Von Willebrand Disease

Inherited deficiencies in plasma coagulation factors resulting in abnormal coagulation; supplemental administration of the deficient factor (vWF +/- FVIII), and / or DDAVP to enhance factor activity is necessary to achieve a coagulation profile adequate for surgery or regional anesthesia; consultation with hematology is essential.

ANESTHETIC CONSIDERATIONS:

- High risk for perioperative bleeding
- Sequelae of bleeding in enclosed spaces with severe disease
  - Joints
  - Intracranial
  - Pericardium
  - Thorax
- Potential contraindication to neuraxial anesthesia and analgesia
  - LEA in parturients with vWD
- Consultation with hematology for factor replacement / supplementation and optimization (generally want >50% normal activity for surgery)
  - DDAVP
  - vWF concentrates – FFP, cryoprecipitate, recombinant vWF concentrates
  - Factor replacement – e.g FVIII:vWF (Humate-P)
  - Antifibrinolytics (EACA, TXA)

ANESTHETIC GOALS:

- Optimize factor activity and coagulation profile in perioperative period
- Techniques for minimizing perioperative blood loss

HISTORY

- Diagnosis known – what treatments are usually instituted for dental work, trauma
- Bleeding history – easy bruising, bleeding, petechiae, mucosal bleeding, epistaxis, menorrhagia
- History of severe and prolonged bleeding after dental extraction, tonsillectomy, other surgery
- Severe deficiency – deep tissue bleeds, hemarthroses, intracranial bleeds with minor trauma
- vWD – is it a subtype that does NOT respond to DDAVP, or is DDAVP contraindicated for thrombocytopenia?

PHYSICAL

- **GENERAL -** Bruises, petechiae
- **HEENT -** Airway – active bleeding can cause airway hematoma
- **MSK -** Joint swelling, deformity

INVESTIGATIONS

- **Labs**
  - CBC, INR, PTT, cross match
    - Routine labs may not demonstrate a defect depending on type
  - Other tests may be ordered by hematology including vWF factor antigen (vWF:Ag), vWF ristocetin cofactor activity (vWF:RCo) and vWF collagen binding activity (vWF:CB)
    - Ristocetin is an antibiotic that can induce GPIb-vWF interaction
- Other investigations as dictated by procedure and patient co-morbidity

OPTIMIZATION

- Consultation with hematologist and / or hemophilia society for appropriate factor management
- Schedule OR early in the week and early in the day (ensure all lab / blood bank / consultant resources available)
- Preoperatively restore factor activity level as dictated by the surgical procedure, repeat factor assay after initial administration to confirm factor activity (within 2 h of expected OR start)
- Continue to monitor factor activity level intra-operatively as dictated by clinical situation
- Avoid all anti-platelet medications
- Consider antifibrinolytics during perioperative period (up to 3-5 days!) – EACA, TXA
- ***Von Willebrand Disease***
  - DDAVP (dose = 0.3 mcg/kg IV provides 3-5-fold increase in activity)
    - Avoid in Types 2B (will cause thrombocytopenia) and 3 (just ineffective)
  - F VIII-vWF concentrates (Humate P)
  - Platelet concentrates (contains vWF)
  - Cryoprecipitate (contains vWF and F VIII)
  - Recombinant F VIII
  - Recombinant F VIIa

Table 3. Summary of Recommended Treatment According to the Phenotypes of von Willebrand's Disease.

Type	Treatment of Choice*	Alternative Therapy
1	Desmopressin†	Factor VIII–von Willebrand factor concentrates
2A	Factor VIII–von Willebrand factor concentrates	Desmopressin
2B	Factor VIII–von Willebrand factor concentrates	None
2M	Factor VIII–von Willebrand factor concentrates	Desmopressin
2N	Factor VIII–von Willebrand factor concentrates	Desmopressin
3		
In patients without alloantibodies	Factor VIII–von Willebrand factor concentrates	Platelet concentrates
In patients with alloantibodies	Recombinant factor VIII	Recombinant activated factor VII

* Adjuvant therapy with antifibrinolytic amino acids is recommended together with first-choice or alternative therapies in all types of von Willebrand's disease. The recommended oral or intravenous dosage of aminocaproic acid is 50 to 60 mg per kilogram of body weight every 4 to 6 hours; the recommended dose of tranexamic acid is 10 to 15 mg per kilogram every 8 to 12 hours.

