

Bleeding Diseases in Orthopedic Clinical ApproachKadri Yildiz¹, Vahit Yildiz²¹Kafkas University, Medicine School, Kars, Turkey²Adnan Menderes University, Medicine School, Aydın, Turkey

Aim Bleeding diseases are rarely studied as complications of an orthopedic surgical procedure with postsurgical bleeding. This study aims to present a retrospective cohort-study about the approach to bleeding disorders in an ordinary orthopedic clinic. **Material and Methods** 344 patients were recorded for our study group between November 2017 and September 2019. These patients were monitored for bleeding disorders, both primary or secondary. **Results** 27 (7.84 %) patients with bleeding diseases [1 (0.29 %) patient with VWD, 1 (0.29 %) patient with haemophilia, 1 (0.29 %) patient with ITP, 15 (4.36 %) patients with drug use, 5 (1.45 %) patients with vascular disorders, 4 (1.16 %) patients with herbal agent use] were detected in all traumatic cases which were admitted to our clinic in this time period. These patients were divided in 6 groups. Patient with VWD was Group 1, patient with haemophilia was Group 2, patient with ITP was Group 3, patients with drug use formed Group 4, patients with vascular disorders – Group 5, patients with herbal agent use – Group 6. **Conclusion** We advise to have a careful preoperative control for postsurgical bleeding risks according to three criteria: i) patient anamnesis should be studied carefully (diathesis/haemophilia searching), ii) platelet counts must be checked (twice is guaranteed), iii) coagulation tests [activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT) and International Normalized Ratio (INR)] must be studied. **Keywords:** bleeding diseases/disorders, VWD), ITP, drugs, herbal therapy, varicose veins

INTRODUCTION

Bleeding disorders occur in primary and secondary haemostasis defects [1], and are assigned to two main groups: acquired and inherited. Acquired conditions may occur during life, and include liver diseases, vitamin K deficiencies, warfarin use, and disseminated intravascular coagulation (DIC). The inherited type typically has a genetic predisposition; congenital disorders are divided into three groups, i.e. haemophilia A and B, Von Willebrand disease (VWD), idiopathic immune thrombocytopenia (ITP), and various clotting factor deficiencies [2]. Oberweis et al. observed that bleeding and thrombotic complications had a frequency of 5.4 %-5.8 % during hip, knee, and spine

orthopaedic surgery [3]. Complication incidences of bleeding diseases are tending to increase. Bolton-Maggs et al. recommended that orthopaedists must be careful about diagnoses, treatments, and postoperative complications from bleeding diseases [4].

We present a retrospective cohort-study on the clinical examination and approach to bleeding disorders in an orthopaedic clinic. However, bleeding disorders are rarely seen as complications of orthopaedic surgical procedures, with post-surgical bleeding. This condition can cause serious morbidities and mortalities. Orthopaedic surgeons must be cognisant of bleeding diseases, because of persistent bleeding may happen post-surgically.

MATERIAL AND METHODS

In our trauma centre, we recruited 344 patients between November 2017 and September 2019. These patients were monitored for bleeding disorders for primary and secondary outcomes. 27 patients (7.84 %) with bleeding disease, one patient (0.29 %) with VWD, one patient (0.29 %) with haemophilia, one patient (0.29 %) with idiopathic immune thrombocytopenia (ITP), 15 (4.36 %) patients with drug use,

five patients (1.45 %) with vascular disorders, and four patients (1.16 %) with herbal agent use were detected in traumatic cases during this period (Table 1). These patients were divided in six groups; patients with VWD – Group 1, patients with haemophilia – Group 2, patients with ITP – Group 3, patients with drug use – Group 4, patients with vascular disorders – Group 5, and patients with herbal agent use – Group 6.

