orphanaesthesia

Anaesthesia recommendations for

Von Willebrand disease

Disease name: Von Willebrand disease

ICD 10: D68.0

Synonyms: Inherited bleeding disorder

Disease summary: There are three major types of VWD disease. Type 1, the most frequent form, is characterized by a partial quantitative deficiency in von Willebrand factor (VWF). Type 2 is a qualitative deficiency, and Type 3 is a virtually complete deficiency. Type 2 VWD is divided into four subtypes. Type 2A includes variants with decreased platelet adhesion caused by a selective deficiency in high-molecular weight VWF multimers (HMWM). Type 2B includes qualitative VWF variants with increased affinity to platelet glycoprotein Ib. Type 2M includes variants with decreased platelet adhesion, but without HMWM deficiency, and type 2N includes variants with markedly decreased affinity for factor VIII. This categorization correlates with therapeutic requirements.

VWF is a plasma glycoprotein produced in megakariocytes and endothelial cells. It plays an important role in primary haemostasis through the mediation of initial platelet adhesion to sites of vascular injury. It also binds and stabilizes factor VIII (FVIII) in the blood.

VWD can be inherited or acquired. Unlike its inherited counterpart, acquired Von Willebrand disease (AVWD) is relatively rare and, usually occurs in elderly patients with no previous history of bleeding and no clinically meaningful family history. Physiopathologically, VWF is normally synthetized in AVWD but is quickly inactivated or eliminated in the plasma. Various underlying diseases have been associated with AVWD, most commonly hematolymphoid tumors, including monoclonal gammopathies, lymphoproliferative disorders, and myeloproliferative neoplasms.

As mentioned above, inherited VWD disease is divided in three major types. The diagnosis, especially of Type 1, may be difficult. In mild cases, VWF levels may overlap with those of normal subjects. The clinical manifestations of the disease may vary from minimal to severe. However, the bleeding risk generally parallels VWF levels. Given that mild decrease of VWF levels is relatively common, the prevalence of the disease varies among studies, and can be as high as 1% of the general population. As a consequence, only a fraction of patients come to medical attention because of bleeding symptoms. A definite diagnosis of VWD type 1 is performed when VWF:Ag is < 30 IU.dL-1, in association with bleeding symptoms. Persons with VWF:Ag levels of 30-50 IU.dL-1 are considered as having a low VWF level, but not a VWD. They may also be at risk of bleeding. During the pre-operative evaluation of those patients, the presence of bleeding symptoms should always outweigh VWF levels in assessing the bleeding risk. Among the signs that should draw the attention of the practitioner, the most common are recurrent and prolonged nosebleeds, bleeding from the gums, increased menstrual blood losses, excessive bleeding from a cut or following a tooth extraction, easy bruising, and family history.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

These patients can be addressed for every type of surgical procedure, but should be managed in centres where a multidisciplinary team and daily laboratory testing of concerned factors are available. Patients managed within specialized haemostasis and thrombosis hospital centres, have a favourable prognosis, even if presenting with a severe form of the disease.

Type of anaesthesia

General anaesthesia is often preferred in these patients. Noteworthy, regional anaesthesia must be performed with caution, particularly when spinal and epi-medullar anaesthetic procedures are planned. In that case, no formal recommendations exist, and contra-indications are relative. Should a neuraxial technique be used, a neurological postoperative surveillance is mandatory due to the increased risk of developing epi-medullar haematoma and compression of neurological structures. In case of neurological symptoms, the diagnosis is confirmed by computed tomography or magnetic resonance imaging. Conventional X-rays exams of the spine are useless.

Each patient should be managed individually, on a case-by-case basis, according to his/her subtype of VWD, severity, and the relative amount of circulating VWF antigen (VWF:Ag), VWF ristocetin cofactor (VWF:RCo), and FVIII pro-coagulant activity (FVIII:C) at the time of the procedure.

Necessary additional pre-operative testing (beside standard care)

No simple, single laboratory test is available to screen for VWD. In addition, initial coagula¬tion tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), may be normal. The aPTT reagents are sensitive to FVIII:C plasma levels lower than 30 IU/dL, while the test may be normal when FVIII level is greater than 40 IU.dL-1.

For patients with a low probability of VWD (e.g., seen in the primary care setting), using a validated bleeding-assessment tool (BAT) is recommended by the latest ASH ISTH NHF WFH 2021 guidelines during the preoperative evaluation to determine who needs specific blood testing over non-standardised clinical assessment. One of those is the ISTH-SSC Bleeding Assessment Tool (https://bleedingscore.certe.nl/).

