6-19-2016

Anesthetic Implications for Patients with von Willebrand Disease

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ANESTHETIC IMPLICATIONS FOR PATIENTS WITH VON WILLEBRAND DISEASE

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Bachelor of Science in Nursing, North Dakota State University, 2011

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

December

2016

PERMISSION

Title Anesthetic Implications for Patients with von Willebrand Disease

Department Nursing

Degree Master of Science

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Abstract

As anesthesia professionals practicing primarily in the intraoperative setting, understanding genetic conditions contributing to surgical blood loss along with available treatment regimens is paramount. As von Willebrand disease continues to be the most recognized and common inherited coagulopathy, an advanced level of understanding of the disease along with prophylactic measures and acute means to control intraoperative hemorrhage is warranted. The purpose of this Independent Project is to provide a thorough and detailed examination of von Willebrand disease along with treatment options both widely accepted in the medical community and new, innovative advances. An expansive literature review was performed through the University of North Dakota's Harley E. French Library of Health Sciences. The literature review provided information on all genetic variants and subtypes of von Willebrand disease along with specific and detailed treatment plans for those undergoing surgical procedures. Treatment modalities include the use of desmopressin, von Willebrand factor concentrates, blood products such as cryoprecipitate, tranexamic acid, and estrogen derivatives. Unfortunately, a curative medication is not available to von Willebrand disease patients. In order to prevent catastrophic hemorrhagic complications, a familiarity of all treatment options available to anesthesia professionals can provide the difference between an uneventful intraoperative course and one with potentially disastrous implications.

Keywords: von Willebrand disease, anesthetic management, desmopressin, vWF concentrate, cryoprecipitate

Anesthetic Implications for Patients with von Willebrand Disease

First described in 1962 by a physician from Finland named Dr. Erik von Willebrand, von Willebrand disease (vWD) continues to be the most common inherited bleeding disorder prevalent in roughly 1 – 2% of the world's population (Nagelhout & Plaus, 2014). The genetic disease originated in the Baltic Sea specifically on a small island where multiple generations of family members died from acute, spontaneous bleeding episodes with no signs of trauma or gross injury. Initially termed pseudohemophilia due to the similarity in the clinical presentation, aside from the obvious fact that this condition affected both males and females, vWD patients were found to have extended or prolonged bleeding times in the absence of thrombocytopenia (Pagon, Adam & Ardinger, 2014). Further advances in clinical identification and laboratory testing continue to be investigated allowing for early diagnosis and treatment of potential catastrophic bleeding complications secondary to vWD.

The perioperative period poses risks to patients with no medical history let alone those with an advanced, inherited coagulation disorder such as vWD. As anesthesia providers, surgical blood loss remains at the forefront of monitoring importance and therefore a knowledge and understanding of inherited coagulation disorders is vital. A thorough appreciation of the coagulation pathway is necessary to adequately understand treatment options for those with bleeding diatheses, specifically those treatment options available to patients with vWD. Furthermore, typical postoperative or intraoperative pain management techniques, such as spinal or epidural anesthesia, are poorly understood by anesthesia practitioners when providing care to vWD patients. Continuing education is necessary to provide proper care for those who provide anesthesia to this patient population (Hara, Kishi & Sata, 2009).

Multiple treatment options are available based on clinical subtype or variant of vWD and anesthesia providers should at the very least be familiar with these medications and therapies. Those medications are desmopressin or DDAVP, blood products such as cryoprecipitate, vWF concentrates such as Haemate-P or Humate-P, tranexamic acid and aminocaproic acid (Neff & Sidonio, 2014). Advances will continue to be made for this patient population and anesthesia providers will need continuing education to adapt to an ever changing hematological landscape.