Table 1

Distribution of patients according to bleeding causes

From a total of 344	Patient Counts	Percent
Group 1 (VWD)	1	0.29 %
Group 2 (Haemophilia)	1	0.29 %
Group 3 (ITP)	1	0.29 %
Group 4 (Drug use)	15	4.36 %
Group 5 (Vascular disorders)	5	1.45 %
Group 6 (Herbal agent use)	4	1.16 %
Total with bleeding disorders	27	7.84 %

RESULTS

Bleeding causes were detected as VWD, haemophilia, idiopathic immune thrombocytopenia, drugs, vascular diseases and herbal therapy.

Group 1 (VWD) A 22 year-old male patient with a unilateral/isolated tibial shaft fracture (AO/OTA 42A2) was referred to our emergency service (Fig. 1). No history of haemophilia disease was recorded at anamnesis. After one night, the patient was prepared for tibial nailing of the tibial shaft fracture. During the operation, abnormal bleeding was observed while proximal screws were being placed. At the first postoperative clinical assessment, purpuric rashes, i.e. ecchymosis, were observed on the operated extremity. A hemogram revealed progressive to severe blood loss, i.e. the hemogram range was

8.4–13.37 g/dl, haematocrit (Hct) was 26–41 %, and platelets (PLT) were 50,000/mm³ to 121,000/mm³ (Table 1). Coagulation tests and bleeding time tests were normal (Table 2). The patient was further assessed by cardiovascular surgeons and a computed topography angiography (CTA) was performed. The CTA revealed an unclear perforation image (Fig. 2), after which a detailed haematological laboratory investigation was performed (Fig. 3). A VWB Type 2 diagnosis was eventually established (Fig. 4). The patient was transferred to the haematology department. At follow-up, haematological and biochemical tests were performed (Hct: 30.6 % and PLT: 201,500/μl). At the end of the second month, a fusion mass was observed in X-rays.

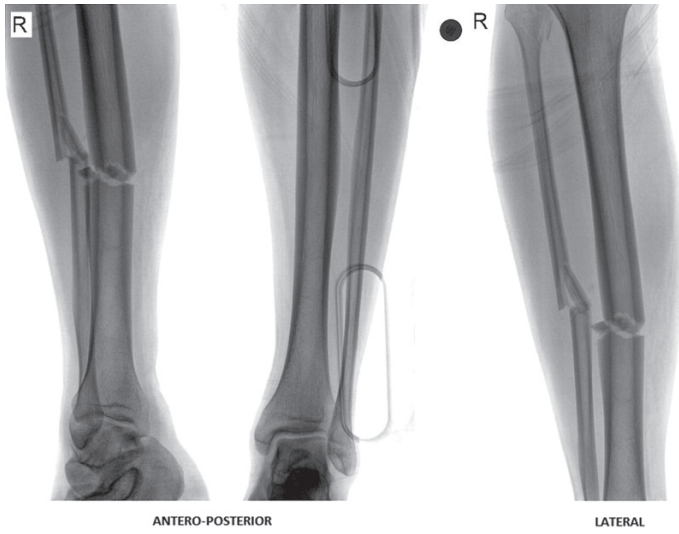


Fig. 1 22-year-old male patient with unilateral/isolated tibial shaft fracture (AO/OTA 42A2)



