is similar to the risk in the general population. The concern for bleeding complications in this population has led to varying practice in providing VTE prophylaxis [5], and the lack of controlled trials preclude development of evidence-based recommendations. Herein, we review our institutional experience with outcomes of TKA and THA in patients with hemophilia and without inhibitors. We also review the literature to estimate the incidence of VTE after arthroplasty in the hemophilia population.

Abbreviations: DVT, deep venous thrombosis; CI, confidence interval; LMWH, low-molecular-weight heparin; POD, postoperative day; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolism.

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Materials and Methods

This study was approved by the Mayo Clinic Institutional Review Board. Nine patients in this series have been reported previously, 1 in a case report [6] and 8 in a case series describing factor concentrate boluses vs continuous infusions for elective surgery [7].

Study Population, Setting, and Design

In this retrospective cohort study, we reviewed the institutional medical records of all patients with hemophilia A or B, enrolled in the Comprehensive Hemophilia Center at Mayo Clinic (Rochester, Minnesota), who underwent arthroplasty from January 1, 1974, through July 31, 2013. Criteria for diagnosis and classification of severity of hemophilia conformed to the recommendations of the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis [8].

Measurements

We (J.P.B., D.B.S., M.S.P., and R.K.P.) abstracted patient data, including age at surgery, type and severity of hemophilia, the joint and type of surgery (primary vs revision arthroplasty), and the operating surgeon's name. We also recorded the type of factor replacement, the daily factor levels, and use (or lack thereof) of VTE prophylaxis (pharmacologic or nonpharmacologic). Operative reports, progress notes, hospital summaries, and subsequent visit notes were reviewed to determine occurrence of symptomatic VTE (DVT and pulmonary embolism) during hospitalization and for up to 3 months postoperatively.

Statistical Analysis

This was a retrospective cohort study. Data were entered into a spreadsheet (Excel; Microsoft Corp) from which sums, medians, ranges and the incidence of VTE were established.

Literature Review

We searched PubMed using the medical subject headings *hemophilia A*, *hemophilia B*, and *joint replacement*. All articles written in English were reviewed. We excluded reports of single cases and series that included only patients with inhibitors. All case series reporting hip or knee replacements (or both) were included in the final review.

Results

Patient Characteristics

During the study period, 42 patients underwent 71 joint arthroplasties. Thirty-eight patients had hemophilia A and 4 had hemophilia B. Twenty-two patients (52%) had severe hemophilia, 8 (19%) had moderate hemophilia, and 12 (29%) had mild hemophilia. Thirty-nine procedures (55%) were TKA and 32 (45%) were THA. Fifty-two procedures (73%) were primary arthroplasties and the remaining 19 (27%) were revisions. The mean age at surgery was 43.2 years (range, 15–74 years). Eleven orthopedic surgeons performed the procedures.

VTE Prophylaxis, Factor Concentrate Infusions, and Factor Activity

Details of VTE prophylaxis, factor replacement therapy, and factor activity are shown in Table 1. The average number of days of factor replacement was 11.78 (range, 4–25 days). The median and range for the maximum daily factor activity levels are presented in the Figure. Maximum daily factor levels were recorded both on the day of surgery and when available in the postoperative period throughout hospitalization(Fig. 1).

VTE Outcomes

One patient with mild hemophilia B (baseline factor IX activity 10%) underwent THA for traumatic hip fracture and received postoperative enoxaparin 30 mg twice daily from postoperative day (POD) 1 through 6 when he was discharged from the hospital. Factor IX replacement was continued at 4000 daily. Symptomatic DVT (deep femoral vein) was diagnosed by compression venous duplex ultrasound on POD 10. Enoxaparin dose was increased to 90 mg every 12 hours and concurrent FIX replacement (3000 units once daily) was continued for 5 days with resolution of the clot by ultrasound. Both factor replacement and anticoagulation were discontinued. As previously described [6], this patient was later found to be heterozygous for factor V Leiden, he had a BMI of 33 and no clinical evidence of postoperative infection, antiphospholipid syndrome or heparin induced thrombocytopenia. The incidence of symptomatic VTE in our series was 1 of 71 cases (1.4%) 95% CI [0, 4.13%].

Estimate of VTE Incidence

In an attempt to quantify the incidence of VTE in this patient population, we undertook a detailed review of 35 published studies, including 1 prospective study. The available data on outcomes after joint replacement surgery in patients with hemophilia are shown in Table 2.

In aggregate, 8 of 843 patients (0.9%) 95% CI [0.26, 1.54%] had VTE (total number of THA and TKA procedures, 1,107). When combining all available published reports and our cohort (without double-counting the 8 patients reported previously), the approximate incidence of symptomatic VTE in the hemophilia population undergoing THA or TKA was 6/1,170 (0.5%), 95% CI [0.1, 0.9%].

Three of the reported thromboses were diagnosed by surveillance ultrasound in the only prospective study published [39]. Two of the 5 cases of symptomatic VTE (DVT and pulmonary embolism, 1 each) occurred in patients with hemophilia B who received intermediate-purity factor IX concentrate, which is associated with a high thrombotic risk [2]; one with a below-the-knee DVT was managed conservatively, and the patient with pulmonary embolism received unfractionated heparin while continuing the postoperative replacement regimen concentrate. Kelley et al. [34] reported 1 symptomatic VTE after a THA, and Chevalier et al. [36] reported 2 symptomatic calf vein thromboses that were managed with elastic compression.

Table 1
VTE Prophylaxis, Perioperative Factor Replacement, and Plasma Factor Activity (N = 71).

Characteristic	Value
Use of VTE prophylaxis, No. (%)	
Compression stockings[a]	71 (100)
SCID[b]	6/57 (10.5)
SCID + low-molecular weight heparin[c]	2 (2.8)
Type of factor replacement	
Cryoprecipitate	12 (16.9)
Cryoprecipitate + plasma-derived factor VIII	3 (4.2)
Plasma-derived factor VIII	25 (35.2)
Plasma-derived factor IX	2 (2.8)
Recombinant factor VIII	27 (38.0)
Recombinant factor IX	2 (2.8)
Form of factor replacement (n = 59)[d]	
Bolus infusion	25 (42.4)
Continuous infusion	34 (57.6)
Preoperative peak factor activity, median (range), %	97.5 (59–318)

Abbreviation: SCID, sequential intermittent compression device (knee high); VTE, venous thromboembolism.

[a] Knee-high stockings were used during hospitalization and until 4–6 weeks postoperatively.

[b] Use of devise not documented for 14 cases.

[c] Both patients had traumatic hip fracture.

[d] Does not include patients receiving cryoprecipitate.