For patients with a strong family history of bleeding, with current symptoms, or a history of increased muco-cutaneous bleeding, and those with a previous VWD diagnosis without laboratory documentation, specific VWD assays should be considered at the first visit.

Coagulation tests vary among teams. They may consist in platelet count, PT, aPTT, fibrinogen concentration, platelet function analysis (PFA-100®, Siemens Healthcare), and FVIII:C, VWF:Ag, VWF:RCo. In type 1, there is an equivalent reduction of VWF:Ag and VWF:RCo. An abnormal VWF:RCo/VWF:Ag ratio (< 0.7) is a simple way to suspect type 2 VWD.

The PFA-100® test has been demonstrated to be abnormal in the majority of VWD patients when VWF is significantly decreased, but is normal in patients with type 2N. However, the usefulness of PFA-100® in screening populations for VWD has not been established.

Other laboratory tests to be performed are a count of blood cells (CBC), blood group, C-reactive protein (CRP), and ferritin (see below).

If the initial VWD assay is positive, patients should be referred to a haemostasis specialist, in order to further investigate VWD subtype, and its responsiveness to desmopressin (DDAVP). Indeed, a test dose of DDAVP is recommended in VWD patients to establish the pattern of biological response, and to predict clinical efficacy. The response in an individual adult patient is constant in time. This desmopressin trial should be performed in non-bleeding patients. The haemostasis specialist will also establish a multidisciplinary managing plan, in preparation to surgery or invasive procedure.

Noteworthy, several conditions such as systemic inflammation (evidenced by elevated CRP and ferritin), pregnancies, oestrogen or oral contraceptives, as well as stress (surgery, exercise, anxiety, crying frightened child,…) can increase the plasma level of VWF, and mask lower baseline values. Of note, also, mean VWF levels are 25% lower in persons with a type 0 blood group. VWF is also low in patients with hypothyroidism.

Aging is known to increase VWF levels, and some patients previously diagnosed as type 1 VWD patients can normalize their VWF levels over time. Caution should be exercised in this case, because the association between increased VWF levels with age and bleeding symptoms is not established.

Particular preparation for airway management

Traumatic orotracheal intubation (OTI) should be avoided. Special attention should be paid to patients with increased risk of difficult intubation such as in the obstetric and paediatric populations. In case of difficult intubation, the use of a fiberscope or video-laryngoscope may reduce the risk of bleeding and mucosal lesions.

Particular preparation for transfusion or administration of blood products

It was recommended that candidates for replacement therapy with VWF/FVIII concentrate beneficiate from a vaccination against hepatitis A and B. Nowadays, the modern virucidal techniques virtually abolish the risk of transmission of blood-borne viruses (e.g. hepatitis viruses and HIV) and make these products safer than blood-bank cryoprecipitate.

Particular preparation for anticoagulation

Patients with VWD should be advised to avoid non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, and any type of platelet-inhibiting medications.

Low dose heparin prophylaxis should be considered in the perioperative period of surgeries with a high thrombotic risk, especially when replacement treatment is administered.

Particular precautions for positioning, transportation and mobilisation

Avoiding any trauma during positioning, transport and mobilisation is the rule.

Interactions of chronic disease and anaesthesia medications

None reported.

Anaesthetic procedure

VWD therapies follow three general strategies. The first aims at increasing plasma concentration of VWF through an endogenous release by desmopressin. The second strategy uses agents that improve haemostasis (tranexamic acid, amino-caproic acid), without modifying plasma levels of VWF. The third approach aims at replacing VWF by human plasma-derived, virus-inactivated concentrates. The panel of available products is highly variable from one country to another. The following list provides examples of such products, and is not exhaustive: Haemate P®(CSL Behring), Wilate®(Octapharma), Alphanate®(Grifols), Fanhdi®(Grifols), Biostate®(CSL Behring), Dried factor VIII fraction type 8Y®(Bio Products Laboratory), Wilfactin®(C.A.F – D.C.F), Veyvondi®(Baxalta Innovations).

The appropriateness of therapeutic choice depends on VWD severity and type, severity of the haemostatic challenge, and nature of the actual or potential bleeding.