Case Report

The case being explored involves a 31 year old, 138 kg patient presenting for a robotic hysterectomy for the removal of a malignant ovarian mass secondary to Cowden's syndrome. The patient was categorized as an ASA 3 with no known allergies. Past medical history included hypertension, hyperlipidemia, anemia, colon and liver cancer, Cowden's syndrome, von Willebrand disease type 2A, depression, anxiety, gastroesophageal reflux disease and a non-corrected hiatal hernia. The patient reports no history of anesthetic complications. Surgical history included a tonsillectomy and adenoidectomy, laparoscopic appendectomy, laparoscopic cholecystectomy and a laparoscopic hemicolectomy. Current medication regimen included lisinopril, citalopram and tramadol with patient admitting to non-compliance with her medications. A thorough preoperative examination included vital signs which were as follows: blood pressure 158/105, heart rate 88, respiratory rate 16, oxygen saturation 98%, and a temperature of 98.1. Laboratory data included a complete blood cell count noting a hemoglobin of 10.2 g/dl, hematocrit of 29 g/dl, platelet count of 180 per mm^3 and a complete metabolic panel that was within normal limits except for a potassium of 3.3 mEq/l and a creatinine of 1.3 mg/dL. The patient's coagulation studies demonstrated a PT/INR of 11.1 sec and 1.3 sec respectively with no vWF levels or factor VIII levels documented. The patient was given 6900 IU of vWF

concentrate 30 minutes prior to surgical incision because the patient had developed tachyphylaxis secondary to multiple administrations of desmopressin.

A rapid sequence was chosen based on the patient's history of reflux disease and hiatal hernia. The patient presented with a Mallampati IV, short thryomental distance, limited neck range of motion and previous documentation of difficult intubation with a grade 2/3 with a video laryngoscope. Pre-oxygenation was performed for 10 minutes with adequate ramping and the medications given were as follows: versed 2mg, fentanyl 150mcg, rocuronium 5mg, propofol 200mg, and succinylcholine 200mg. The patient's airway was secured using a video laryngoscope confirmed with the presence of an end tidal carbon dioxide wave form and auscultated bilateral breath sounds. The 7.0 endotracheal tube was taped and secured while the patient was placed on pressure control ventilation (PCV) with an inspiratory pressure of 22, rate of 14, peak end expiratory pressure (PEEP) of 5 and tidal volume achieved was 520 – 560 mLs. An orogastric tube was then placed to decompress the stomach to allow satisfactory visualization of the surgical field.

Depth of anesthesia was maintained using Desflurane 7 – 8% with doses of fentanyl 25-50 mcg, rocuronium 10 – 20 mg and 1 gram of Ofirmev given prior to surgical incision. The patient was then placed in steep Trendelenburg position and the intraoperative course proceeded uneventfully. Muscle relaxants were reversed with neostigmine 5mg and glycopyrrolate 0.8mg. Anti-emetics were given which included Zofran 4mg and Decadron 5mg. A total of 2300 mLs of intravenous fluid was infused, urine output was 200 mLs and total estimated blood loss was 150 mLs. An awake extubation was performed uneventfully in the operating room, patient was placed on a non-rebreather at 10 liters per minute and once in the post anesthesia care unit (PACU) the patient was placed on Bipap mask which was planned and not due to respiratory

distress or hypercapnia. The patient reported being comfortable with a pain level of 2/10 and did not report any post-operative nausea, vomiting or intraoperative awareness. Subsequently, the patient was discharged from PACU and was discharged home 3 days later after a successful hospital stay which include no adverse hemorrhagic events.

