Perioperative thromboprophylaxis in patients with hemophilia and von Willebrand disease undergoing major orthopedic surgery

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A B S T R A C T

With the availability of efficient and safe coagulation factor concentrates and improved surgical techniques, elective total joint arthroplasty is increasingly performed in subjects with hemophilia suffering from chronic hemophilic arthropathy. Although most guidelines advocate thromboembolic prophylaxis in the general population undergoing major orthopedic surgery, no such standard of care is in place for hemophilic patients. The actual risk of symptomatic and subclinical venous thromboembolism (VTE) in patients with hemophilia following major orthopedic surgery, however, appears to be low and comparable to that observed in non-hemophilic patients receiving pharmacological thromboprophylaxis, even with new oral anticoagulants. These data suggest that in most patients with hemophilia, joint replacement surgery can be performed safely without routine pharmacological VTE prophylaxis and without increasing the risk of thromboembolic events. Pharmacological VTE prophylaxis may be considered in carefully selected patients with known additional risk factors for VTE. For patients with von Willebrand disease receiving factor concentrate replacement therapy undergoing surgical procedures, the FVIII plasma levels should be carefully monitored and thromboprophylaxis considered if any other thrombosis risk factor is present.

Learning goals

At the conclusion of this activity, participants should:
- appreciate the reported incidence of symptomatic and subclinical VTE following major orthopedic surgery in patients with hemophilia;
- understand the protective measures and the risk factors for VTE in patients with hemophilia in this setting;
- be able to identify patients with hemophilia undergoing knee or hip arthroplasty who could benefit from pharmacological prophylaxis.

Introduction

Severe hemophilia is characterized by recurrent hemarthroses affecting mainly the ankles, knees and elbows.[1] Hip arthropathy is also a frequent complication in patients with hemophilia.[2] Recurrent hemarthroses that occur in patients with hemophilia lead to chronic hemophilic arthropathy. With the availability of efficient and safe coagulation factor concentrates, and improved surgical techniques and anesthetic procedures, total knee and hip arthroplasty are frequently performed in hemophilic patients suffering from chronic hemophilic arthropathy.[3,4] They account for 97% of major orthopedic procedures performed in these individuals[5] and have repeatedly shown beneficial outcomes, improving the quality of life with diminished post-operative bleeding episodes.[6-8] Although many patients with hemophilia have been operated on at a relatively young age, it is likely that in the future older individuals with hemophilic arthropathy will require orthopedic surgery and that an increased proportion of hemophilic patients will also live long enough to need revision surgery. In the aging hemophilic population it is also likely that more surgical procedures will need to be performed for degenerative arthropathy such as osteoarthritis. Interestingly, the proportion of patients with hemophilia A (HA) who require arthroplasties has been reported to be higher than that of hemophilia B (HB) patients, suggesting that these two inherited coagulation disorders may have a different severity of clinical phenotype.[5,9]

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 clinically patent VTE up to 35 days after major orthopedic surgery has been estimated to be 4.3% without prophylaxis.[10] A recent systematic review of phase III randomized controlled trials of VTE prevention that compared new anticoagulants (fondaparinux, rivaroxaban, dabigatran, apixaban) with low weight molecular heparin (LMWH, enoxaparin) provided a unique opportunity to re-examine the contemporary risk of VTE, mortality and bleeding following major elective orthopedic surgery. Fourteen studies, which enrolled 40,285 patients, were included in the analyses. The combined median rates (ranges)

