CLINICAL REVIEW

Von Willebrand Disease

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Von Willebrand's disease (VWD) is the most common hereditary bleeding disorder in humans and is caused by inherited defects in the concentration, structure, or function of von Willebrand factor (VWF). VWF is a protein that binds platelets to exposed subendothelium on the vessel wall (primary hemostasis) and also carries plasma factor VIII (FVIII) in circulation, so it can participate in the coagulation cascade (secondary hemostasis). Clinically, patients with VWD usually present with excessive mucosal and/or postsurgical bleeding. VWD is classified according to the specific quantitative or qualitative defect in VWF; the severity of symptoms is variable depending on the degree of vWF and FVIII reduction. Type 1 VWD is the most common (80%) and typically is characterized by only minor bleeding abnormalities unless the hemostatic system is challenged. Type 2 and Type 3 VWD can have more severe bleeding problems. Diagnosis requires a thorough bleeding history and a specialized array of laboratory tests. Treatment typically involves the prophylactic use of desmopressin (DDAVP) or VWF/FVIII concentrates. Antifibrinolytic agents are often used as an adjunctive therapy. Consultation with a hematologist is recommended whenever a patient with VWD undergoes surgery or develops bleeding complications.

Case Presentation

An 86-year-old male with a history of hypertension, hyperlipidemia, coronary artery disease, and von Willebrand's disease (VWD) presented to the UCLA preoperative clinic with severe left knee osteoarthritis and upcoming left knee replacement. He had progressively worsening left knee pain for over ten years. His knee pain was severe with weight-bearing activities, and he had increasing disability and varus deformity. He failed conservative treatments and used hydrocodone/acetaminophen several times daily for pain control. Radiographs showed severe tricompartmental osteoarthritis. He was diagnosed with VWD type 2A by an outside Hematologist three years prior after he suffered postsurgical bleeding. There was long history of easy bruising and epistaxis, and he had suffered several significant bleeding complications over the past several years including postoperative bleeding after carpal tunnel surgery, which began after he had left the hospital; a lumbar epidural hematoma after an epidural steroid injection requiring emergency surgery; a calf hematoma after minor trauma requiring surgical drainage; and two gastrointestinal bleeds requiring blood transfusions. He had received DDAVP and factor replacement on several occasions in the past during bleeding episodes. Diagnosis of VWD was based on low Factor VIII levels, low VWF antigen levels, and a von Willebrand multimeric analysis, which showed an absence of high molecular weight multimers, consistent with VWD type 2A.

Given this significant bleeding disorder, Hematology consultation was obtained preoperatively. The patient underwent left knee replacement and was infused with factor replacement (VWF/factor VIII) prior to surgery as well as DDAVP. He was followed throughout his hospitalization by Hematology and levels of factor levels were monitored; he received daily factor infusions and was discharged on home factor infusions. Despite this aggressive treatment, the patient required several blood transfusions after surgery and developed significant postoperative complications including several re-hospitalizations over a four-month period for re-bleeding from his surgical wound and subsequent wound infection. He required two subsequent surgeries, one to washout a hematoma and another irrigation and debridement due to suspected infection. He was treated with antibiotics intravenously for several months and remains on long-term suppressive antibiotics. In the following review, we discuss the etiology, pathogenesis, diagnosis, and treatment of the most common hereditary bleeding disorder in humans, von Willebrand's disease.