Discussion

von Willebrand Disease

The inherited coagulation disorder, vWD, is characterized by a malfunctioning clotting factor called von Willebrand factor (vWF). The level to which factor is defective depends on the variant or subtype of vWD either type 1, type 2A, type 2B, type 2M, type 2N or type 3 (Pagon, Adam, & Ardinger, 2014). The role of vWF in the clotting cascade involves assisting in platelet adhesion while working synergistically with plasma factor VIII (Nagelhout & Plaus 2014). The vWF is a large glycoprotein located within and produced in plasma, platelets, endothelial cells and megakaryocytes. When a tissue injury occurs, vWF attracts platelets to the site of the injury to assist in the formation of a platelet plug, initiates the transport of factor VIII to form fibrin clots and finally protects factor VIII from an internal degradation process known as in vivo proteolysis (Mannucci et al., 2002). The mucocutaneous bleeding events in the vWD patients are not only the result of defective vWF but also due to an abnormal communication between vWF and glycoprotein Ib receptors (Federici, 2014). The inherited bleeding disorder may only be discovered post-traumatic injury and has been known to increase in severity as a patient ages (Pagon, Adam, & Ardinger, 2014).

vWD Subtypes/Variants

Classification of the specific variant of vWD allows advanced medical providers to adequately treat, both prophylactically and acutely, in those patients with vWD of all subtypes. The International Society on Thrombosis and Haemostasis (ISTH) proposed the classification of vWD patients in 2010 and this continues to be the preferred classification method (Laffen et al., 2014).

Type 1

The most commonly occurring form of vWD is the type 1 variant which occurs in 65% of patients with vWD and tends to be heterogeneous in nature. A wide range of intrinsic vWF levels are found to occur in this population with levels ranging from 5% to 40% depending on specific patient pathology. Mutations of vWF are present in 65% to 70% of vWD type 1 patients with the mutations being represented by missense substitutions, leaving 35% of vWD patients with no mutations within intrinsic vWF. Studies in type 1 vWD patients focus on endothelial cells, which produce vWF, to determine specific disease severity (James & Lillicrap, 2013). Mucocutaneous bleeding is the primary manifestation in this variant of vWD (Pagon, Adam, & Ardinger, 2014).

Type 2

The type 2 variant of vWD presents with four separate subtypes used to further classify disease pathology. Type 2A patients represent 20% to 25% of those with vWD and appear to have clinically lost platelet dependent functions. Laboratory values which indicate the type 2A subtype include low vWF antigen and low vWF ristocetin cofactor activity. Comparatively, missense and substitution mutations account for this subtype as well as the type 1 variant of

vWD (James & Lillicrap, 2012). This patient population presents with either mild or moderate bleeding in the mucocutaneous centers of the body (Pagon, Adam, & Ardinger, 2014).

The clinically significant difference between type 2B and the other type 2 variants is the presence of accompanying thrombocytopenia. This unique clinical feature is the result of a specific missense mutation present in only this subtype. Exclusively, this subtype seems to drastically worsen during both pregnancy and stress which increases the mutant protein in the circulating plasma. This results in platelet clumping further exacerbating bleeding risk (James & Lillicrap, 2013). The clinical presentation in this subtype manifests as mild to moderate mucocutaneous bleeding with the unique feature of thrombocytopenia (Pagon, Adam, & Ardinger, 2014).

The type 2M variant of vWD is characterized by vWF mutations resulting in the loss of function of glycoprotein Ib receptors as well as decreased collagen binding. Again, missense mutations are the culprit for this specific vWD variant leading to its unique clinical presentation. The classic laboratory test for type 2M vWD is the poor response to the administration of desmopressin (James & Lillicrap, 2013). The clinical presentation is generally mild to moderate mucocutaneous bleeding (Pagon, Adam, & Ardinger, 2014).

The type 2N variant results in a severe deficiency in intrinsic factor VIII levels and generally presents in a genetically recessive fashion which is contrary to the genetically dominant fashion of the other variants. Intrinsic factor VIII levels in this population are 5% to 40% of normal (Lillicrap, 2013). Clinical presentation includes the potential for catastrophic and fatal bleeding episodes which tend to follow patterns seen with hemophilia A (Pagon, Adam, & Ardinger, 2014).

