Evidence-Based Minireview: Perioperative management of the VWD patient at elevated thrombotic risk

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Learning Objectives

- Review data on peak factor VIII and von Willebrand factor activity levels recommended to minimize thrombotic risk in the perioperative setting
- Compare pharmacologic profiles of von Willebrand factor/factor VIII concentrates used in a perioperative setting
- Discuss venous thromboembolism prophylaxis strategies in patients with von Willebrand disease at elevated thrombotic risk

Clinical case

A 73-year-old man with mild type 1 von Willebrand disease (VWD), hypertension, type 2 diabetes mellitus, and history of recent ischemic stroke receiving daily aspirin 81 mg requires coronary artery bypass graft surgery for multivessel ischemic heart disease with unstable angina. Recent evaluation of his plasma von Willebrand factor (VWF) levels reveal VWF antigen level of 25%, ristocetin cofactor activity level of 19%, and factor VIII (FVIII) activity level of 30%. He is now referred for advice regarding a perioperative hemostatic management plan for this upcoming inpatient procedure.

Introduction

Persons with VWD, despite having a bleeding disorder, are not immune to thrombosis, especially with exposure to risk factors including smoking, obesity, critical medical illness, and surgery.[1-5] Similar to those with hemophilia, persons with VWD can develop cardiovascular disease as they age, and can experience acute ischemic stroke and myocardial infarction at rates similar to the general population.[6] Patients with VWD often require treatments to achieve hemostatic VWF and FVIII activity for invasive procedures. Despite general dosing recommendations, in vivo levels are influenced by individual pharmacokinetics and physiologic elevation from acute phase reactivity or endothelial injury. Stimate or pharmacologic desmopressin (DDAVP) can raise VWF and FVIII in some patients with type 1 VWD and is appropriate to consider in responsive patients for low-risk procedures. Other situations require intravenous concentrates that contain variable amounts of FVIII and VWF ristocetin cofactor activity (VWF:RCo). Disproportionate elevations in FVIII relative to VWF:RCo can lead to bioaccumulation of FVIII, generating concern for thrombotic risk, especially in older persons with recent ischemic events or risk factors. There are few data on the incidence of arterial and venous thrombotic complications because of transient elevations in FVIII and VWF with surgery, although it has been reported to be as high as 3.8% in subjects with transient elevations in FVIII and/or VWF:RCo above 150%.[4]

For these challenging patients at risk for both bleeding and thrombosis, persons with VWD should be managed at centers with expertise in bleeding disorders and with laboratory capability for rapid turnover of hemostatic monitoring assays, including of FVIII and VWF activity levels.[7] An individual pharmacokinetics study with the planned replacement agent should be conducted preoperatively, if possible, but does not obviate the need for real-time monitoring before, during, and after planned surgery with expected variance in the dynamic postsurgical setting.

Target peak VWF and FVIII levels

In the 2008 National Heart, Lung, and Blood Institute Expert Panel guidelines for VWD diagnosis and management,[7] experts suggested maintenance of FVIII levels lower than 250% and VWF:RCo lower than 200% based on limited evidence[1,2] *(Grade C, level IV)*. Although there are few additional data since that time, Gill and Mannucci reported on the incidence of venous thromboembolism (VTE) in subjects who had transient elevations of FVIII and/or VWF:RCo levels higher than 150%.[4] Although the overall incidence of VTE was low (3.8%), occurring in 2 of 53 subjects studied with elevated FVIII and/or VWF:RCo levels, both affected subjects had additional VTE risk factors (eg, advanced age, orthopedic surgery).

DDAVP (desmopressin)

We generally avoid use of these products in those requiring major surgery because of less predictable VWF/FVIII response, tachyphylaxis with repeated dosing, and fluid and electrolyte imbalances associated with this therapy *(Grade C, level IV)*.

VWF-containing concentrates

In the United States, 4 VWF-containing concentrates are commercially available for use (Table 1), although use may be restricted on the basis of hospital formulary regulations and/or a patient's prescription medication coverage. Alphanate is a plasma-derived combined VWF/FVIII concentrate with a ratio that varies by lot but "generally exceeds >0.4:1.0 IU VWF RCo/ FVIII."[8] With repeated dosing, this ratio risks FVIII bioaccumulation and is poorly suited for patients in whom tight control of VWF and FVIII levels are desired. Humate-P, among the most widely available agents, is a combined concentrate with VWF:RCo to FVIII ratio of 2.4:1.0.[9] Wilate contains a more physiologic VWF RCo:FVIII ratio of 1:1. Both Humate-P and Wilate are approved for all VWD subtypes, in both adult and pediatric populations.[9,10,12] Vonicog alfa (Vonvendi)

Conflict-of-interest disclosure: H.D.H. and S.H. declare no competing financial interests.

Off-label drug use: None disclosed.