Discussion

In 1926, a Finnish physician, Erik von Willebrand, first described an inherited bleeding disorder that was characterized by signs of excessive mucocutaneous hemorrhage.[1] The laboratory investigation of this disorder revealed a normal coagulation time and platelet count but a prolonged bleeding time. VWD is now recognized as the most common inherited bleeding disorder in humans with an estimated prevalence of around 1-2% but with a much lower prevalence of clinically relevant cases.[2] VWD is caused by inherited (mainly autosomal dominant) defects in the concentration, structure, or function of VWF. VWF has an essential role in both primary hemostasis (by acting as a bridging molecule between platelets and the vessel wall) and secondary hemostasis (stabilizing and protecting FVIII from early breakdown by the activated protein C system). As a result of a VWF deficiency or structural abnormality, levels of FVIII, the coagulation protein deficient in hemophilia A, may be variably reduced.[2] A variety of quantitative (Type 1 VWD and Type 3 VWD) and qualitative (Type 2 VWD) defects in VWF have been described, are the basis of the classification of VWD, and account for the wide range of clinical manifestations of the disease. Clinically,

excessive mucosal or postsurgical bleeding is the hallmark of VWD. The goal of therapy in VWD is to correct the hemostatic defects by increasing the endogenous production of VWF using DDAVP or by administering VWF concentrates. Multiple factors are important in determining the correct therapeutic agent and treatment should be individualized.

VWF is synthesized in vascular endothelial cells and megakaryocytes and circulates in plasma as a large multimeric protein complex.[3] VWF plays a major role in both primary and secondary hemostasis. In primary hemostasis, VWF enables platelets to adhere to injured vascular endothelium by acting as a bridge between the platelet receptor glycoprotein Ib (GpIb) and the subendothelial matrix. VWF also is important for subsequent platelet aggregation. During secondary hemostasis, VWF binds to and stabilizes FVIII to protect it from degradation and to concentrate FVIII at the site of tissue injury where its participation in the coagulation cascade is necessary for fibrin formation to secure the platelet plug.[3] In the presence of VWF the half-life of FVIII is 8-12 hours, in the absence of VWF it is < 1 hour.[4]

VWD is caused by an inherited defect in the VWF protein and displays extreme clinical and genetic heterogeneity. VWD is the most common inherited bleeding disorder in humans, but the exact frequency of VWD is difficult to determine because many cases (especially type 1 VWD) go undetected until surgery or major trauma challenges the coagulation system.[3] There is also variable penetrance and expression of VWD mutations leading to a large variability in the severity of clinical manifestations. More than 20 clinical subtypes of VWD exist and can be classified into three general types based on clinical severity, the quantity of plasma VWF, and the qualitative defects in VWF structure and function (**Table 1**).[2, 3, 5]

Type 1 VWD and Type 3 VWD are quantitative disorders characterized by variably reduced levels of VWF. Type 1 VWD accounts for 70-80% of all cases and is inherited in an autosomal dominant fashion with incomplete penetrance. It is a mild, quantitative disorder in which there is partial decrease in the amount of VWF protein in both platelets and plasma. VWF is normal in structure and function and levels are 10% to 50% of normal.[2, 3] Type 3 VWD is rare, inherited as an autosomal recessive trait, and characterized by undetectable levels of VWF (usually < 3 IU/dL).[2, 6] As a result of the near complete absence of VWF, affected individuals have much more severe clinical manifestations and typically suffer spontaneous bleeds early in life. Due to the dual functions of VWF and subsequent very low levels of FVIII, these patients manifest features of both severe VWD (mucocutaneous bleeding) and moderately severe hemophilia A (hemarthrosis and deep muscle hematomas). FVIII levels are typically 2% to 10% of normal.[6]

Type 2 VWD accounts for 10-20% of all cases and includes several variants that all have in common qualitative defects of VWF.[3,5] Type 2A variants (mainly autosomal dominant inheritance) are the most frequent and all have in common the lack of large and intermediate size VWF multimers. This is due to impaired multimerization or increased susceptibility of multimers to breakdown resulting in absence of high molecular weight (HMW) multimers of VWF.[2,6] In type 2B VWD, a gain of function mutation causes an increased affinity of VWF for the platelet GpIb receptor, leading to removal of HMW multimers from plasma and associated thrombocytopenia.[4]