† Indications for desmopressin cannot be assumed unless a test infusion has shown that factor VIII and von Willebrand factor levels rise adequately for that given bleeding episode or hemostatic challenge.

Table 2. Average Recommended Dosages of Factor VIII (Coagulant Activity) and von Willebrand Factor (Ristocetin Cofactor Activity) for Patients with Phenotypes of von Willebrand's Disease Associated with Severely Reduced Factor Levels (10 Percent or Less of Normal Levels).

Type of Hemorrhage	Dose (IU/kg)*	Frequency of Infusions	Target
Major surgery	50	Daily	Trough factor VIII level >50% of normal level until healing is complete (usually, 5–10 days)
Minor surgery	40	Daily or every other day	Trough factor VIII level >30% of normal level until healing is complete (usually, 2–4 days)
Dental extraction	30	Single dose	Factor VIII level >50% of normal level for 12 hr
Spontaneous bleeding episode	25	Daily	Factor VIII level >30% of normal level until bleeding stops (usually, 2–4 days)
Delivery and puerperium	40	Daily before delivery and in the postpartum period	Factor VIII level >50% of normal level for 3–4 days

* In children, all doses should be increased by 20 percent to account for the greater plasma volume. (For instance, instead of receiving a dose of 40 to 50 IU per kilogram, a child would receive 48 to 60 IU per kilogram.)

ANESTHETIC OPTIONS

- Surgery must be done in a centre capable of doing rapid assays for factor activity level, readily available supply of the factors necessary for treatment [DDAVP, Humate P (F VIII-vWF), F VIII, F IX, rF VIIa]
- Criteria for factor replacement for safe neuraxial technique
    - Hemophilia A and B: 70 - 100% activity
    - vWD: >50 % activity of F VIII and vWF
    - Platelets – usual cut-offs, stable count, providing factor level criteria met

ANESTHETIC SETUP

- **Drugs**
    - Antifibrinolytics (as infusion to continue postoperatively)
    - DDAVP available

- Emergency drugs
- **Equipment**
  - CAS + monitors as dictated by procedure and patient co-morbidities
  - Large bore IV
  - Temperature probe, blood warmer, rapid infuser, cell salvage
  - Consider arterial line for sampling if frequent factor activity assays to be measured
  - Deficient factor (recombinant, human derived) available
  - Cross-match completed prior to OR – may be delays for antibody investigation

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Dictated by co-morbid disease and procedure
- **Maintenance**
  - Avoid conditions that will promote bleeding or inhibit clotting – hypertension, hypothermia, anticoagulants
- **Emergence**
  - Ensure no ongoing bleeding

DISPOSITION & MONITORING

- Factor activity assay (more for hemophilias) on arrival in PACU
- Continued supplementation of factor in perioperative period based on procedure and severity of deficiency
- Goals for factor activity generally:
  - 100% Day 1-3
  - 50% - 100% Day 4-7
  - 30 % Day 7-14

COMPLICATIONS

- Hemorrhage

PREGNANCY

- Prophylactic treatment is reserved for patients with a FVIII level <25%
- vWD types 1 and 2A, DDAVP 0.3mcg/kg IV should be given as labour begins and given every 12 hours
- For patients with no response to DDAVP or its use is contraindicated, FFP, cryo or Humate-P should be given
- During labour, FVIII levels should be maintained at 50% normal
  - If C-section necessary, then FVIII levels should be maintained at 80% normal
- FVIII levels should be checked dailt during the postpartum period