for all five anticoagulants for symptomatic VTE and mortality to the end of follow up were 0.99% (0.15%-2.58%) and 0.26% (0%-0.92%), respectively.[11] The rates of asymptomatic, radiologically detected VTE are much higher. Thus, providing thromboprophylaxis (pharmacological, non-pharmacological, or both) in non-hemophilic patients undergoing major orthopedic surgery is the standard of care.[12] Yet the need for pharmacological prophylaxis of VTE in patients with hemophilia undergoing major orthopedic surgery remains a subject of controversy. With the exception of retrospective case reports and small series, the actual risk and incidence of VTE disease in hemophilic patients after major orthopedic surgery is still unclear. Very few appropriately sized studies have really objectively evaluated the need, appropriate timing, dosage, and duration of mechanical or pharmacological prophylaxis in this setting, and no evidence-based guidelines, consensus statements or prospective clinical trials address thromboprophylaxis in patients with hemophilia. This paper discusses the scope of the problem of VTE in patients with hemophilia undergoing major orthopedic surgery and reviews the published approaches to the use of prophylactic anticoagulation in this setting.

Incidence of symptomatic VTE in patients with hemophilia undergoing major orthopedic surgery

Several authors have reported the results of their experience of major orthopedic surgery primarily in patients with severe HA without inhibitors and retrospective studies found no evidence of clinical VTE (Table 1). Kasper *et al*.[13] reported a cohort of 72 hemophilic subjects undergoing a variety of major surgical procedures with no evidence of VTE. Dulbegovic[14] also found no VTE in a series of 27 individuals undergoing orthopedic surgery. Franchini *et al*.[15] reported no evidence of VTE in individuals with bleeding disorders after major orthopedic surgery nor did Rodriguez-Merchan *et al*.[16] who reported their series of 35 individuals undergoing knee arthroplasty without VTE. The study of Miles *et al*.[7] reported no VTE in 34 individuals after hip surgery. Krause *et al*. focused specifically on the incidence of DVT following TKA and THA, and found that, in 32 patients with HA undergoing 44 procedures who received no post-operative chemoprophylaxis, there were no documented cases of venous thrombosis.[17] Raza *et al*. reviewed 23 patients with hemophilia (18 HA; 5 HB) who underwent high-risk surgeries (39% THA; 61% TKA). The VTE prophylaxis included sequential compression device (n=12, 52%) and prophylactic enoxaparin (n=1, 4%). Ten (43%) patients did not receive VTE prophylaxis. At a 1-year follow up, they did not find any evidence of clinical VTE in their patients.[18]

By contrast, in their study of the long-term results of primary total knee replacement in 68 patients using no post-operative thromboprophylaxis, Silva reported a single case of non-fatal pulmonary embolism (PE).[19] Perez Botero recently reviewed records of 42 consecutive patients with hemophilia A or B who underwent 71 hip or knee replacements over a 39-year period. All patients used compression stockings for up to six weeks after surgery; in addition, 6 cases (10.5%; 57 with available data) used sequential intermittent compression devices and 2 (2.8%) post-operatively received LMWH. One patient (1.4%) who received LMWH had a symptomatic, lower extremity, deep venous thrombosis ten days after hip replacement for traumatic fracture. None of the other 70 surgical cases had symptomatic VTE within three months after the procedure.[10] In an attempt to quantify the incidence of VTE in this patient population, the same authors undertook a detailed review of 35 published studies. In aggregate, 8 of 843 patients [0.9%; 95%CI (0.26, 1.54%)] had VTE (total number of THA and TKA procedures: 1107). When combining all available published reports and their own 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 of 1170 [0.5%; 95%CI (0.1, 0.9%)]. A major limitation of this literature review, as in most reports on this topic, is the inconsistent reporting and/or use of VTE prophylaxis. Although 9 reports addressed VTE prophylaxis in the Methods section, 3 indicated pharmacological prophylaxis was not used without specifying whether non-pharmacological prophylaxis was undertaken, 4 used compression stockings on all patients, and 2 only administered LMWH to all patients. Although 26 studies did not address thromboprophylaxis in the Methods section, it is reasonable to conclude that pharmacological thromboprophylaxis was probably not used.