VWD can also rarely present as an acquired syndrome and has been described in association with a range of lymphoproliferative, myeloproliferative, cardiovascular, autoimmune, and other disorders.[7] These disorders can lead to structural or functional alterations in VWF. The specific defects in acquired von Willebrand syndrome (AVWS) depend on the underlying cause. In lymphoproliferative disorders such as monoclonal gammopathy of undetermined significance (MGUS) and some cancers, autoimmune clearance due to binding of paraproteins or inhibition of VWF results in very low levels. In myeloproliferative disorders, there is increased binding of VWF to cell surfaces of platelets. Cardiovascular conditions such as aortic stenosis can lead to increases in fluid shear stress resulting in depletion of HMW multimers of VWF. Differentiating AVWS from congenital Type 1 and 2 VWD can be complicated and expert hematologic consultation is necessary. AVWS should be considered in all patients who develop a bleeding disorder (especially later in life) and have laboratory findings that suggest VWD, especially if an AVWS associated disorder is present. Treatment of the underlying associated condition with immunosuppressants, surgery, or chemotherapy can lead to a remission of AVWS in some patients. In some cases, plasmapharesis or intravenous immumoglobulins (IVIG) may be used to treat AVWS.[7]

Clinically, due to the dual action of VWF in helping to form platelet plugs and also to stabilize FVIII, individuals with VWD can present with symptoms that reflect defects in both primary and secondary hemostasis. Defective primary hemostasis manifests with bruising, petechiae, epistaxis, bleeding from mucus membranes, and gastrointestinal bleeding. The most prominent symptoms are usually from mucocutaneous bleeding (epistaxis, menorrhagia, easy bruising). Those with severe reductions in FVIII due to defective VWF can show signs of defective secondary hemostasis such as hematomas in muscles and joints much like hemophilia patients.[3] Patients with Type 1 VWD often have mild symptoms, while those with Type 2 and Type 3 VWD can have more serious bleeding problems. In general, the severity of mucocutaneous bleeding correlates with the degree of reduction of VWF and FVIII.[2] Bleeding after dental extraction is the most common post-operative bleeding manifestation. Severe bleeding complications such deep muscle hematomas or hemarthrosis are rare in Type 1 VWD and usually only seen after trauma, while in Type 3 VWD, the severity of bleeding can be similar to hemophilia. Gastrointestinal bleeding can be problematic especially in patients lacking HMW multimers (Type 2A VWD). Postoperative bleeding is typically uncommon and mild in Type 1 VWD patients, whereas prophylaxis with VWF/FVIII concentrates is always required in Type 3 VWD.[2]

The diagnosis and classification of VWD requires evidence of a bleeding history, a specialized array of laboratory tests showing reduced VWF activity, and usually evidence of other affected family members (inheritance).[2,6] Diagnosis is straightforward in patients with severe bleeding and markedly reduced VWF levels. In cases of mild bleeding and laboratory abnormalities, diagnosis is more difficult. It is important to remember that screening tests of the coagulation system, including the bleeding time, can be normal in patients with VWD even though it is a disease that disrupts primary hemostasis. Also, VWD can manifest temporal variability so repeat testing may be necessary in patients with a suggestive bleeding history even when initial studies are normal.[3]

Three main problems complicate the diagnosis of VWD. First, at least one bleeding symptom may be reported in 50% of normal individuals and two or more symptoms in as many as 10%. Bleeding symptoms are common in 'normal' individuals and care must be taken to avoid over-medicalization of patients with a mild bleeding history. The most useful questions to begin with are whether there is a family history of a bleeding disorder or a history of excessive bleeding from simple wounds. It is also important to ask about mucocutaneous bleeding, menorrhagia, epistaxis, gastrointestinal bleeding, previous postsurgical bleeding, and joint bleeding.[5] To ensure accuracy, studies have demonstrated the importance of a standardized approach in collecting a bleeding history and use of structured bleeding questionnaires.[8] One such bleeding assessment tool has been endorsed by the International Society of Thrombosis and Hemostasis and allows calculation of a bleeding score.[9] Data suggests that a bleeding score of 3 or over in males and of 5 or over in females is a useful cutoff in determining who should undergo further testing of VWF activity to look for a bleeding diathesis.[2] In general, to reach a significant bleeding score, at least three different bleeding symptoms requiring medical attention or at least one major symptom requiring specific medical intervention are required.[9]