Fig. 2 CTA shows an unclear perforation

T.C. KAFKAS ÜNİVERSİTESİ SAĞLIK ARAŞTIRMA VE UYGULAMA MERKEZİ					
BİYOKİMYA LABORATUVARI					
T.C. Kimlik No : 23627719872	Doğum Numarası : 897611				
Hasta Adı : NESİP ÖZDEMİR	Bilgi Numarası : 2017469				
Cinsiyet : Erkek Yaş : 24	Beyan No : 1854006				
Doğum Tarihi : 01.12.1995	Bölüm Adı : ORTOPEDİ SERVİSİ				
Doğum Yeri : ÇALDIRI	Dişker Adı : KADİR YILDIZ				
Test Çabası : BİYOKİMYA MANUEL BİYOKİMYA TETKİKLERİ DİŞLAB HORMON TETKİKLERİ DİŞAR TETKİKLERİ					
Örnek Numarası: 06220946					
BİYOKİMYA TETKİKLERİ					
İstenilen Tarih : 31.10.2018 14:56	Numune : KAN				
Kabul Tarihi : 31.10.2018 14:56	İstenilen Tarih : 31.10.2018 15:55:51				
	Çekim Tarihi : 31.10.2018 17:32				
Parametre Adı	Sonuç	Durum	Birim	Referans Aralığı	Açıklama
DEMİR BAĞLAMA KAPASİTESİ	179		µg/dl	125 - 315	
Biyolog Fatih BOY Sıclı No:1515 Dr.Öğretim Üyesi Fahri ODABAŞOĞLU Sıclı No:628					
Örnek Numarası: 06220948					
HORMON TETKİKLERİ					
İstenilen Tarih : 31.10.2018 14:56	Numune : SERUM	İstenilen Tarih : 31.10.2018 15:54:46			
Kabul Tarihi : 31.10.2018 14:56	Numune Kabul Tarihi : 31.10.2018 15:12	Çekim Tarihi : 31.10.2018 16:62			
Parametre Adı	Sonuç	Durum	Birim	Referans Aralığı	Açıklama
FERRİTİN	145,9		ng/mL	23,9 - 336,2	
Biyolog Fatih BOY Sıclı No:1515 Dr.Öğretim Üyesi Fahri ODABAŞOĞLU Sıclı No:628					
Örnek Numarası: 06220949					
DİŞLAB					
İstenilen Tarih : 31.10.2018 14:56	Numune : DİŞLAB/BAV/BAF/BAK1	İstenilen Tarih : 31.10.2018 14:16:55			
Kabul Tarihi : 31.10.2018 14:56	Numune Kabul Tarihi : 31.10.2018 15:39	Çekim Tarihi : 31.10.2018 14:36			
Parametre Adı	Sonuç	Durum	Birim	Referans Aralığı	Açıklama
FAKTÖR 9	SONUÇ VERİLDİ				
FAKTÖR 7	SONUÇ VERİLDİ				
FAKTÖR 5	SONUÇ VERİLDİ				
FAKTÖR 10	SONUÇ VERİLDİ				
FAKTÖR 13 (HER BİR FAKTÖR İÇİN)	SONUÇ VERİLDİ				
VON WILLEBRANT FAKTÖR	SONUÇ VERİLDİ				
RİSTOSETİN KOFAKTÖR	SONUÇ VERİLDİ				
FAKTÖR 2	SONUÇ VERİLDİ				
Biyolog Fatih BOY Sıclı No:1515 Arş.Gör.Dr.Seda ÇELİK Sıclı No:2773					

Fig. 3 Haematological laboratory data

SYNLAB		www.synlab.com.tr		
TIBBİ İNCELEME RAPORU (ORJİNAL RAPOR)				
Adı Soyadı	: NESİP ÖZDEMİR	Gönderen Birim	: *KARS KAFKAS ÜNİVERSİTESİ TIP FAK.HASTANE	
T.C. Kimlik No	: 23627719872	Doktor	: LABORATUVAR DOKTOR	
Protokol No	: 28084016	Referans ID	:	
Cinsiyet / Yaşı	: Erkek / 22	Numune Türü	: Plazma	
Adresi	:	Rapor Basım	: 06.11.2018 18:16	
Numune Alma Tarihi	: 02.11.2018 09:42			
Lab. Kabul Tarihi	: 03.11.2018 10:27			
HEMATOLOJİ				
Test	Sonuç	Birim	Referans Aralığı	Yön
Von Willebrant Faktör,Ristocetin Kofaktör	↓ 24.00	%	50 - 150	Koagül
* Test tekrarlanmıştır.Klinik uyumsuzluk halinde testi etkileyen analiz öncesi koşullara dikkat edilerek alınacak uygun yeni numune ile testin tekrar önerilir.				
Faktör II (Protrombin)	79.00	%	50 - 150	Koagül
Faktör V (Proakselerin)	52.00	%	50 - 150	Koagül
Faktör VII (Prokonvertin)	52.00	%	50 - 150	Koagül
Faktör X (Stuart Faktör)	58.00	%	50 - 150	Koagül
*Faktör IX (Christmas)	129.00	%	50 - 150	Koagül
Faktör XIII (Tarsma)				Koagül
PIHTI ERİMESİ GÖRÜLMEMİŞTİR.SONUÇ NORMALDİR.				
Not: Faktör XIII tarama testi kalitatif bir testtir; pihti erimesi sadece şiddetli Faktör XIII eksikliği olan (normal aktivitenin %1 inden az) örneklerde gözlenir.				