PATHOPHYSIOLOGY

- **vWD**
  - Most common hereditary bleeding disorder (autosomal dominant or recessive inheritance)
    - Prevalence 1 in 100 to 3 in 100,000
  - vWF is a carrier protein for FVIII increasing its plasma half-life
  - vWF is synthesized by endothelieal cells, megakaryocytes and platelets
  - vWF acts at multiple sites to aid in coagulation
    - Links circulating collagen to damaged sub-endothelium
    - Binds platelets to collagen via GPIb receptor
    - Binds platelets to platelets for platelet aggregation via GP IIb/IIIa receptor
  - Abnormal levels or abnormal structure of vWF results in decreased ability to form a platelet plug at the site of injury as well as a decrease in circulating levels of F VIII, thus impairing the coagulation cascade
  - DDAVP stimulates the release of vWF from the endothelial cells to produce an immediate rise in plasma vWF and FVIII activity
    - Enhances platelet function and shortens bleeding time
    - May also be used for mild Hemophilia A undergoing minor surgery
    - Platelet functional abnormalities (ASA, GP IIb/IIIa inhibitors, uremia, liver disease) may be partially corrected by DDAVP's release of very large vWF multimers
    - Type 1 shows the best response, Type 2 patients show poor, if any response, and Type 3 do not response
      - DDAVP contraindicated in 2B as may worsen thrombocytopenia
    - DDAVP 0.3mcg/kg IV should be diluted in 30-50ml of saline and infused over 10-20 minutes to minimize side effects (tachycardia, hypoTN, headache, nausea, water intoxication)
    - Nasal spray 300mcg can be given to women with menorrhagia and Type 1 disease
    - Tachyphylaxis can occur
  - vWF replacement is considered more reliable for severe bleeding and surgical prophylaxis
    - Transfusion of cryoprecipitate or purified concentrates containing the vWF-FVIII complex
    - Cryo has fibrinogen, vWF, and factors VIII and XIII
    - Purified commercial preparation of FVIII-vWF concentrate are now recommended because of small infection risk with cryo
  - Type 1 (70-80%) = quantitative defect
    - Normal structure, decreased circulating vWF and FVIII
    - If history of repeated and severe bleeding episodes, vWF activity likely <15-25%
      - These pts should be treated aggressively for any bleeding episode and should be given prophylaxis treatment even for minor procedures
    - Type 1 appears to result from a defect in vWF release from the Weibel-Palade bodies of endothelial cells
    - Generally responds to DDAVP alone (3-5 fold increase in circulating vWF)
  - Type 2 (20-30%) = qualitative defect

        - Abnormal structure, normal or decreased circulating amounts
        - Generally requires FVIII-vWF concentrates (Humate P) in addition to DDAVP
        - DDAVP contraindicated in Type 2B, as this promotes thrombocytopenia
        - Type 2A
            - Defect in hemostatically active high and intermediate-weight vWF multimers
            - Moderate to moderately severe bleeding
        - Type 2B and 2M
            - Missense mutations causing either and increase (2B) or decrease (2M) in the binding of vWF to platelet GPIb
            - Type 2B
                - Moderate to moderately severe bleeding
                - The increased binding of vWF to platelet GPIb results in its sequestration or loss from circulation
            - Type 2M
                - Results in decreased platelet adhesion
                - Often have significant bleeding episodes
        - Type 2N (N=Normandy)
            - Caused by a defect in binding of vWF to FVIII
            - Present with low levels of FVIII (5-15%) and appear **similar to hemophilia A** because if this
    - Type 3 (rare)
        - Little or no circulating vWF
        - Very low levels of vWF activity and FVIII (3-10% normal)
        - Bleeding pattern the same as Hemophilia A (i.e. severe)
            - However, **unlike classic Hemophilia A, their bleeding times are very prolonged**
        - Require treatment with FVIII-vWF concentrates, platelets if thrombocytopenic
        - DDAVP of no benefit

REFERENCES

- Miller 7th, Barash 6th, Coexisiting 5th
- Blood Transfusion Therapy 7th Ed. American Association of Blood Banks
- World Federation of Hemophilia www.wfh.org
- hemophiliaemergencycare.com