The second problem with diagnosing VWD is that the level of VWF in patients with mild Type 1 VWF and normal subjects overlap considerably. In general, VWF levels below 30 IU/dL are strongly associated with the presence of mutations in the VWF gene and clinically significant bleeding as assessed by a bleeding score. However, mild VWD may be present in individuals with VWF levels under 40 IU/dL and other family members with similar levels.[2] Pediatric cases are evaluated with less stringent criteria. The third obstacle to diagnosis lies in the fact that VWD is a genetic disease with variable penetrance and inheritance is often difficult to establish.[6] Finding another first degree family member with reduced VWF is helpful in confirming the diagnosis. In practice, however, this is not easily applicable and not required for severe forms of the disease.

If the clinical suspicion of VWD is high based upon bleeding symptoms and a bleeding score, then further testing is indicated. The three tests most commonly used tests to diagnose VWD are the VWF antigen test (VWF:Ag), the VWF-Ristocentin Cofactor Activity test (VWF:RCo), and the FVIII coagulant assay.[10] All patients with VWD should have reduced VWF function (<40 IU/dL), which is measured by a functional assay (VWF:RCo). This test measures the ability of patients' plasma VWF to bind to normal platelets via the platelet GpIb receptor. Further characterization of VWD type is based on specific tests to quantify the VWF level measured in terms of the antigen (VWF:Ag), FVIII activity, and multimer pattern.[5,6] The VWF:Ag test measures the concentration of VWF in the plasma and results are typically reported in IU/dL. Multimer analysis is abnormal in some Type 2 VWD variants. All types of VWD will have abnormalities on one or more of these tests on repeat testing.[3] Results of these laboratory tests in conjunction with clinical findings often provide sufficient evidence for a diagnosis of VWD and should allow for determination of the disease type and subtype.[5] Type 1 VWD is characterized by an equivalent mild to moderately severe reduction of VWF:Ag and VWF:RCo in plasma and reduced FVIII levels with normal HMW multimers. In Type 2 VWD (qualitative defects), there is a greatly reduced VWF:RCo/VWF:Ag ratio. To further subclassify VWD or diagnose variant forms of type 2 VWD, evaluation of the molecular weight profile of VWF (multimer analysis, which is abnormal in Type 2A VWD) and an assessment of reactivity to the platelet-agglutinating agent ristocetin may be needed.[2,3,6] Hematology consultation is recommended for all patients suspected of having VWD as diagnosis can be complicated.

Once VWD has been diagnosed, the main goal of therapy is to correct the dual defect of hemostasis.[2,4,6] Patients with VWD not only require treatment during bleeding events but also need effective prophylactic strategies to prepare for events ranging from minor dental procedures to major surgery. Therapeutic agents are broadly classified into therapies that increase the level of activity of intrinsic VWF (DDAVP), therapies that replace VWF using an exogenous source (concentrates), and therapies that enhance alternative prothrombotic pathways or decrease fibrinolysis.[5] DDAVP and replacement therapy with VWF/FVIII or VWF concentrates to increase VWF and FVIII levels are the mainstay of treatment. Antifibrinolyic agents are also important adjunctive treatment options especially for mucous membrane bleeding. The choice of treatment depends on a number of factors including the severity of the bleed, the subtype and severity of VWD, the procedure planned, the duration of treatment, the age and comorbidities of the patient, and the previous response to treatment.[2, 3, 4]