Fig. 4 VWD Type 2 diagnosis

Group 2 (Haemophilia) A 36 year-old male was diagnosed with haemophilia A (FVIII deficiency) when he was 14 years old (Fig. 5). In his third decade, he increasingly complained of knee pain, with multiple haemarthroses. A bilateral total knee replacement was performed (Fig. 6), and the patient was clinically followed-up.

Medula Eczane Sayfa 1 / 1

SADLIK ECZANESİ (18360108) Rapor Görme

Geri Dön

Reçete

e-Reçete Sorgu

Reçete Giriş

Reçete Listesi

Reçete Listesi (Gönlük)

Reçete Sorgu

İade Reçete

İlaç Bilgisi

Silasma Kartı

Manuel Reçete Giriş

Fatura

Fatura Sonlandırma

Eski Fatura Sorgu

İade/Keşit Sorgu

Emekli İlaç Katılım

Hak Sahibi

İlaç Sorgu

Rapor Sorgu/Giriş

Müeyye Sorgu

Müşahhik Sorgu

Yurtdışı Sigortalı

Mesaj

Mesaj Görüntüleme

Kullanıcı İstatistikleri

İstatistik Bilgisi *

Sifre Değiştir

Bilgi Güncelleme

Çıkış Yap

Rapor Görme

Hak Sahibi Bilgileri

T.C. Kimlik No : 38071696****

Cinsiyeti : Erkek

Adı / Soyadı : MUHAMMER ÇOĞUR

Doğum Tarihi : 01/10/1984

Rapor Numarası (*) : 13880

Protokol No : A-2906-155-005-A-200519-00000547

Açıklama : 11360001

Teşis Kodu (*) : KARS HARAKANI DEVLET HASTANESİ

Teşis Ünvani : MEHMET SERDAR SAYAN

Rapor Tarihi (*) : 20/05/2019

Düzenleme Türü : Sağlık Kurulu Raporu

Kayıt Şekli : Elektronik İmzalı Rapor

Rapor Takip No : 297971018

Eklenme Zamanı

HAFIF VE ORTA SİDDETTLİ KANAMALARDA FAKTÖR DÜZEYİNİN %20-%40 ARALIĞINDA SAĞLANMASI DANA CİDDİ KANAMALARDA FAKTÖR VIII DÜZEYİ %50-%60 YAKSAM YENİSİ EDEN KANAMALARDA VE OPERASYONLARDA FAKTÖR VIII %60-%100 ARALIĞINDA TUTULMASI ÖNERİLİR. AYDA 3 TENE FAZLA EKLEM İÇİ KANAMASI NEDENİ İLE HAFTADA 3 GÜN 1500 ÜNİTE FAKTÖR 8 PROFİLAKSİSİ KULLANMASI UYGUNDUR. (SAG VE SOL OZ EKLEM SAG KALÇA EKLEM) FAKTÖR 8 DÜZEYİ %1 İNİHİBLÖR 180 3 VESİT AĞIRLIĞI 80 KG

Tanı Bilgileri

08.01.13 - Faktör noksanlıklarına bağlı hastalıklar (Hemofiller)(D65-D68)