For minor surgery, prophylaxis should achieve VWF:RCo and FVIII:C levels ≥ 50 IU.dL-1 on the day of surgery and during the first postoperative day, and > 30 IU.dL-1 during 2 to 5 days thereafter, or until scab fall. For major surgery, such as cardiac or neurosurgery, the levels of VWF:RCo and FVIII:C should be around 100 IU.dL-1 on the day of surgery and during the first postoperative day, and should be maintained ≥ 50 IU.dL-1 for 7 to 14 days or until healing is complete.

Desmopressin:

Desmopressin stimulates VWF release through its agonist effect on vasopressin V2 receptors. FVIII levels also increase acutely following its administration. When administered intravenously in healthy patients, it increases plasma VWF and FVIII from two to fivefold over baseline levels. Children younger than 2 years have a lower response rate than older children. Standard dosing is 0.3 µg.Kg-1. This dose must be diluted into 50 to 100 mL of isotonic saline, and intravenously infused over 30 minutes. In that case, the peak effect occurs within 30 to 90 minutes. A concentrated formulation for subcutaneous administration is also available. Desmopressin may eventually be repeated every 12 hours but response diminishes with repeated administration (tachyphylaxis). This is due to depletion of VWF into the cell storage compartment. In addition to tachyphylaxis, hyponatremia may complicate repeated administration. Ionic monitoring, fluid restriction, and isotonic infusions are recommended, particularly in children. Adult patients, and particularly elderly patients, should be evaluated for potential cardiovascular diseases. Indeed, precipitation of myocardial infarction by desmopressin therapy has been reported, although rarely.

Desmopressin is usually effective in Type 1 VWD. Type 2A patients rarely respond relevantly. Type 2B patients were previously considered as a contraindication to desmopressin. The reason was a frequent fall in platelet count after desmopressin stimulation. However, thrombocytopenia is usually transient, and is usually not associated with bleeding or thrombosis. Hence, Type 2B is a relative contraindication to desmopressin. In type 2M, the efficacy of desmopressin is variable. In type 2N, desmopressin raises VWF, but very shortly. Patients with type 3 VWD do not respond to desmopressin at all.

Antifibrinolytic agents:

Currently, tranexamic acid (TXA) is the most widely used antifibrinolytic agent. The drug inhibits the conversion of plasminogen into plasmin, thereby stabilizing previously formed clots. TXA can be used orally or intravenously. Dose and administration mode vary among teams. Intravenously, the bolus dose of TXA is 10-15 mg.Kg-1 repeated every 8-12 hours or followed by a maintenance infusion of 10 mg.Kg-1.h-1. If used as a wash-mouth for oral surgery, the frequency of administration can be increased. TXA is contraindicated for the management of renal or upper urinary tract bleeding, because of the risk of ureteral clots and subsequent hydronephrosis.

Replacement therapy:

Replacement therapy aims at correcting VWF deficiency, allowing platelet adhesion and aggregation, and increasing potentially low FVIII:C level. All plasma-derived concentrates contain both purified VWF and FVIII except for two of them, containing only VWF (see below). The main between-products difference is the VWF:RCo/FVIII:C ratio. For example, the ratios of Haemate P®, Alphanate®, Fanhdi®, Biostate®, Dried factor VIII fraction type 8Y®, and Wilate® are 2.4/1, 1.2/1, 1.15/1, 2/1, 3/1 and 1/1, respectively. Noteworthy, the 1.2/1 ratio of Alphanate® is highly variable from one lot to another.

All those concentrates can be considered as bioequivalent in terms of VWF pharmacokinetic properties. The Wilate® 1:1 VWF/FVIII ratio should theoretically facilitate dosing and laboratory monitoring of VWF. However, it can also increase FVIII to too high levels, particularly when its baseline concentration is only mildly reduced. Very high levels of FVIII increase the risk of thromboembolic events. All plasma-derived concentrates should be used with caution in patients with increased thrombotic risks, insofar as there have been some reports of venous thromboembolism associated with high levels of FVIII. The risk is even higher when the replacement therapy is combined with an antifibrinolytic therapy.

Wilfactin® (C.A.F – D.C.F) and Veyvondi® (Baxalta Innovations) are products that contain VWF uniquely. It is therefore not suitable for the immediate correction of low FVIII:C levels to haemostatic levels. They can be useful when the patient has normal or mildly low FVIII levels. When used for elective surgery, the first dose should be given 12 to 24 hours prior to surgery, in order to provide adequate haemostasis, insofar as there is a secondary rise of endogenous FVIII due to the stabilizing effect of infused VWF. Switching to products containing VWF only should also be considered when combined VWF/FVIII therapy increases FVIII to too high levels, thereby increasing the thromboembolic risks.