DDAVP (1-deamino-8-d-arginine vasopressin) is a synthetic analogue of the natural antidiuretic hormone that was originally designed for the treatment of diabetes insipidus. The ability of intravenously administered DDAVP to treat selected patients with VWD was first described by Mannucci in 1977.[11] DDAVP is now in widespread use although there is little clinical trial data available to guide treatment. Following DDAVP administration, VWF and FVIII are released from cellular stores in the vascular endothelial cells into plasma. DDAVP is most effective in patients with Type 1 VWD who have functionally normal VWF. Approximately 80-90% of these patients will have a clinically meaningful hemostatic response to DDAVP making it the treatment of choice for Type 1

VWD.[12] In a prospective trial of DDAVP in patients with Type 1 VWD, 84% of patients had a complete response and 13% of patients had a partial response.[13] DDAVP is also used in mild Type 2A disease but is contraindicated in Type 2B disease as it can precipitate thrombocytopenia.[5] A DDAVP challenge test is recommended before first use to assess individual response to treatment.

DDAVP has been studied in responsive patients and when used in combination with adjunctive antifibrinolytic therapy. It is effective for bleeding events, adenotonsillar procedures, minor oral and dental surgeries, and menorrhagia. DDAVP use is not well studied in major surgery and is not an appropriate treatment choice in most major surgical procedures requiring extended hemostasis as explained below.[12] DDAVP is inexpensive; carries no risk of transmission of blood-borne viruses; and can be administered intravenously, subcutaneously, or intranasally. Intravenous (IV) infusion at a dose of 0.3 µg/kg (given diluted in saline over 30 minutes) will lead to a 2-4 fold increase in the plasma levels of both FVIII and VWF within 30 minutes and typically these high levels last in the plasma for 6-8 hours.[2,4] The primary limitation of DDAVP use is development of tachyphylaxis (the progressive reduction of responsiveness after multiple treatments) after repeated dosing, and this should be considered when prolonged dosing is anticipated. After treatment for several days with DDAVP, the levels of FVIII and VWF attained after infusion are significantly reduced. Due to tachyphylaxis, DDAVP is not expected to be effective when given at consistent intervals less than 24 hours apart or when repeated dosing is given for greater than 2-4 days.[4, 12]

Most adverse effects associated with DDAVP are mild vasomotor effects such as tachycardia, mild hypotension, headache, and facial flushing and can often be mediated by slowing the rate of infusion. Mild to severe hyponatremia and hyponatremia-related seizures are the most serious adverse effects associated with DDAVP use. Fluid restriction and monitoring of sodium levels along with cautious use in patients with medical disorders such as heart failure and renal disorders is advised.[3] Rarely, arterial thrombosis (myocardial infarction, stroke) have been reported in elderly patients after DDAVP use and caution is indicated in those with significant underlying vascular disease or uncontrolled hypertension.[12] DDAVP is contraindicated in Type 2B VWD because it induces thrombocytopenia as a result of the release of abnormal VWF that demonstrates hyperactivity with platelet GpIb.[3] Patients with Type 3 VWD are unresponsive to DDAVP. In responsive patients, DDAVP should is the preferred treatment of choice when hemostasis is needed for no longer than 2-3 days, thus not exceeding the 3-4 infusions after which tachyphylaxis can occur. A recent study of practice patterns of US hematologists caring for patients with VWD showed that DDAVP was prescribed to treat >80% of bleeding events and used in >85% of surgical procedures in patients with Type 1 VWD. DDAVP was also used to treat around 50% of bleeding events and 40% of surgical procedures in Type 2 VWD.[12]