A recent systematic review of prospective studies (1990-2011) reporting safety data of factor concentrates in patients with HA, HB and von Willebrand disease (VWD) was recently conducted to identify the incidence and type of thrombotic adverse events.[20] In 71 studies (45 HA, 15

Table 1. Reports of symptomatic venous thromboembolism in patients with hemophilia undergoing major orthopedic surgery.

N. of procedures	Thromboprophylaxis	VTE	Authors
71	Compression stockings (all), intermittent compression device (6), LMWH (2)	One symptomatic DVT	Perez Botero J *et al*. 2015[10]
23	12 compression device, 1 LMWH, 10 none	No clinical VTE	Raza *et al*. 2014[18]
34	Not used	No clinical VTE	Miles *et al*. 2008[7]
35	Not used	No clinical VTE	Rodriguez-Merchan *et al*. 2007[17]
90	Not used	1 non-fatal PE	Silva and Luck *et al*. 2005[19]
44	Not used	No clinical VTE	Krause *et al*. 2005[16]
32	Not used	No clinical VTE	Franchini *et al*. 2004[15]
27	Not used	No clinical VTE	Djulbegovic *et al*. 1995[14]
72	Not used	No clinical VTE	Kasper 1973[13]

VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism.

HB, 11 VWD) enrolling 5528 patients treated with 27 different concentrates, 20 thrombotic adverse events (2 HA, 11 HB, 7 VWD) were reported, including 2 major venous thromboembolic episodes, both occurring in VWD patients who had received prolonged factor replacement for surgery and being associated with abnormally high FVIII levels. This finding confirms the results of a questionnaire-based survey carried out by Mannucci in 2002[21] that obtained data from 160 hemophilia treatment centers worldwide. This survey found that venous thromboembolism is very rare in hemophilia, with only 2 reported and published episodes of DVT, only one of which was associated with orthopedic surgery.[21-23] These data confirm the low risk of symptomatic VTE in persons with hemophilia who are undergoing surgery. The small number of thrombotic events in these different reports highlights the need for large-scale and long-term pharmacovigilance programs, such as those currently ongoing in the European Haemophilia Safety Surveillance system (EUHASS).[24]

Incidence of subclinical VTE in patients with hemophilia undergoing major orthopedic surgery

In 2010, our group reported a series of 29 major orthopedic procedures in which originally Doppler ultrasound had been used to screen for VTE.[25] During post-operative surveillance, no case of clinical DVT or PT occurred. Nonetheless, distal DVT involving a single (n=2) or 2 (n=1) calf veins without proximal extension was observed in 2 patients with severe HA after unilateral total knee replacement, and in one patient with mild HB after decompressive laminectomy for lumbar stenosis, respectively. In the 2 HA patients who developed DVT, the thrombus resolved spontaneously without any anti-thrombotic therapy. The mild HB patient who developed a thrombus involving 2 calf veins was treated with a 2-week course of LMWH at half-therapeutic dosage (enoxaparin 0.5 mg/kg, twice a day) resulting in thrombus resolution. This low incidence of DVT in most reports can be accounted for by several factors, such as under-diagnosis, hemophilic disease, young patient age, use of mechanical or pharmacological anti-thrombotic methods, and early rehabilitation. Since publication of the first results in 2010, the study has been continued and has so far included 36 different patients (32 HA, 4 HB) who had undergone 52 major orthopedic procedures of the lower limbs. In total, 4 cases of subclinical and distal DVT have been detected with a total incidence of 7% (C. Hermans, personal communication, 2015). In a recent retrospective study, Takedani *et al*. reviewed 46 cases of TKA in 33 Japanese patients with hemophilia using ultrasonography to determine the prevalence of lower extremity DVT; no DVT was detected.[26]

Protective and risks factors for VTE in patients with hemophilia

Patients with hemophilia are considered to be protected against VTE by virtue of their coagulation factor deficiency, and reports of spontaneous venous thromboembolism are rare.[23,27,28] However, there have been few reports of VTE in association with surgery. In this setting, it has been postulated that the protection against VTE is counter-balanced by the administration of clotting factor concentrate.[22,28] In patients without hemophilia, high FVIII levels are associated with a risk of VTE.[29-33] Furthermore, in non-hemophilic individuals, FVIII levels have been shown to double from baseline within 24 h of surgery, with high FVIII levels persisting for several days.[34] However, for patients with HA, FVIII levels are usually carefully controlled, are not generally permitted to increase to levels noted in non-hemophilic subjects, and are not maintained in a high range for long periods of time.

