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Subclinical deep venous thrombosis observed in 10% of hemophilic patients undergoing major orthopedic surgery

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Deep venous thrombosis (DVT) is a common postoperative complication in patients undergoing major orthopedic surgery of the lower limbs, such as total hip replacement (THR), total knee replacement (TKR) or hip fracture surgery (HFS). In the absence of thromboprophylaxis, subclinical venous thrombosis rates as high as 60% have been reported when using systematic bilateral phlebography after orthopedic surgery. As a result, routine pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH) or an alternative antithrombotic agent is strongly recommended in patients undergoing these procedures [1].

With the availability of efficient and safe clotting factor concentrates, THR, TKR as well as ankle arthrodesis are frequently performed in subjects with hemophilia suffering from chronic hemophilic arthropathy [2]. Yet, pharmacological prophylaxis of venous thromboembolism (VTE) in this patient group remains controversial. With the exception of retrospective case reports and small series, the incidence of VTE disease in hemophilic patients after major orthopedic surgery is still unclear. Despite the concern that pharmacological thromboprophylaxis might increase bleeding complications in these patients, no properly sized study has objectively evaluated the need, appropriate timing, dosage and duration of low-molecular weight heparin (LMWH) prophylaxis in this setting.

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We conducted a prospective study in order to evaluate by imaging techniques the incidence of subclinical DVT in consecutive hemophilic patients referred to our Centre for major orthopaedic surgery between June 2002 and June 2008. Twenty patients with an average age of 43 ± 14 years (range: 18–74) suffering from severe (n = 16), moderate (n = 4), or mild (n = 2) hemophilia A, or mild hemophilia B (n = 2) were included in the study. In total, 29 major orthopedic surgical procedures were performed, among which five THRs, 15 TKRs, four ankle arthrodeses, one decompressive laminectomy for lumbar stenosis and four femoral osteosyntheses. Screening for DVT was performed by unilateral (13) or bilateral (16) compression ultrasonography (US) between 4 and 14 days after surgery.

None of the patients had a personal or family history of venous thrombosis or pulmonary embolism (PE). All patients were treated with continuous infusion of recombinant clotting factor (F)VIII or FIX concentrate during a period ranging from 12 to 16 days delivered by a central venous catheter inserted pre-operatively after a bolus infusion of FVIII or FIX concentrate. No heparin was administered. Coagulation factor levels were maintained between 80% and 100% during the first 5 post-operative days, and then above 50% until discharge. None of the patients received pharmacological thromboprophylaxis. All wore grade 1 compression above-knee stockings, except for the operated TKR side. A single infusion of an antifibrinolytic agent (1 g tranexamic acid) was given in the operating room during most surgeries, with rehabilitation starting the day after surgery by mobilization of the operated limb. Extensive US-Doppler (Model IU 22, Koninklijke Philips Electronics N.V, Eindhoven, equipped with 4- to 12-MHz linear transducers) of the lower limb evaluating proximal veins and calf veins was performed by the same experienced radiologist on either the operated side(s) or both sides between Day 4 and Day 14 after surgery.

During post-operative surveillance, no case of clinical DVT or PE occurred. Nonetheless, distal DVT involving a single ($n = 2$) or two calf veins ($n = 1$) without proximal extension was observed in two patients with severe hemophilia A after unilateral TKR, and in one patient with mild hemophilia B after decompressive laminectomy for lumbar stenosis, respectively. In the two hemophilia A patients who developed DVT, the thrombus resolved spontaneously without any antithrombotic therapy. The mild hemophilia B patient who developed a thrombus involving two calf veins was treated using a 2-week course of LMWH at half-therapeutic dosage (enoxaparin, 0.5 mg kg^{-1}, twice a day), resulting in thrombus resolution.

To our knowledge, this is the first prospective study evaluating the incidence of VTE in hemophilic patients undergoing major orthopedic surgery. Systematic US-Doppler evaluation revealed that three out of 22 patients undergoing 29 major orthopedic surgeries developed subclinical distal DVT (Table 1). With 10%, the overall incidence of DVT in our study was significantly lower than that reported in non-hemophilic patients [3].

This low incidence of DVT can be accounted for by several factors, such as under-diagnosis due to the diagnostic method (US-Doppler) used, hemophilic disease, young patients, use of mechanical antithrombotic methods and early rehabilitation.

As extensive US-Doppler was performed by the same experienced radiologist, it is unlikely that the incidence of DVT was underestimated as compared with results that would have been obtained with phlebography. Because of risk of bleeding and lack of expertise with lower-limb phlebography in hemophilic patients, this diagnostic technique was not used in our study.

Although our patients received intensive replacement with continuous infusion in the immediate post-operative period, FVIII levels remained lower than the supra-physiological FVIII levels (> 200%) seen in non-hemophilic patients after surgery. For this reason, we do not believe that DVT in the two patients with hemophilia A was induced by replacement therapy. With regards to the patient with hemophilia B, post-operative FIX levels were comparable to those seen in non-hemophiliacs. As a result of the small size and small number of hemophilic B patients included in the study, no definite conclusions as to the impact of hemophilia type on post-operative DVT incidence can be drawn.