In cases where DDAVP is ineffective (all patients with Type 3 VWD) or contraindicated (Type 2B VWD), VWF and FVIII concentrated blood products can be infused to restore proper levels and achieve hemostasis.[4] Patients with severe Type 1 or Type 2A also may also require factor concentrate infusions. Many products are available that are shown to be effective in acute bleeds and surgical procedures. There are no data that one product is superior to any other, and patients vary in their response to infusions of VWF-containing concentrates. Haemate P is the best studied concentrate and was 91-100% effective in preventing bleeding complications in 7 clinical trials.[5] Typically, the VWF:Rco and FVIII levels are monitored and different levels are recommended depending on whether a major operative procedure or minor surgery is being undertaken. For major surgery, the recommended dose is typically 50 IU/kg of VWF:RCo on the day of surgery and daily until healing is complete. Lower doses are needed for minor surgery, and a single dose is typically given for dental extractions. Expert guidance by a hematologist is necessary. In an emergency, cryoprecipitate (contains VWF, FVIII, factor IX, and fibrinogen) remains a treatment option. A dose of 8 to 10 units of cryoprecipitate is believed to be adequate to obtain hemostasis in patients with VWD.[5] It is important to note that sustained high levels of FVIII have been associated with an increased incidence of thromboembolic events and should be avoided. Factor VIII levels should be monitored to avoid excessive levels.[6,14] Venous thromboprophylaxis, at the same dosing schedule as for non-vWD patients, is recommended for major surgery in patients at high risk of venous thromboembolism.[2,14,15]

Several adjunctive hemostatic agents, such as the antifibrinolytic drugs, tranexamic acid, and epsilon amino caproic acid are available and often prevent the need to resort to blood component infusion. These agents can be especially useful as prophylactic agents for mucosal bleeding such as prolonged oral bleeding after dental extraction, minor surgery, and for woman with heavy menstrual bleeding. Mucosal bleeding is characterized by high fibrinolytic activity and these agents work by inhibiting the conversion of plasminogen to plasmin, thus inhibiting fibrinolyisis and thereby helping stabilize clots that have been formed.[4] These drugs can be given either orally, intravenously, or topically and can be useful alone or as an adjunct to replacement therapy (DDAVP or concentrates) to prevent mucosal bleeding or during minor or major surgery involving mucosal surfaces. Local use of topical thrombin and agents such as Gelfoam can also be helpful in reducing bleeding from dental procedures.[2,3] Platelets contain 10-15% of the total blood VWF and can be given to control bleeding that is not responsive to replacement therapy with VWF concentrate.[4] Recombinant VWF is currently undergoing studies in Type 3 VWD and is likely to be an additional treatment option in the future.

Management suggestions for specific situations and bleeding problems have been published and are briefly summarized here.[2,4] For dental treatments, oral antifibrinolytics should be commenced before treatment and DDAVP or VWF-concentrate can be used for more invasive treatments. Menorrhagia is

common in women with VWD. In fact, in some studies, up to 20% of women with menorrhagia turned out to have mild VWD. In addition, menorrhagia affects 80-90% of women with VWD and treatment with medical or surgical therapy is frequently needed. In general, treatment options are similar to those used for women without a bleeding disorder. The combined oral contraceptive pill, tranexamic acid, DDAVP, and the levonorgesterel-releasing intrauterine system have all been used to control bleeding. DDAVP has been used successfully for subcutaneous or intranasal home-treatment administration.[6] It should be noted that surgical treatment with hysterectomy may be required in up to a quarter of women with menorrhagia and full gynecological evaluation is recommended.[4] Physicians should also be aware that iron supplementation is often needed in these patients as well.

For severe spontaneous or trauma-induced bleeding in patients with VWD, the VWF:RCo and FVIII levels should be increased to approximately 80 IU/dL until bleeding is controlled.[4] If possible, all patients with VWD should be evaluated by a hematologist prior to elective surgical procedures and a detailed perioperative plan should be conveyed to the patient, the anesthesiologist, and the surgeon. Regular assessment and correction of hemostasis is needed pre- and post-operatively. When undergoing surgery, individuals with different subtypes of VWD have different product requirements (**Table 2**).[4] It should be noted that antifibrinolytic therapy, given both pre- and post-operatively (until wound healing complete) can be used as an adjunctive treatment in both minor and major surgical procedures. A VWF:RCo and FVIII of 50 IU/dL is usually adequate for minor procedures and often only one infusion is needed. Antifibrinolytics can also be administered.