The observation that venous thrombosis is rare in patients with hemophilia has recently provided the rationale for using antibodies which induce only a partial inhibition of FVIII as an innovative antithrombotic agent.[35] A phase II study investigated the efficacy and safety of a single administration of TB-402, a novel anticoagulant monoclonal antibody with a prolonged antithrombotic effect resulting from its partial FVIII inhibition and long half-life, for the prevention of VTE after total knee replacement. TB-402, as a single post-operative administration, was associated with a lower rate of VTE in all doses tested compared with enoxaparin. These findings support the concept that low FVIII levels in the post-operative period, as found in patients with HA, provide protection against VTE. Similarly, reducing factor XI levels with a 2nd-generation antisense oligonucleotide in patients undergoing elective primary unilateral total knee arthroplasty was recently reported to provide an effective method for VTE prevention and appeared to be safe with respect to the risk of bleeding.[36]

This protection afforded by the clotting factor deficiency in patients with HA is probably not applicable to patients with HB undergoing major orthopedic surgery. Indeed, by contrast with factor IX levels (which are carefully monitored and controlled), post-operative FVIII can reach very high levels in HB patients. It is still not known whether patients with HB are at higher risk of VTE in this setting. Due to the limited data available, no definite conclusions as to the impact of hemophilia type on post-operative VTE incidence and management can be drawn.[9]

Since underlying thrombophilia is a common risk factor for VTE in the general population, the question as to whether the acquisition or inheritance of thrombophilia markers increases the risk of thrombosis for hemophilia has aroused interest.[27] Several groups have evaluated the potential influence of factor V Leiden in ameliorating the bleeding phenotype of severe hemophilia, and have postulated that this thrombophilic trait may increase the risk of thrombosis by "removing" any protection afforded by the coagulation factor deficiency.[28,37] Some small published series of patients found a milder clinical phenotype with less bleeding in patients who had inherited thrombophilic abnormalities.[38,39] However, this was not a consistent finding, and other groups have found no similar significant effect. There have been reports of thrombosis occurring in individuals with hemophilia and abnormalities such as factor V Leiden undergoing major joint surgery; these events are rare and their significance is far from clear.[40] There is insufficient evidence to support screening for thrombophilic abnormalities during the pre-operative assessment of hemophiliacs, and much larger studies would be needed to clarify the value of such an approach.[40]

Hemophilia patients in need of surgery such as total joint arthroplasty are relatively young and tend to have

fewer risk factors for VTE than older patients without hemophilia undergoing arthroplasty. As the number of elderly patients with hemophilia increases, the risk factor of VTE in the patients will also increase. At present the risk of VTE in patients with hemophilia after TKA may be lower than in the general population; the risk factors for VTE in the aging hemophilia population should be carefully studied in the future.

Contemporary trials of anticoagulants in orthopedic thromboprophylaxis

Very interestingly, the incidence of symptomatic and subclinical VTE in patients with hemophilia undergoing THA or TKA in the absence of pharmacological thromboprophylaxis is very close to that reported in patients without hemophilia receiving pharmacological thromboprophylaxis for major orthopedic surgery either with LMWH or with one of the new oral anticoagulants.[11] A recent systematic review of the literature of phase III randomized trials demonstrated that the median symptomatic VTE rates were all low and similar among anticoagulants: 1.06% for fondaparinux, 0.79% for apixaban, 0.62% for rivaroxaban, 0.87% for dabigatran, and 1.20% for enoxaparin. The median rates of venographic DVT for the new anticoagulants and enoxaparin were 6.95% and 8.58%, respectively.[11] By comparison, in patients with hemophilia not receiving pharmacological thromboprophylaxis, the incidence of symptomatic VTE was 0.5%[10] and the incidence of subclinical VTE varied between 0 and 10%.[25,26]

