Review Article

Perioperative management of patients with Von Willebrand's disease

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This review focuses on the pathophysiology of the Factor VIII molecule as it relates to Von Willebrand's disease. Three major categories of Von Willebrand's disease are identified. The perioperative diagnosis and management of all categories are reviewed. 1-Deamino-8-D-argnine vasopressin (DDAVP) is presented as an alternative to the transfusion of blood and blood products for the management of a bleeding diathesis.

Cette revue met l'emphase sur la pathophysiologie du facteur VIII relié à la maladie de Von Willebrand. Trois catégories majeures de la maladie de Von Willebrand sont identifiées. Le diagnostic périopératoire et la conduite face à ces trois catégories sont revus. Le 1-deamino-8-D-arginine vasopressine (DDAVP) est présenté comme une alternative à la transfusion sanguine et les dérivés du sang pour la conduite lors d'une diathèse hémorragique.

In 1926, Erich Von Willebrand described a bleeding disorder in a young girl and 23 of her 66 family members.[1] This was the first report of a haemorrhagic disorder affecting both sexes and involving a prolonged bleeding time, despite normal platelet counts. Since that time, several investigators have identified the Factor VIII molecule as being responsible for the haemorrhagic defect. However, the fact that both haemophilia A and Von Willebrand's disease share an abnormality of the Factor VIII molecule and frequently receive the same treatment has generated confusion about the origin of the coagulation abnormality in Von Willebrand's disease. The purpose of this paper is to review the clinical spectrum of Von Willebrand's disease, as well as the current concepts regarding the Factor VIII molecule and its relationship to the bleeding defect. Finally, the current treatment available to manage patients with this bleeding disorder in the perioperative period will be discussed.

Key words
BLOOD: coagulation, haemorrhage, replacement.

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Clinical spectrum

The usual pattern of genetic inheritance of "Von Willebrand's Disease" is autosomal dominant,[2] which differs from the sex-linked recessive pattern of classic haemophilia. The incidence of the disease is unknown due to the several forms of clinical expression. It is known, however, that approximately 15 per cent of the population have an abnormality of haemostasis that results in a bleeding tendency.[28] Of those referred for investigation, 15–20 per cent will be diagnosed as Von Willebrand's disease. The incidence, therefore, of *mild* Von Willebrand's disease may be as high as two to three per cent of the general population. The incidence of *severe* (genetically homozygous) Von Willebrand's disease is much lower, being approximately 1:10,000, which is similar to haemophilia.

Clinical presentation

Patients with homozygous Von Willebrand's disease usually have a dual bleeding defect involving both superficial (cutaneous and mucous membrane) bleeding and deep tissue (muscle and joint) bleeding. The majority of patients with Von Willebrand's disease tend to have clinical defects that are only associated with superficial bleeding.

There is no specific age of onset of the disease, and a history of cutaneous or mucosal bleeding which includes epistaxis, menorrhagia, easy bruising or failure to clot after dental extraction, justifies baseline laboratory inves-

TABLE I Preoperative laboratory evaluation

	Screening tests	*Specialized haematology*
Suspicious clinical history	1 Complete blood count 2 Platelet count 3 Prothrombin time (PT) 4 Partial prothrombin time (PPT) 5 Bleeding time (BT)	1 Glass beads 2 Ristocetin cofactor 3 Individual factor assay 4 Chromatography

tigations (Table I). The coagulation screening tests should include complete blood count (haemoglobin and white blood cell), platelet count, prothrombin time (PT), partial prothrombin time (PTT), and a bleeding time. If any of these tests are abnormal then the patient should be referred to a haematologist for a more detailed investigation before surgery.

Preoperative laboratory evaluation

Several non-specific laboratory tests are currently used to evaluate the severity of coagulation defects. Examination of the partial thromboplastin time (PTT) is utilized to assess the function of the intrinsic coagulation system, including the Factor VIII complex. However, this test is a reflection of the haemophilic (VIII C) portion of the Factor VIII complex rather than the Von Willebrand Factor (VWF).