For major surgery, a VWF-concetrate dose is calculated and infused with the goal of increasing the VWF:RCo level to 80-100 IU/dL at the time of surgery. This level should be maintained above 50 IU/dL until hemostasis is secure. The FVIII level should be raised around 100 IU/dL perioperatively and maintained above 50 IU/dL until wound healing is complete. Regular monitoring of both VWF:RCo and FVIII and repeat infusion of concentrate are required.[4] The risk of venous thromboembolism should be assessed in all patients undergoing major surgery. As mentioned previously, it is recommended to administer usual thromboprophylaxis in those at high risk for venous thrombosis, and it is important to avoid high levels of FVIII.[2,15] Hematology consultation and expertise is necessary for dosing of VWF concentrate and management of levels in all patients with VWD undergoing procedures.

While individuals with VWD most commonly suffer from mucosal bleeding, patients with severe forms of VWD may have frequent hemarthrosis and spontaneous muscular bleeding (resembling the bleeding seen in hemophilia A). Some of these patients may benefit from secondary long-term prophylaxis to prevent recurrent spontaneous hemorrhage although the optimal regimen has not yet been established. Studies are currently underway to compare on-demand and prophylactic treatment with VWF concentrates.[4]

In conclusion, VWD is the most common inherited bleeding disorder in humans, and a basic understanding of the pathophysiology, diagnosis, and treatment of VWD is important for all physicians. There are several types of VWD, all characterized by quantitative or qualitative defects in VWF with variable bleeding risks and different treatment strategies. Treatment should be individualized depending on the type of VWD and the specific situation. Careful planning with hematologic consultation is always preferred, if possible, when any procedures are planned. The patient we described was managed by a hematologist with expertise in bleeding disorders and was treated with concentrates and DDAVP both preoperatively and postoperatively and still developed significant and prolonged bleeding complications following major orthopedic surgery.

Tables

Table 1. **Classification of VWD***

Quantitative defect of VWF	a. Type 1: partial deficiency b. Type 3: nearly complete deficiency
Qualitative defect of VWF	a. Type 2: qualitative defect b. Type 2A: variants with decreased function associated with absence of HMW multimers c. Type 2B: variants with increased affinity of platelet GpIb with absence of HMW mulitimers. d. Type 2M, 2N: other less common variants with qualitative defects

* Castaman G, Goodeve A, Eikenboom J. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013;98(5):667-74.

Table 2. **Treatment Recommended for Minor and Major Surgery in Patients with VWD[1]***

Type 1 VWD	a. Minor surgery: DDAVP b. Major surgery: VWF concentrate
Type 2 VWD	a. Minor surgery: DDAVP (type 2A), VWF concentrate (type 2B) b. Major surgery: VWF concentrate.
Type 3 vWD	a. Minor surgery: VWF concentrate b. Major surgery: VWF concentrate

[1] Adjunctive antifibrinolytic agents should also be considered. ***** adapted Tuohy E, Litt E, Alikhan R. Treatment of patients with von Willebrand disease. Journal of Blood Medicine. 2011;2:49-57.