The same systematic review demonstrated that the median rate of clinically important bleeding complications among patients without hemophilia receiving pharmacological thromboprophylaxis for major orthopedic surgery either with LMWH or with one of the new oral anticoagulants was 3.44% (range 2.25%-7.74%).[11] Even if data are not available, this rate would probably be much higher in patients with hemophilia receiving pharmacological thrombophylaxis. For instance, in a retrospective evaluation of 72 total knee replacements in 51 hemophilia A and B patients using continuous infusion of factor concentrates (CIFC) and no pharmacological thromboprophylaxis, 26 hematomas (36.1%) and 2 hemarthroses (2.7%) occurred in 38.8% of cases during the first three post-operative weeks, with no significant impact on the orthopedic outcome.[41] The risk of bleeding should be carefully considered, even in carefully selected hemophilic patients with known additional risk factors for VTE and deemed eligible for pharmacological thromboprophylaxis.

Risk of VTE in patients with von Willebrand disease

In patients with VWD, the situation differs from hemophilia both with regard to the variation in the disease and in clotting factor concentrates used for replacement therapy.[42] Thrombosis is rare in VWD, but according to available data it occurs more frequently than in hemophilia. VWD is classified into distinctly different forms with a broad spectrum of laboratory findings and clinical phenotypes. Type 1 VWD has a reduced level of VWF, Type 2 has a qualitative abnormality of VWF, and Type 3 has virtually no VWF in plasma and platelets. As VWF serves as a carrier of FVIII, the levels of FVIII will also be impacted. In addition, the ratio between VWF (VWF:RCo) and FVIII varies among products: in the range of 1-2.5 for most concentrates, and much higher for a purified VWF concentrate. Infusion with the first group of concentrates provides an immediate rise in VWF and FVIII that is beneficial when treating acute bleeds and in major surgery. A secondary rise in FVIII levels occurs with some concentrates after 12-24 h; in others, a parallel decay over time for VWF and FVIII has been reported.[43-46] However, infusion of virtually pure VWF will also restore FVIII levels due to binding and stabilization of endogenous FVIII. This will take from 12-24 h and, in the treatment of acute bleeds and in major surgery, infusion of exogenous FVIII is sometimes needed. Infusion of VWF will cause a rise in the endogenous level and this, added to infused FVIII, may result in supranormal levels, signifying a real risk for thrombosis.[21]

Patients with VWD who receive repeated doses of a VWF/FVIII concentrate are theoretically at risk of thrombosis because FVIII can accumulate to supraphysiological levels; this possibility should be considered after major surgery.[47] It may be prudent to institute routine thromboprophylaxis measures when other risk factors are present.[48] Therefore, when repeated infusions of VWF/FVIII concentrates are necessary, such as during surgical procedures, FVIII plasma levels should be measured daily to avoid values in excess of 150 U/dL. However, even in healthy individuals without VWD, FVIII levels may increase to or above these levels due to acute phase response. To reduce potential thrombogenicity of VWF replacement treatment during surgery, European studies recommend that the dosage and timing of FVIII/VWF administration be carefully planned to maintain FVIII concentrations between 50 and 150 U/dL during the post-operative period.[49]

VTE in individuals with hemophilia and inhibitors

Hemophilia patients with inhibitors commonly present much more severe musculoskeletal problems than patients without inhibitors. With hematologic advances using recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC), it is now possible to perform orthopedic procedures in these patients with a certain rate of success when managed by an experienced team of hematologists and orthopedic surgeons. Most reports have focused on the hemostatic efficacy of the treatment by these two bypassing agents. The methods, if any, used for thromboprophylaxis are inconsistently described. VTE other than local thrombophlebitis[50] are also not reported. Once again, there have been no published reports specific to this field of study.