D66 KALITSAL FAKTÖR VIII EKSKİLİĞİ

Başlangıç : 20/05/2019

Bitiş : 18/05/2020

Doktor Bilgileri	Dip. Tescil No	Branş	Adı	Soyadı
Dr. Diploma No	142767	İç Hastalıkları -> Hematoloji	TOLUY	ÖZGÜMÜŞ
12064	158681	İç Hastalıklar (Ana Branş)	SİNEM	KUL
12956	161118	İç Hastalıklar (Ana Branş)	MÜSEMMA	ÖĞÜZ
1204-A-049				

Rapor Etkin Maddesi Bilgileri

Kodu	Adı	Form	Tedavi Şekli	Adet / Miktar	İçerik Nis.	Eklenme Zamanı
SGKFW	FAKTÖR VIII	Parenteral	Haftada 3 x 1500.0 Ünite			20/05/2019 15:08

uygmedcc74 Sosyal Güvenlik Kurumu © 2010-2020 Sürüm : 1.853

Fig. 5 36 year-old haemophilia patient's data



Fig. 6 Bilateral total knee replacements in a 36-year-old haemophilia patient

Group 3 (ITP) A 19 year-old female was brought to our trauma service with a left bimalleolar fracture sustained in a traffic accident, diagnosed as Weber Type 3 (Fig. 7). Patient anamnesis revealed a disease-free status, except her isolated thrombocytopenia was 80,000/ml. After a second review, her PLT count was 77,000/ml. The patient was operated on with two cannulated screws for a medial malleolar fracture and a plate with screws for a fibular fracture. On the second postoperative day, isolated thrombocytopenia was 47,000/ml, and ecchymosis and swelling were observed at the site of the intervention (Fig. 8). The patient was controlled for postoperative bleeding and compartment syndrome for seven days. Medication was applied internally. At clinical follow-up, the patient's extremity had returned to normal.

Group 4 A 59 year-old female patient was operated for proximal humerus fracture and distal radius fracture on the left side (Fig. 9). In the anamnesis of the patient, there was no record about bleeding diseases. Patients and patients' relatives did not inform health professionals about her intake of acetylsalicylic acid

(Coraspin® 100 mg 30 tabs, Bayer) 3 days before. On the first postoperative day, there were ecchymosis and swelling in the shoulder area of the patient. On the third day, ecchymosis and swelling subsided (Fig. 10).



Fig. 7 19 year-old female with a left bimalleolar fracture, diagnosed as Weber Type 3



Fig. 8 Isolated thrombocytopenia at follow-up



Fig. 9 59 year-old female with a proximal humerus fracture and a distal radius fracture (left side)



Fig. 10 Preoperative and postoperative ecchymosis, and subsiding swelling

Group 5 A 71 year-old male with distal tibial fracture (AO/OTA 43A1) after being attacked by a dog was operated by tibial nailing. He had no history of bleeding diseases. The varicose veins of the broken leg were noted before the operation. Sixth hours after the operation, there was little bleeding seen as infiltration. The patient was brought to the operating room 24 hours after due to disturbing bleeding symptoms. Varicose veins were cauterized at the proximal screw level. At clinical follow-up examination, the patient had improved physical examination (Fig. 11).



Fig. 11 71 year-old male with distal tibial fracture (AO/OTA 43A1), showing varicose veins

Group 6 A 60 years-old female patient was referred to our trauma center with a proximal humeral fracture. The patient was operated using plate osteosynthesis and screws via a minimal invasive procedures. In the operation room, bleeding as infiltration was observed during all the operation time (Fig. 12). The patient was questioned for anticoagulation therapy. The patient and her daughter reported ginger tea drinking for a month.



Fig. 12 60 year-old female patient with a proximal humeral fracture; infiltration bleeding (extensive ginger tea taken during a month prior to surgery)

DISCUSSION

Patients suspected for bleeding diseases must be closely questioned at anamnesis (e.g. epistaxis, oral injuries, dental extractions and menorrhagia, etc.). Also, information on family history, malignancy, uraemia, parturition, hepatic cirrhosis, transfusions, collagen vascular disorders, and dietary habits or antibiotic use (vitamin K deficiency) must be ascertained [1]. All mucocutaneous bleeding patterns are important for diagnosis [5].