Of note, all product except Veyvondi® are derived from plasma through fractionation plus virus inactivation, but this may not protect against Parvovirus B19 infection. Since Veyvondi® is a recombinant von Willebrand factor, viral infections are not an issue. Adverse reactions to replacement therapy are rare, but may be severe and include allergic and anaphylactic symptoms, urticaria, chest tightness, rash, pruritus, and oedema. Severe allergic reactions may reveal the onset of an inhibitor against VWF, rarely and exclusively observed in some type 3 VWD patients. It should be kept in mind that a sodium load is to be expected due to the significant sodium content of some of the replacement therapies. The dose of VWF concentrate should always follow the licensed product recommended dosage. Doses are usually given in labelled VWF:RCo units. One IU.Kg-1 of VWF:RCo is considered to increase plasma VWF:RCo by approximatively 2%. The loading dose can be calculated as = (Δ×bw)/IVR, where Δ is the targeted VWF:RCo increase (IU.dL-1) to achieve the desired plasma level, bw is the body weight in kilograms, and IVR is the half-life of incremental in vivo recovery (IVR). VWF concentrate administration is usually repeated every 24 hours postoperatively. Maintenance doses should be adapted to the daily measured levels of FVIII:C and VWF:RCo. The monitoring of VWF:RCo and FVIII:C is also used to avoid the risk of perioperative thrombosis. VWF:RCo and FVIII:C levels should not exceed 150-200 IU.dL-1.

In an emergency situation, when the baseline level is unknown, the initial bolus dose is 50 IU.Kg-1.

In case of AVWD, etiological treatment of the causal pathology is the most effective treatment when possible. However, it's not always feasible in the perioperative setting. In that case, treatment relies on either desmopressin or replacement therapy, with the same criteria as in inherited VWD, or on immunoglobulins. Immunoglobulins is a specific treatment to quiescent monoclonal gammopathy, that is efficient in 83% of these subtype patients.

Particular or additional monitoring

Monitoring modalities are related to the type of surgery, and the risk of bleeding. Secure venous access is mandatory, but the necessity of an arterial catheter should be discussed on a case-by-case basis. Iterative arterial blood sampling through direct needle arterial puncture should be avoided.

Possible complications

The outbreak of an inhibitor against VWF or FVIII is one of the most severe encountered complications during the treatment of type 3 VWD patients.

Thromboembolic events due to the increase in FVIII can occur, as discussed above.

The risk of viral contamination following the administration of factor concentrate is very low, but not null.

Post-operative care

The goal is to maintain normal FVIII:C and VWF:RCo levels as long as the haemostatic challenge persists. This period ranges between 1 to 5 days for minor surgery, to up to 14 days for major surgery such as neurosurgery. Special care should be used for tonsillectomy, insofar as, after 6-7 days postoperatively, scab falls with inherent risk of bleeding. As mentioned above, factors levels should be monitored daily during replacement therapy and dosing should also be adapted to the obtained results. This management often results in prolonged hospitalization times. Patients still require a close follow up after being released from the hospital. Neurological evaluation after neuraxial blocks is mandatory.

Disease-related acute problems and effect on anaesthesia and recovery

In case of uncontrolled haemorrhage despite adequate VWF:RCo/FVIII:C levels, and after the exclusion of an anatomic aetiology, platelet transfusion should be considered, in addition to the administration of supplementary FVIII-VWF concentrate and/or desmopressin in responsive patients. These measures most often stop the bleeding. In case of uncontrolled haemorrhage, and inadequate VWF:RCo/FVIII:C levels despite proper administration, the rare possibility of an inhibitor should be kept in mind, especially in Type 3 VWD. Insofar as such an event is particularly rare, the recommended therapy has not been defined yet. Possible

therapeutic approaches include recombinant factor VIII, or bypassing agents such as recombinant factor VIIa (rFVIIa).

Ambulatory anaesthesia

Only patients with mild type VWD, and scheduled for a low bleeding risk surgery can safely beneficiate from ambulatory anaesthesia.

Obstetrical anaesthesia

As a reminder: each patient is unique. Management should be discussed on a case-by-case basis.