Additional tests such as bleeding times are used to reflect platelet function indirectly. Traditionally the IVY bleeding method was used to measure bleeding times. In this test, a blood pressure cuff on the upper arm is inflated to 40 mmHg in order to maintain back pressure on potential haemostatic plugs. Two incisions, 9 mm long and 1 mm deep are made with a Number 11 Bard Parker blade on the volar surface of the forearm. Excess blood is blotted away every 30 seconds with filter paper until blood no longer stains the paper. Because the cuts are made free-hand, there is a large variability in the depth of the cuts and both the reproducibility and accuracy of the results are variable. Therefore, a template method is more commonly utilized. In this techique, a template is used to ensure 1 mm cuts in depth. This allows the test to be more reproducible and less dependent upon technician variability. The normal bleeding time using the template method is up to nine minutes. Unfortunately, this test leaves fine scars, and the patient should be informed of this.

***In vitro* tests: glass beads, ristocetin cofactor**

Several *in vitro* studies have been developed to evaluate specifically the platelet/VWF abnormality associated with Von Willebrand's disease. Unfortunately, none has been entirely satisfactory. One test uses glass beads to test "platelet adhesiveness." In this test, two separate blood samples are collected from an upper limb and the platelet counts compared. The first sample is collected from the vein into a vacutainer for analysis. In the second sample, the blood passes through a column of glass beads prior to being collected in the vacutainer. This sample is also sent for platelet count analysis. The percentage decrease in the platelet count of whole blood that has passed through a column of beads is a measure of glass bead adhesion. In patients with Von Willebrand's disease, platelet adherence to the glass beads is usually decreased (less than 20 per cent). Therefore the platelet counts between the two samples will be similar. This test may also be abnormal in patients with uraemia or a low haematocrit (less than 0.3). In practical terms, however, it is a simple, fast and readily available method of establishing a presumptive diagnosis before surgery.

Another more quantitative test involves the use of the antibiotic ristocetin. Ristocetin induces binding of VWF to the platelet surface. The mechanism is thought to be related to ristocetin's net positive charge. Both VWF and the platelet surface have an electro-negative charge, which repel each other. Ristocetin acts locally on the platelet surface to reduce the net negative charge and allow binding of VWF to its binding site on the platelet surface. In the ristocetin cofactor test, the addition of ristocetin to a test tube containing normal platelets and normal plasma (with normal VWF) results in platelet agglutination. This control is compared with a sample containing ristocetin, normal platelets and a sample of the patient's plasma. Therefore, the only variable is the amount of VMF in the patient's plasma. If the VMF is qualitatively abnormal or quantitatively absent then platelet aggregation cannot occur.[20]

The Factor VIII molecular complex

Historically, the terminology associated with the Factor VIII molecule (see Table II for a suggested terminology),[3] has been very confusing, and the relationship between haemophilia and Von Willebrand's disease has been poorly understood. Originally, it was thought that the Factor VIII molecule was a single molecule with different "activities" which represented the normal coagulative functions that were absent in both haemophilia and Von Willebrand's disease. Recent evidence, however, has supported the concept that the haemophilia (VIII C) and the Von Willebrand's factors are present in plasma as a complex of two distinct molecules.[4–6] In relative terms, VWF comprises 99 per cent of the Factor VIII, VIII C/VWF complex,[7] and behaves as a "carrier" molecule for the haemophilic portion. Because the VWF behaves as a carrier, reductions in the total amounts of available VWF result in a corresponding reduction in the amount of available haemophilic portions (VIII C). Although the

TABLE II Terminology for Factor VIII molecular complex

1 *Factor VIII procoagulant activity protein (VIII C)*
The protein that corrects the coagulation abnormality in Haemophilia A.
1(a) VIII C:Ag
The antigenic expression of VIII C

2 *Von Willebrand factor protein (VWF)*
The protein that corrects the bleeding time abnormality in Von Willebrand's disease.
2(a) VIII R:Ag
The antigenic expression of Von Willebrand Factor

3 *Ristocetin Cofactor (VIII:RCo)*
A property of VWF that promotes agglutination of platelets in the presence of the antibiotic Ristocetin.