As part of the pathophysiology of VWD and Bernard-Soulier disease (BSD), PLT adhesion dysfunction is indicated [1]. In some populations, the VWD prevalence is approximately 1–3 % [6]. VWD is a genetic and multifactorial disease, shows an autosomal dominant inheritance pattern [7], and is the most frequent inherited bleeding disease [8]. Plasma levels of Von Willebrand factor (VWF) are typically low. Certain factors exacerbate VWF levels, e.g. gravida, oestrogen, progesterone, glucocorticoids, adrenalin increases (e.g. stress and fear), hard physical exercise, hyperthyroidism, inflammatory diseases, vasculitis, diabetes mellitus, liver/kidney diseases; however hypothyroidism and valproic acid decrease VWD. Populations with the O Rhesus blood group show reduced VWF levels, as much as 25 %.

The effects of VWF deficiency during orthopaedic operations are not well documented in the literature [9]. VWD has been described after vascular surgeries, coronary artery grafts, liver and renal transplants and abdominal surgeries. VWD may cause persistent bleeding during operations and postoperative periods

[10]. In most cases, VWD is regarded as a single episode, with chronic frequent relapses [11], and patients should be followed-up long-term [12]. Nose and gingival bleeds, heavy menstrual periods, bruising and post-surgical/post-traumatic bleeding may be observed. Type I VWD is the mildest disease, Type II involves increasing symptoms and Type III is the severest type. It was observed that VWD prevalence was 0.6 % [13]. In Type I, there is a partial lack of VWF (75–80 % of all types; VWF levels > 30 %). Type 2 disease occurs when VWF exhibits structural (quantitative) abnormalities. Type 2 (1–30 % VWF levels) is comprised of four subtypes; 2A (15–20 %), 2B (5 %), 2M (very rare) and 2N (autosomal recessive inheritance). Type 3 is defined as the complete absence of VWF (VWF levels < 1 %, i.e. autosomal recessive inheritance). If the patient has VWF levels < 30 IU/dl, significant bleeding may occur, however if levels are 0–50 IU/dl, the disease cannot be diagnosed unless bleeding occurs [14].

VWF is a haemostatic protein produced by endothelial cells and megakaryocytes, with the following functions: i) it forms bridges between damaged vascular structures and PLTs and ii) it stabilises factor VIII. VWF acts during PLT adhesion to expose collagen in damaged vascular endothelial area. The D1 and D2 domains help build the VWF pro-peptide, which is cleaved to produce the mature VWF [15].

VWD exhibits three VWF level defects, comprising; Type 1 (VWF levels < 50 IU/dl), Type 2 showing qualitative defects (variant VWF levels) and Type

3, totally defective (undetectable VWF levels) [16]. Diagnostic tests include activated partial thromboplastin time (aPTT), bleeding time (BT), factor VIII:C ristocetin cofactor (FVIII:C ristocetin) and VWF antigen. Ristocetin-induced PLT adhesion (RIPA), multimeric structure and collagen-binding test and gen-analysis are made for diagnosis [16].

Definitive diagnoses are made using the following parameters: i) mucocutaneous bleeding, ii) low levels of VWF, iii) family history/anamnesis. Treatment should consist of local haemostatics, anti-fibrinolytics, hormonal therapy and replacement coagulation-helper products. Local haemostasis is performed by physical localised pressure, sponge gels and Surgicel. Tranexamic acid (Transamin) acts as an anti-fibrinolytic and is used at 250–500 mg doses. The oestrogen analogue, LHRH may also be used. Similarly, for replacement therapy, fresh frozen plasma (FFP), cryoprecipitates, factor VIII/VWF concentrations and PLT transfusions may be performed [17].