Our study involved only patients with hemophilia A or B. DVT has previously been described in hemophilic patients

Table 1 Patients characteristics and results of DVT screening

Patient number	Age (years)	Hemophilia		Surgical procedure	Hospital stay (days)	Localization	US-doppler Timing (days)	Results
		Type	Severity (%)					
1	20	A	13	Ankle arthrodesis	7	Bilateral	14	Negative
2	60	A	9	Right THR	12	Bilateral	10	Negative
	64			Left THR	12	Bilateral	8	Negative
3	68	A	1	Left TKR	46	Unilateral	5	Negative
4	47	A	1	Right THR	13	Unilateral	8	Negative
	50			Femoral osteosynthesis	24	Bilateral	8	Negative
	50			Femoral osteosynthesis	24	Unilateral	4	Negative
5	55	A	< 1	Bilateral TKR	31	Bilateral	7	Negative
6	34	A	< 1	Right TKR	15	Unilateral	6	Negative
	36			Left TKR	10	Bilateral	6	Negative
7	31	A	< 1	Femoral osteosynthesis	10	Unilateral	4	Negative
	34			Right TKR	15	Bilateral	10	Negative
8	40	A	< 1	Bilateral TKR	14	Bilateral	7	Negative
	41			Left THR	10	Unilateral	7	Negative
9	38	A	< 1	Left TKR	15	Bilateral	10	Negative
10	35	A	< 1	Ankle arthrodesis	7	Bilateral	7	Negative
	37			Left TKR	34	Unilateral	10	Distal DVT
11	18	A	< 1	Femoral osteosynthesis	9	Bilateral	7	Negative
12	37	A	< 1	Right TKR	16	Unilateral	6	Negative
13	46	A	2	Ankle arthrodesis	9	Bilateral	7	Negative
14	44	A	< 1	Left TKR	16	Unilateral	5	Negative
15	52	A	< 1	Right TKR	13	Bilateral	9	Distal DVT
16	39	A	< 1	Right TKR	20	Bilateral	5	Negative
17	31	A	< 1	Right TKR	28	Unilateral	6	Negative
18	74	A	5	Left THR	12	Bilateral	8	Negative
19	48	A	< 1	Right TKR	13	Unilateral	7	Negative
20	29	A	< 1	Right TKR	12	Unilateral	8	Negative
21	21	B	4	Ankle arthrodesis	10	Unilateral	4	Negative
22	71	B	5	Lumbar stenosis	14	Bilateral	8	Distal DVT

DVT, deep venous thrombosis; THR, total hip replacement; TKR, total knee replacement.

receiving high doses of clotting factor concentrates during surgical intervention [4]. Recent studies have shown that patients with von Willebrand disease may, paradoxically, experience thrombotic events due to prothrombotic risk factor interactions [3,4].

Despite its originality, our study has several limitations. The study was a single-center trial, with a small sample size, involving mainly patients with hemophilia A. Patients were evaluated in the immediate post-operative period, and imaging techniques were not repeated 4–5 weeks after surgery to rule out delayed DVT. Ultrasonography study was performed on the operated side only in nearly half the cases. Ideally, the study should have included more older patients and patients with hemophilia B. As no thrombophilia screening was performed, we do not know whether the three patients who developed DVT had a genetic predisposition. It is also uncertain whether thrombophilic work-up might help identify hemophilic patients at higher risk of VTE.

Our findings show that subclinical DVT occurred in up to 10% of hemophilic patients undergoing major orthopedic surgery. Thrombotic events were distal and resolved spontaneously or with a short course of low-dose LMWH, without any bleeding complications. Based on these findings, routine pharmacological thromboprophylaxis may not be indicated in all hemophilic patients undergoing major orthopedic surgery. Yet, despite the absence of evidence-based studies, half of the hemophilia comprehensive centers in Europe reported using pharmacological antithrombotic prophylaxis after major orthopedic surgery [5].

In conclusion, further studies involving larger sample sizes are necessary to clearly establish whether or not systematic pharmacological thromboprophylaxis is required in the post-operative setting. Should this be the case, appropriate timing, dosage and duration of treatment must be clearly defined.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Coated-platelet levels may explain some variability in clinical phenotypes observed with severe hemophilia

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Hemophilia A is an inherited, X-linked disorder due to a deficiency of factor (F)VIII. It is the second most common clotting factor abnormality after von Willebrand disease with a frequency of approximately 1 per 5000 males [1], and over 1200 mutations causing hemophilia have been documented (HAMSTERS database; http://hadb.org.uk). While there is a spectrum of FVIII levels in hemophilia patients, severe hemophilia is defined as < 1% of normal FVIII activity, and it is these latter patients that are most susceptible to spontaneous hemorrhage from early infancy and likely to require clotting factor replacement [1].