4 *Factor VIII/Von Willebrand Factor Complex (FVIII/VWF)*
The form in which VIII C and VWF usually circulate in plasma.

haemophilic portion (VIII C) may be mildly decreased in Von Willebrand's disease, the deficiency is rarely of haemostatic significance. In general terms clinical bleeding and laboratory abnormalities only occur when the haemophilic portion (VIII C) is less than 20 per cent (20 units · ml blood) of normal values. Therefore, both PT and PTT are frequently normal except in the severe homozygous form of the disease where the VIII C deficiency is similar to that observed in classic haemophilia A.

The Von Willebrand's factor itself is a multimeric molecular complex, composed of variable numbers of glycopeptide sub-units.[8] These sub-units polymerize to form small, medium or large units. Only the "large" multimers play an active role in binding platelets to sites of tissue damage, and play a significant role in haemostasis.[9] Overall, the "large" multimeric forms predominate in normal individuals.

Recent evidence suggests that the carbohydrate moiety of the glycoprotein sub-unit may be responsible for the Von Willebrand-platelet interaction. In particular, the absence of terminal sialic acid residues may be part of the molecular defect in some forms of Von Willebrand's disease.[10] In fact, these residues may be responsible for the intra-vascular survival of VWF because its half-life without sialic acid in rabbits is five minutes, compared with 240 min for intact VWF.[11]

Body compartments of VWF

Von Willebrand's factor is normally found in four body compartments:
1 plasma,
2 platelets and megakaryocytes,
3 endothelial cells, and
4 intact sub-endothelium
Endothelial cells[12] and megakaryocytes[13] have been demonstrated to synthesize Von Willebrand's factor while the cell of origin of VIII C appears to be hepatic sinusoidal endothelium.[14]

Platelets contain approximately 15 per cent of the total amount of VWF. The largest portion of platelet VWF is stored in the alpha granules, which probably play an important role in haemostasis at the site of vascular injury.[15]

In the various categories of Von Willebrand's disease, the molecular defect may be present in one of three forms: (1) all the Von Willebrand's multimers are structurally normal, but are either quantitatively decreased or absent, (2) the large multimeric forms are quantitatively decreased or absent, and (3) the Von Willebrand's multimers are qualitatively abnormal, which results in either a decreased affinity for sites of tissue damage, or an increased affinity for the binding sites on platelets.

The platelet in Von Willebrand's disease

Traditionally, the presence of an abnormal bleeding time in Von Willebrand's disease has been explained by a platelet defect. However, infusion of normal platelets into a patient with Von Willebrand's disease does not correct the bleeding time.[16] As well, bleeding in patients with aplastic anaemia may be stopped by infusing platelets donated from patients with Von Willebrand's disease.[17] In addition, the bleeding time in patients with Von Willebrand's disease can be corrected by the infusion of plasma from patients with haemophilia.[18] These data suggest that the platelets in Von Willebrand's disease are intrinsically *normal*, but lack a plasma cofactor that allows the platelets to function normally.