One study included 1218 participants who were evaluated for VWF levels, where ristocetin cofactor activity of VWF was measured using the Macfarlane method [18]. Also, the Newman Keuls test demonstrated lower levels of VWF. In this study group, the male/female ratio was 1.0. In terms of clinical symptoms, epistaxis accounted for 38 %, bleeding via extraction was 20 %, menorrhagia was 18 %, postpartum haemorrhage was 8 %, prolonged bleeding after superficial injuries was 4 %, tonsillectomy/adenoidectomy was 4.5 %, after surgery was 3.5 %, easy bruising was 2 % and others were 1 %. The incidence in the population is unknown. Miller et al. classified as symptomatic as many as 23 % of normal subjects [19].

BSD is characterised by defective PLT binding to collagen, and the inability of the PLT membrane glycoprotein, GPIb-IX-V complex to adhere to VWF [20]. ITP (also known as primary immune thrombocytopenia) is an acquired bleeding disease. Peripheral PLT counts are < 100,000 cells/ μ l [21, 22]. Auto-antibodies destruct PLTs [23].

In the largest fracture study in persons with haemophilia (PWH), Caviglia et al. established a higher incidence of LL (lower limb) fractures in the period 1986–1990. The ratio LL/UL changed as UL (upper limb) fractures became more frequent. These authors showed that treatments decreased orthopaedic complications, and improved the quality of life in PWH [24].

In another study, a rare haemophilia disease was identified from bleeding complications after an orthopaedic surgery, and diagnosed as Thrombotic Thrombocytopenic Purpura (TTP) [25]. Iosifidis et al. proposed treatments including; 1) urgent plasma exchange, 2) plasmapheresis, 3) initial treatment with plasma infusion and glucocorticoids, 4) plasma infusion, 5) γ -globulin or glucocorticoid administration, and 6) antiplatelet drugs (dipyridamole and aspirin). If desired outcomes were not forthcoming, plasma exchange was repeated twice daily. These authors emphasised that TTP (Moschowitz's syndrome) was a rare, life-threatening disease, with a mortality rate

approaching 80–90 %, especially during orthopaedic operations where greater bleeding frequencies were often observed. They suggested that orthopaedists should be alert to TTP [25], and for mild forms, the synthetic agent, desmopressin, could be indicated [16].

Haemophilia diseases are X-linked recessive disorders. Haemophilia A is defined as factor VIII deficiency, while haemophilia B exhibits factor IX deficiency. The clinical manifestations of haemophilia are typically observed in men, in 1/5000–1/50,000 male births [26, 27]. Factor activity levels are defined as mild, with > 5 % activity, moderate at 1–5 % activity, or severe at < 1 % activity. The classifications match the clinical symptoms. Haemophilia may lead to chronic haemophilic arthropathy and arthrofibrosis, whereas other complications include compartment syndrome, infection and pseudo-tumours [28, 29].

Secondary bleeding diseases

Drugs such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), clopidogrel and herbals, and the condition, uraemia, can limit PLT function. Aspirin inhibits PLTs by the acetylation of PLT cyclooxygenase-1 (COX-1), and inhibition of thromboxane A₂ (TXA₂) synthesis. The incidence of minor bleeding is 5 %–10 %, whereas major bleeding is 1–2 % [30]. Thienopyridines, such as clopidogrel, ticlopidine and prasugrel antagonise adenosine diphosphate (ADP) stimulation, both selectively and irreversibly [31, 32]. Herbal preparations such as ginkgo biloba, garlic, and ginseng can interfere with blood clotting by affecting PLT function. Other medications such as ginger, feverfew, clove, kava kava, white willow bark may also affect clotting functions. Other suspected supplements may include vitamins A and E and fish oil [33]. Thrombophilias, liver disease, vitamin K deficiency are the other secondary bleeding causes. Desmopressin (0.3 μ g/kg) may be used and vitamin K administration (1 to 25 mg) excludes deficiency [34]. The clotting factors II, VII, IX, and X, as well as proteins C and S require vitamin K [35].