REFERENCES

1. **Von Willebrand EA**. Herditar pseudohemofili. *Finska Lakarsallskapets Handle.* 1926; 67:7-112.
2. **Castaman G, Goodeve A, Eikenboom J; European Group on von Willebrand Disease**. Principles of care for the diagnosis and treatment of von Willebrand disease. *Haematologica.* 2013 May;98(5):667-74. doi: 10.3324/haematol.2012.077263. Review. PubMed PMID: 23633542; PubMed Central PMCID: PMC3640108.
3. **Murray EW, Lillicrap D**. von Willebrand disease: pathogenesis, classification, and management. *Transfus Med Rev*. 1996 Apr;10(2):93-110. Review. PubMed PMID:8721967.
4. **Tuohy E, Litt E, Alikhan R**. Treatment of patients with von Willebrand disease. *J Blood Med*. 2011;2:49-57. doi: 10.2147/JBM.S9890. Erratum in: J Blood Med. 2013 May 20;4:57-8. PubMed PMID: 22287863; PubMed Central PMCID: PMC3262353.
5. **Mazzeffi MA, Stone ME.** Perioperative management of von Willebrand disease: a review for the anesthesiologist. *J Clin Anesth*. 2011 Aug;23(5):418-26. doi:10.1016/j.jclinane.2011.02.003. Review. PubMed PMID: 21741810.
6. **Rodeghiero F**. Von Willebrand disease: pathogenesis and management. *Thromb Res*. 2013 Jan;131 Suppl 1:S47-50. doi: 10.1016/S0049-3848(13)70021-5. PubMed PMID:23452742.
7. **Tiede A.** Diagnosis and treatment of acquired von Willebrand syndrome. *Thromb Res*. 2012 Dec;130 Suppl 2:S2-6. doi: 10.1016/S0049-3848(13)70003-3. PubMed PMID: 23439003.
8. **Rodeghiero F, Castaman G, Tosetto A, Batlle J, Baudo F, Cappelletti A, Casana P, De Bosch N, Eikenboom JC, Federici AB, Lethagen S, Linari S, Srivastava A**. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *J Thromb Haemost*. 2005 Dec;3(12):2619-26. Erratum in: J Thromb Haemost. 2006 Apr;4(4):925. PubMed PMID: 16359502.
9. **Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, Neunert C, Lillicrap D; ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group**.. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost*. 2010 Sep;8(9):2063-5. doi: 10.1111/j.1538-7836.2010.03975.x. PubMed PMID: 20626619.
10. The diagnosis, evaluation and management of von Willebrand Disease. Clinical practice guidelines: Hemophilia and von Willebrand's disease. Bethesda (Md): National Heart Lung and Blood Institute; 2007 [NIH Pub. No. 09-5832].
11. **Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A**. 1-Deamino-8-d-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrands' diseases. *Lancet*. 1977 Apr 23;1(8017):869-72. PubMed PMID:67283.
12. **Leissinger C, Carcao M, Gill JC, Journeycake J, Singleton T, Valentino L**. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia*. 2014 Mar;20(2):158-67. doi: 10.1111/hae.12254. Review. PubMed PMID: 23937614.
13. **Castaman G, Lethagen S, Federici AB, Tosetto A, Goodeve A, Budde U, Batlle J, Meyer D, Mazurier C, Fressinaud E, Goudemand J, Eikenboom J, Schneppenheim R, Ingerslev J, Vorlova Z, Habart D, Holmberg L, Pasi J, Hill F, Peake I, Rodeghiero F**. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (VWD): results from the European Study MCMDM-1VWD. *Blood*. 2008 Apr 1;111(7):3531-9. doi: 10.1182/blood-2007-08-109231. PubMed PMID:18230755.
14. **Ozelo MC**. Surgery in patients with hemophilia: is thromboprophylaxis mandatory? *Thromb Res*. 2012 Oct;130 Suppl 1:S23-6. doi:10.1016/j.thromres.2012.08.265. Review. PubMed PMID: 23026653.
15. **Mannucci PM, Franchini M, Castaman G, Federici AB; Italian Association of Hemophilia Centers.** Evidence-based recommendations on the treatment of von Willebrand disease in Italy. *Blood Transfus*. 2009 Apr;7(2):117-26. doi:10.2450/2008.0052-08. PubMed PMID: 19503633; PubMed Central PMCID: PMC2689066.

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