Non-anaesthetic considerations:

- Genetic counselling is desirable, optimally before conception, particularly to those at risk of having a child with type 3 VWD
- Even though there appears to be a higher incidence of vaginal bleeding during the first trimester in women with VWD, there is no increase in the miscarriage rate.
- An inherited bleeding disorder in the mother or foetus, by itself, is not an indication for a caesarean section delivery. The mode of delivery should be determined by obstetrical considerations.
- Neonates at risk of significant VWF decrease are at risk of head bleedings (scalp haematoma and intra-cerebral haemorrhage) during labour and delivery. Hence, the use of invasive foetal heart rate monitoring techniques and instrumental deliveries should be avoided.
- Woman with VWD are 1.5 times more likely to develop a postpartum haemorrhage (PPH), with a higher risk of both transfusion (5-fold) and death (10-fold).
- Pregnancy in women with VWD should be managed by an expert multidisciplinary team, including an obstetrician, a specialist in haemostasis, and an anaesthesiologist. It should be conducted in centres where resources for laboratory testing and clotting factor treatments are readily available.

Normal pregnancy and childbirth are associated with significant haemostatic changes that create a pro-coagulant state. This occurs through an increase in the majority of clotting factors, including FVIII and VWF.

Factor levels, including FVIII:C, VWF:Ag, and VWF:RCo, should be measured at presentation and at least once during the third trimester, as well as before any invasive procedure.

Changes in VWF during pregnancy vary according to VWD type. In Type 1 VWD, FVIII:C, VWF:Ag, and VWF activity usually progressively increases. The most significant increase occurs during the third trimester and most women achieve normal ranges of VWF by the third trimester. In Type 2 VWD, FVIII:C and VWF:Ag levels often increase, but most studies show minimal or no increase in VWF activity, as well as a persistently abnormal pattern of multimers, reflecting the increased production of abnormal VWF. Women with Type 3 VWD show little or no increase in FVIII and VWF plasma levels.

As a consequence, neuraxial anaesthesia is often possible in women suffering from Type 1 VWD. However, VWF and FVIII must be > 50 IU.dL-1, and this must be documented by a laboratory testing during the third trimester. If an epidural catheter is used, preferably a round-tip catheter, the epidural space should be well dilated before its introduction. Even with these recommendations, there is a risk of neuraxial hematoma.

Neuraxial anaesthesia is usually not recommended in Type 2 and 3 VWD. Exceptions are possible when factor levels are above 50 IU.dL-1 following a prophylactic treatment.

It is recommended that normal levels be maintained for the duration of catheter placement, and for at least 6 hours after catheter removal, insofar as, after uterine emptying, the levels of FVIII and VWF decrease rapidly. In any case, the neuraxial blocks must be carried out by an experienced anaesthesiologist and repeated attempts to puncture should be avoided.

Prophylactic treatment should be given when factor levels are below 50 IU.dL-1, in order to cover invasive procedures and delivery. Desmopressin can and has been safely used during pregnancy, particularly during the first trimester of pregnancy to cover invasive procedures such as villocentesis and amniocentesis, but it should be used cautiously during gestation. Repeated administrations or use in preeclamptic patients should be avoided. Close monitoring for water retention must be the rule. Tranexamic acid can also be used for the prevention or control of post-partum haemorrhage (PPH). Due to the lack of studies investigating its use during pregnancy, the 2021 guidelines from the American Society of Haematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Haemophilia Foundation (NHF), and the World Federation of Haemophilia (WFH) suggests, as a conditional recommendation based on low certainty in the evidence of effects, the use of tranexamic acid over not using it in women with type 1 VWD or low VWF levels (and this may also apply to types 2 and 3 VWD) during the postpartum period. However, it has been used successfully, and without any apparent maternal or foetal adverse effects, in a few case reports found in the literature. Replacement therapies follow the same scheme as described above. In women who require clotting factors replacement, FVIII:C and VWF:Ag levels should be monitored daily, and maintained above 50 IU.dL-1 for at least 3 to 5 days, and up to 7 days in case of caesarean section.

Factor levels that may have normalised during pregnancy tend to return to baseline within 7 to 21 days after delivery.

Women with VWD have a significantly higher risk of both primary and secondary PPH. Women with early PPH associated with low factor levels should be managed using factor replacement therapy or desmopressin for those who are responsive. Desmopressin has been detected in milk of lactating women. In breastfeeding mothers, factor replacement therapy should therefore be preferred. Tranexamic acid should be considered to prevent or control secondary postpartum haemorrhage. This medication is safe in breastfeeding mothers.

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Date last modified: **November 2022**

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Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

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Editorial review 2022

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Disclosure The reviewers have no financial or other competing interest to disclose.