Platelet adhesion

Although the exact inter-relationship between platelets and VWF is not entirely understood, the general sequence of thrombus generation and adhesion of platelets to sites of tissue damage is generally accepted. First, exposed collagen results in the adhesion of platelets to sub-endothelium. The platelets then release granules (ADP, serotonin, VWF) which produce secondary aggregation of platelets and thrombus formation. The VWF mediates the adhesion of platelets to damaged endothelium. Since VWF is a large molecule, it probably performs this function by acting as a "bridge" between the platelet and the damaged tissue. It may be that a platelet membrane glycoprotein (GPIb) is the specific binding site for the VWF factor.[19]

Classification of Von Willebrand's disease

The following classification is based on the fact that abnormalities in Von Willebrand's disease may be both qualitative and quantitative. The subdivision of Von

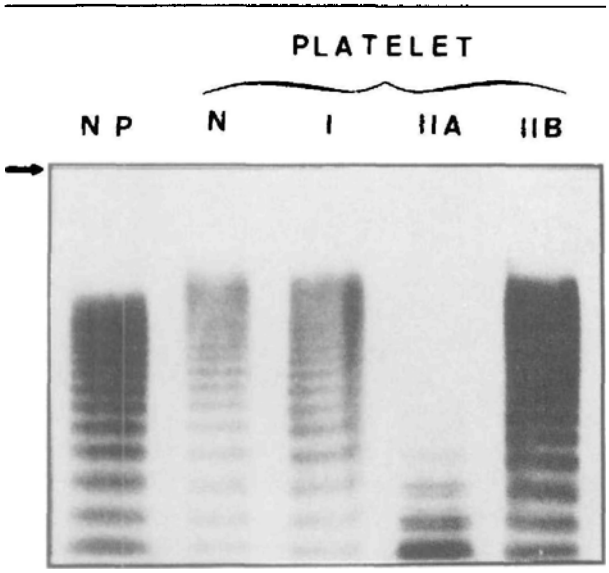

FIGURE Multimeric composition of Von Willebrand Factor (VWF) in normal plasma (NP) compared with that found in platelets of normal patients (N) and platelets from patients with Von Willebrand disease types I, IIA and IIB. In Type I, VWF is decreased in plasma, but not on the platelet membrane. In Type IIA, VWF is abnormal and has a decreased affinity for the platelet membrane. In Type IIB, VWF is abnormal and has an increased affinity for the platelet membrane. Plasma was analysed by SOS-agarose gel electrophoresis and the VWF multitimers visualized by reaction with ^{125}I-anti-VWF antibody. (Reproduced with permission from *Ruggeri et al.*[22])

Willebrand's Disease into three major types begins to explain the clinical spectrum of the disease, and provides the basis for appropriate therapy[21] (see Table III).

Type I

This is the most common form of Von Willebrand's disease and constitutes approximately 90 per cent of the total spectrum (Figure). It is characterized by a quantitative decrease in all VWF multimers. The haemophilic portion (VIII C) may also be decreased but the PT and PTT are usually normal. The multimeric sub-unit composition of the VWF in this form of disease is normal. Typically, the bleeding time is prolonged, but it may be normal in some individuals despite a significant bleeding history. In addition, pregnancy, liver disease, inflammatory disorders and renal disease may result in an increase in VWF, which may convert a prolonged bleeding time to normal. Also, there tends to be considerable variability in bleeding times when measured on different occasions in the same individual. Therefore, in patients with known Von Willebrand's disease, appropriate coagulation studies (PT, PTT, bleeding time) should be repeated prior to all major surgical procedures in order to clarify a patient's current coagulation status.

Von Willebrand's Factor is generally increased by oestrogens. The decrease in oestrogens noted at the menopause may result in exacerbation of VWD which will be manifested clinically by menorrhagia. This is of particular concern for the menopausal woman scheduled for an elective hysterectomy for excessive menstrual bleeding. The aetiology of her bleeding may be medical, i.e., VWD, rather than structural. Therefore, a detailed bleeding history is mandatory in these patients.

Type II

This category comprises a group of variants whose characteristic is that the large VWF multimers are either decreased or absent from the plasma. Sub-types are defined by different platelet and plasma multimeric patterns, or evidence of specific qualitative abnormalities of the VWF.