Other medications such as heparin, low-molecular-weight heparin, warfarin, and direct thrombin inhibitors are also other causes of secondary haemostasis [36]. Rivaroxaban and apixaban inhibits and binds directly to factor Xa, blocking its interaction with substrates [37]. Unfractionated heparin (UFH) inactivates thrombin, and factors VIIa, IXa, Xa, and XIa. Low-molecular-weight heparin, such as enoxaparin, inactivates factor Xa and should be preoperatively stopped at 12–24 hours [38]. Warfarin inhibits factors II, VII, IX, X and the anticoagulant proteins C and S, and it inactivates vitamin K-dependent γ -carboxylation of pro-coagulant factors [39]. Warfarin may be resumed postoperatively after 12–24 hours [30].

Orthopaedic clinics and bleeding disorders

Barg et al. studied 34 patients with ankle osteoarthritis (14 haemophilia Type A, and 20 with VWD) treated with total ankle replacement. They showed that patient groups with bleeding diseases had significantly higher pain relief, and significantly lower ROM than control groups, with normal ankles [40]. Zulfikar et al. stated that VWD

management was difficult because of bleeding; and that perioperative and postoperative patients must be monitored closely and carefully [41]. Vascular malformations can cause problems in some orthopaedic surgeries, e.g. bleeding, pain, deformity and functional limitations, with such patients also showing cardiovascular and haematological abnormalities. In vascular abnormalities, thromboembolic diseases are increased, wound infections are more common, and bleeding may continue during the postoperative course [42]. In a study investigating 168 arthroplasties (79 knees, 30 hips, three ankles and one elbow), in the congenital coagulation disorder group, spontaneous intraarticular bleedings resulted in damage to the joints and periarticular structures [43]. Accordingly, this study recommended that orthopaedic and haematological teams must evaluate these patients, both preoperatively and postoperatively [43]. Between 1997 and 2014, 825 surgical procedures were undertaken in 286 severe haemophilic patients [44]. A study compared post-operative standard rehabilitation (SR) and plus water rehabilitation (WR) in patients with haemophilia, undergoing total joint replacement.

184 patients [(233 rehabilitation programs; 160 total knee replacements (TKR), 37 total ankle replacements (TAR) and 36 total hip replacements (THR)]. 28 (25 %) patients were treated with WR in addition to SR (32 for TKR, 19 for TAR and seven for THR), with an average 5.7 hours for WR. Muscle strength, pain and perceived health status improved significantly [45]. Erturan et al. reviewed 20 years of publications on haemophilia patients with inhibitors, undergoing orthopaedic surgical operations, and found that patients with bleeding disorders were concerns for medical care when considering the benefits in quality of life against the prevalent complications [46].

Mansour et al. recommended the following for coagulopathic orthopaedic patients: i) a careful patient's history, mandatory physical examination and laboratory evaluations and ii) primary and secondary haemostasis must be comprehensively ascertained. They also emphasised that clinical bleeding disorder presentations must be well documented, but their most important point was the multidisciplinary approach of haematologists, cardiologists and surgeons [1].

CONCLUSIONS

A careful history (patient's anamnesis), full-featured physical examination, and all laboratory tests on bleeding diseases must be provided before orthopedic surgical procedures. Counts and functions of platelets, all bleeding tests and all medications taken by the patient are important for effective preoperative preparation for an orthopaedic operation. A multidisciplinary team that consists of surgeons, hematologists, and cardiovascular specialists must be organized in all hospitals. As the first step, a total blood count (must include the platelet counts), prothrombin time (PT), and activated partial

thromboplastin time (aPTT) are the screening methods. At the next steps, other laboratory tests must be applied for detecting bleeding diseases.

We advise to make a preoperative careful control for postsurgical bleeding risks according to three criteria: i) patient's anamnesis should be taken carefully (diathesis/hemophilia search); ii) platelet counts must be studied (twice is guaranteed); iii) coagulation tests [activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT) and international normalized ratio (INR)] must be included.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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