Current practice of thromboprophylaxis in hemophilic surgical patients

The routine use of pharmacological VTE prophylaxis in patients with hemophilia remains controversial, and practices vary greatly among different centers. A survey of European hemophilia treatment centers suggests that pharmacological VTE prophylaxis is used by more than half of the respondents.[51] Zakarija and Aledort reported that in 19

adult centers in the USA, 47% used post-operative thromboprophylaxis with either LMWH or fondaparinux.[52] A recent survey of 60 US treatment centers by Pradhan *et al*.[53] revealed that 67% of respondents believed that patients with hemophilia undergoing joint replacement had high enough VTE risk to warrant some type of VTE prophylaxis, but only 37% indicated that they routinely provide prophylaxis for this purpose. Thirty percent of respondents believed in high risk of VTE but provided prophylaxis only for select patients (e.g. a high-risk patient with coagulation factor levels above 100%). Prophylaxis measures included compression stockings (32%), sequential intermittent compression devices (35%), and pharmacological agents (33%) such as LMWH, warfarin, unfractionated heparin fondaparinux, and aspirin (in decreasing order of frequency).

Risk assessment of VTE in patients with hemophilia

Most existing guidelines of thromboprophylaxis following major orthopedic surgery concentrate on VTE risk assessment and management. This approach may not be applicable to patients with hemophilia for whom, in the absence of other factors, the overall risk of thrombosis may be low, and mechanical thromboprophylaxis may offer a better risk benefit profile. Alternatively, for those individuals with multiple risk factors, coagulation factor deficiency may not protect against VTE, especially in the surgical setting where therapeutic correction of coagulation occurs. Thus, a detailed risk analysis for each individual patient is warranted. The following factors could affect the decision to provide pharmacological thromboprophylaxis: personal or family history of VTE, known thrombophilia, active cancer, mild hemophilia, history of major bleeding, hemophilia B (in association with other risk factors). Although this option has so far not been validated, one could suggest that pharmacological thromboprophylaxis in patients with hemophilia undergoing major orthopedic surgery could be restricted to the first few post-operative days as long as there is still high factor substitution therapy. Conceptually, indeed, by factor substitution the patient with hemophilia is 'normalized' and this would warrant thromboprophylaxis. However, protocols for replacement therapy during surgery will never give sustained high levels of FVIII in the range of those seen in hemostatically normal people during surgery. For hemophilia B, however, endogenous FVIII behaves as in patients without hemophilia; this may also be different among patients with mild hemophilia, but no studies of this have been carried out so far.

Conclusions

The limited published literature suggests that the incidence not only of symptomatic but also of subclinical VTE is low in individuals with hemophilia who undergo major orthopedic surgery. Although most procedures have so far been performed in relatively young patients, more older individuals with hemophilic arthropathy will require orthopedic surgery in the future and an increased proportion of hemophilic patients will also live long enough to need revision surgery. In this context, further studies involving larger sample sizes will be necessary to clearly establish the risk of VTE, and determine whether or not systematic pharmacological thromboprophylaxis is required in patients with hemophilia following major orthopedic surgery. Ideally, future studies should report the use of VTE prophylaxis (or lack thereof) and whether it was mechanical or pharmacological. Prospective studies also exploring subclinical VTE may help clarify, and possibly stratify, patients with hemophilia at risk of VTE and standardize future clinical practice. Patients with VWD intensively treated with VWF/FVIII concentrates are at higher risk of thrombosis because FVIII can accumulate to supraphysiological levels.

For the time being, routine use of mechanical VTE prophylaxis and pharmacological VTE prophylaxis in selected high-risk patients appears to be a reasonable approach. In patients with VWD undergoing major orthopedic surgery, FVIII levels should be carefully monitored and controlled.

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