Type IIa

This sub-type constitutes approximately nine per cent of all patients with VWD and is characterized by the absence

TABLE III Comparison of Von Willebrand's disease and classical haemophilia

	Von Willebrand Type I, II A, II B	*Haemophilia A*	*Von Willibrand Type III*
Clinical	Autosomal dominant	X-linked recessive	Autosomal recessive
Bleeding	Mucous membranes	Haemarthroses	Both superficial and deep bleeding
	Gastrointestinal	Muscle	
	Skin	Soft tissue	
Laboratory			
– Factor VIII C	Variable	Moderate to low	Low
– Bleeding time	Prolonged	Normal	Prolonged
– Antigen level	Decreased	Normal	Decreased
– Ristocetin co-factor	Decreased	Normal	Decreased
– Platelet aggregation	Normal	Normal	Normal
– Glass bead adhesion	Decreased	Normal	Decreased

of large VWF multimers from both the plasma and the platelets. Ristocetin cofactor activity is markedly reduced, and VIII C levels may be normal or reduced (PT, PTT may be normal). The increase in VWF and other clotting factors associated with pregnancy does not entirely correct the bleeding time, since the VWF is structurally abnormal.

Type IIb

This category constitutes less than one per cent of patients with VWD and the large multimers are reduced in the plasma of these patients, but they are present in greater amounts on the surface of the platelet membrane. Presumably, this reflects an abnormal increase in the affinity of VWF for the platelet surface membrane. Therefore, VWF that is released from vascular endothelium in response to a stimulus is rapidly eliminated from the plasma and bound to the platelets. This qualitative abnormality in the VWF results in decreased platelet survival, and a mild to moderate thrombocytopenia. The persistent thrombocytopenia may serve as a marker for this category of patients and help to identify them prior to surgery.

Type III

This is the most severe and rarest (less than one per cent) form of VWD, and is inherited by an autosomal recessive genetic pattern. In this category, the entire VWF molecule is undetectable in plasma, platelets or endothelial cells. Therefore, the haemophilic portion (VIII C) is also undetectable and this is the only category of VWD where the PTT will be consistently abnormal.

Treatment

The cornerstone of treatment for Von Willebrand's disease has been the replacement of the VWF factor. This is currently available from several sources:

Cryoprecipitate

This readily available blood product is very effective in correcting the abnormalities in bleeding time associated with Von Willebrand's disease. It is rich in *large* multimers, and is usually administered in a dose of 1 unit $\cdot$ 5–6 kg^{-1}. This dose will raise the Factor VIII C level by 15–20 per cent, and will provide enough high molecular weight VWF to correct the bleeding time in most circumstances.[23]

During the intraoperative period, the consumption of VWF is increased, and may require the administration of cryoprecipitate as frequently as every 6–8 hr. However, in the postoperative period, the administration of cryoprecipitate may be extended to every 8–12 hr, after reviewing the bleeding time and the clinical response.

Both cryoprecipitate and fresh frozen plasma have the same risk of disease transmission. However, the advantage of cryoprecipitate over plasma is that equal amounts of VWF can be administered to patients in a much smaller volume of fluid.

Fresh frozen plasma

The capacity of fresh frozen plasma (FFP) to correct the abnormality in VWD is similar to cryoprecipitate, but administration may be associated with circulatory volume overload. Usually, 20 $ml \cdot kg^{-1}$ FFP every eight hours will control clinical bleeding. If volume overload is a consideration, then a diuretic may be given before the administration of the plasma.

Commercial Factor VIII

The VWF in commercial Factor VIII concentrates lack the large multimers, and therefore fails to correct the bleeding time abnormality in VWD, and should *not* be used.[9]

Platelets

Transfused platelets do not correct the bleeding time in patients with VWD. However, platelets may be required in addition to cryoprecipitate in a patient who may be thrombocytopenic secondary to blood loss or plasma dilution during surgery or trauma. Usually 1 unit $\cdot$ 5–6 kg^{-1} will raise the platelet count 50–75 $\times$ $10^9 \cdot L^{-1}$. Platelets should be administered when blood loss exceeds half of a patient's circulating blood volume, or when the absolute platelet count has decreased to less than 50–80 $\times$ $10^9 \cdot L^{-1}$.