Table 1. VWF/FVIII concentrates

Characteristic	Alphanate	Humate-P	Wilate	Vonvendi
VWF RCo:FVIII ratio	>0.4:1.0, varies by lot	2.4:1.0	1.0:1.0	1.3:1.0*
Mean VWF RCo t 1/2, hours, ± SD	7.67 ± 3.32	12.2 ± 5.2	19.6 ± 6.9	19.3 ± 10.99
Derivation	Plasma-derived	Plasma-derived	Plasma-derived	Recombinant
Indications	Hemophilia A and VWD type I/II	All VWD subtypes, adult and pediatric	All VWD subtypes, adult and pediatric	All VWD subtypes, adults >18 years
Clinical notes	Not indicated in severe type 3 VWD because of increased risk for alloantibody formation[1]	Contains HMW VWF multimers	Contains ultralarge and HMW multimers; does not increase FVIII:C in type 3 VWD. Separate FVIII replacement may be necessary	

HMW, high molecular weight; SD, standard deviation; t 1/2, half-life.
*Although it contains no FVIII, it can increase endogenous FVIII:C level above 40% within 6 hours in majority of patients.[11]

is the only recombinant VWF concentrate commercially available in the United States, approved by the US Food and Drug Administration for use only in adults aged 18 years and older, of any VWD subtype. Because vonicog alfa contains VWF only, FVIII replacement may be necessary with the first infusion, although is reported to raise endogenous FVIII levels by 40% with initial infusion.[11]

Thromboprophylaxis

Pharmacologic prophylaxis

For patients with VWD at elevated thrombotic risk in whom hemostatic therapy either maintains FVIII and VWF:RCo levels within normal range or has led to supranormal levels, standard pharmacologic VTE prophylaxis should be strongly considered.[1,4,7] In general, these include either unfractionated or low-molecular-weight heparin, but can include aspirin in some orthopedic surgery protocols. There are no data to guide the choice of agent in patients with VWD, but choice should take into account patient-specific factors and risks/benefits of each agent in the specific surgery or procedure.

Mechanical prophylaxis

In those with low baseline VWF activity levels (<10%) or a severe bleeding phenotype, especially in whom postsurgical VWF:RCo/FVIII pharmacokinetics are yet unestablished, sole use of mechanical prophylaxis devices such as intermittent pneumatic compression and sequential compression devices may be considered. Isometric calf exercises or early ambulation, when medically appropriate, should be encouraged in all postsurgical patients, where it has shown benefit for VTE prevention and other clinical outcomes, although it should be noted that the precise amount of activity that affords this protection is not well-defined.[13-15]

Concomitant antiplatelet agents

In certain clinical scenarios (eg, acute arterial ischemia, placement of drug-eluting stent), single- or dual-antiplatelet therapy may be specifically indicated over anticoagulation to maintain device patency or prevent progression of an unstable atherosclerotic plaque. In postsurgical patients with VWD, exogenous FVIII and VWF replacement may initially facilitate antiplatelet use with less concern for bleeding risk. However, as VWF and FVIII return to subnormal preoperative baseline levels, a multidisciplinary team of providers should discuss the timing and duration of continued antiplatelet therapy with the patient, considering the risk/benefit ratio of bleeding vs ischemic risks and patient preferences.

Peaks, troughs, duration

We recommend referral to the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations) Guidelines and 2008 National Heart, Lung, and Blood Institute Expert Panel guidelines for VWD diagnosis and management,[7] and 2019 Update in the ASH Education manuscript entitled "Perioperative management of patients with VWD" for more detailed information regarding considerations for measurement of peaks/troughs, duration of therapy, and procedure-specific FVIII and VWF RCo target levels for specific procedures.

Recommendations

In patients with VWD for whom hemostatic replacement therapy is needed and there is above-average thrombotic risk, we recommend maintaining peak FVIII and VWF:RCo activity levels lower than 200 *(Grade C, level IV)*. In patients with a recent ischemic event or VTE in whom therapy cannot be postponed, we recommend maintaining peak FVIII and VWF:RCo activity levels as close to 100% as possible and, ideally, lower than 150% *(Grade C, level IV)*. In patients with VWD with elevated thrombotic risk or a recent ischemic event, we recommend consideration of VTE prophylaxis in conjunction with hemostatic therapy as long as VWF and FVIII activity levels are within or above hemostatic range *(Grade C, level IV)*.[1,4,7]

For our 73-year-old patient undergoing urgent coronary artery bypass graft surgery, Humate-P was the only available agent for immediate inpatient use. We recommended initial treatment at a dose of 30 IU FVIII:Co/kg. This dose was expected to elevate his FVIII activity from 30% to 90%, while raising VWF:RCo by 144%, resulting in a preoperative VWF:RCo of 163%. Depending on the duration of surgery and clinical course, we recommended obtaining VWF and FVIII activity levels 8 to 12 hours after initial dosing, followed by trough and peak VWF and FVIII activity levels with targeted repletion thereafter. Postoperatively, resumption of aspirin was recommended with close monitoring for new or increased bleeding symptoms.

Acknowledgments

S.H. is supported by the National Heart, Lung, and Blood Institute (HL136430, HL144457).

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