DDAVP

All of the preceeding treatments involve the transfusion of blood or blood products. Recently, there has been a growing concern that blood products are involved in the transmission of several diseases, including AIDS and Non-A/Non-B hepatitis. Although this does not appear to be a frequent problem in Canada, public awareness and fear have led some patients to refuse appropriate therapy. In addition, some patients refuse blood products on the basis of their religious affiliation. Therefore, the ability to treat VWD, or other coagulation defects, without the use of blood products has been an important therapeutic advance.

As early as 1977, 1-deamino-8-D-argenine vasopressin (DDAVP) was described by Mannucci[24] to increase Factor VIII levels. Since that time, several investigators have successfully used it to treat uremia,[25] platelet disorders[26] and VWD.[27] Although the drug is a synthetic analogue of anti-diuretic hormone, excessive fluid retention is an uncommon side effect. Fluid balance should be monitored closely, however, and excessive perioperative fluids should be avoided. If fluid retention should occur,

low doses of furosemide (0.25–0.50 $mg \cdot kg^{-1}$) will produce an appropriate diuresis.

The exact method by which DDAVP reduces the bleeding time in VWD is not known, but it is believed that it acts as a "non-specific" stimulus for the release of Factor VIII (VIII C and VWF) from tissue stores.[27] Therefore, in order to be effective, it is necessary that there be adequate tissue stores of Factor VIII, and that the Factor VIII that is released be qualitatively normal. Accordingly, DDAVP is most effective in patients with Type I Von Willebrand's disease, produces a variable response in patients with Type II disease, and a poor response in patients with Type III disease. Since the classification of the patient preoperatively is often unknown, it may be necessary to administer DDAVP (0.3 $\mu g \cdot kg^{-1}$ or 10 $\mu g \cdot m^{-2}$ IV over 20 min) and to re-check the coagulation studies after one hour. If the bleeding time has shortened, then it can be assumed that DDAVP will be effective in the perioperative period. If the bleeding time is unchanged, the traditional use of blood products for the treatment of Von Willebrand's would be more appropriate.

As previously mentioned, patients with Type II B disease frequently have an associated mild thrombocytopenia. Treatment with DDAVP increases platelet/VWF binding, and transiently exacerbates the thrombocytopenia. Therefore, the administration of DDAVP is contraindicated in patients with Type II B disease.

The use of DDAVP is elective surgery is slowly being investigated and presented in the literature. Recent articles have documented its efficacy in reducing blood loss during spinal fusions,[29] and after open heart surgery.[30] However, its use intraoperatively with an undiagnosed bleeding diathesis is currently empirical. We suggest that in the absence of a definitive diagnosis, DDAVP can be used safely as an adjunct to blood products. The only contraindication is where the patient has documented thrombocytopenia preoperatively which is presumptive of a patient with VWD Type II B disease.

Finally, it is important to note that the response to DDAVP may become attenuated with time. Because of this rapid development of tachyphylaxis, the "test dose" should ideally be given two to three days preoperatively. Then, at the time of surgery, the DDAVP should be administered as a single dose for minor procedures, or every 12–24 hr for more complicated situations. If the drug is used for more than 2–3 doses, both fluids and electrolytes must be monitored closely for the potential development of the syndrome of inappropriate ADH (SIADH). In general, more than three doses in a 48-hour period would not be recommended.

Summary

In summary, both haemophilia and Von Willebrand's disease involve defects in the Factor VIII molecular complex. Current understanding of this complex has allowed a more accurate classification of Von Willebrand's disease. Although the administration of cryoprecipitate and other blood products has traditionally been the cornerstone of treatment for VWD, the recent development of DDAVP for clinical use may provide an effective alternative to replacement therapy with blood products.

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