Type 3

The most severe subtype of vWD has been identified as type 3. Intrinsic levels of vWF are often less than 5% or even undetectable in specific patients. Mutations of vWF for this subtype involve both missense and deletion pathology which prevents the production of intrinsic factor VIII (Lillicrap, 2013). Clinical manifestations in this subtype include excessive bleeding such as musculoskeletal bleeding episodes leading to potential permanent immobility (Pagon, Adam, & Ardinger, 2014).

Clinical Presentation

Clinical manifestations in vWD patients vary greatly and depend highly on the specific variant or subtyped identified via extensive laboratory testing. As previously stated, this data can assist practitioners with both diagnosis and treatment. Specific coagulopathy can manifest with bleeding in the mucocutaneous areas of the body or delayed hemostasis post injury or surgical incision (Federici, 2014). One of the most commonly reported symptoms in the female patient is menorrhagia since menarche with males also likely to present with genitourinary bleeding. Other clinical manifestations include bruising of an unknown origin, prolonged or recurrent epistaxis, bleeding following routine or daily dental maintenance or examinations, gastrointestinal bleeding and hypovolemia related hypotension from blood loss due to childbirth (Pagon, Adam, & Ardinger, 2014). Unfortunately, this coagulation disorder may not be recognized until a traumatic event because the disease can be silent with little warning of its existence (Auerswald & Kreuz, 2008).

Demographics

The inherited genetic coagulation disorder vWD tends to affect females at a greater frequency than males, roughly 2:1 in recent demographic studies. However, this data has been questioned by multiple researchers due to the diseases appearance during the onset of female menses. No geographic or ethnic population has been identified to be at greater risk for inheriting vWD (Lillicrap, 2013). The majority of patients afflicted with vWD in the United States are Caucasian, roughly 75% according to the Centers for Disease Control. On a global scale, racial distribution appears to be 65% Caucasian, 28% African American and the rest represented by people of Middle East, Far East and Native American decent (Flood et al., 2011).

Laboratory Analysis

In general, an overreaching and expansive approach is used when trying to determine the nature and severity of an individual's coagulopathy and vWD is not exempt from this detection strategy. Detailed laboratory analysis is part of the three main criteria used to diagnose vWD which includes the following: a bleeding history since childhood, reduced vWF activity in the plasma and lastly a genetically identified bleeding history encompassing more than two generations in a lineage (Federici, 2014).

Complete blood cell (CBC) analysis is typically normal with some vWD patients presenting with microcytic anemia or in the case of vWD type 2B, thrombocytopenia can occur concurrently with other analyses suggesting vWD. Activated partial thromboplastin time (aPTT) is also generally within normal limits, however when severe deficiency in factor VIII is observed, as is the case with type 3 vWD, aPTT can be prolonged. Other general laboratory tests

used include skin bleeding times and platelet function assays but these tests will not be able to identify vWD from other disorders of coagulation (Pagon, Adam, & Ardinger, 2014).

Fortunately, a more specific hematological analysis is available when vWD is suspected from general analysis or clinical presentation and includes specific hematology assays. A ristocetin cofactor assay (vWF:RCo.) specifically measures the functional ability of vWF and its ability to cohere to platelets with a normal range being 50 – 200 IU/dL. The quantity of vWF protein or antigen (vWF:Ag.) directly measures plasma levels of the antigen with a normal range of 50 – 200 IU/dL. Finally, the activity of factor VIII in the clotting cascade can directly be measured by factor VIII:C levels with a normal range identified to be between 50 – 150 IU/dL (Pagon, Adam, & Ardinger, 2014).

The previously mentioned laboratory analysis is specific for the diagnosis of vWD but does not provide specific information on the variant or subtype. If any of the hemostasis factor assays result in abnormal values, specific subtypes and vWD variants can be identified with the following tests: vWF multimer analysis, ristocetin-induced platelet agglutination, binding of factor VIII by vWF, and collagen binding assay. The vWF multimer analysis identifies vWF oligomers in blood plasma which is useful in identifying specifically vWD type 2A or 2B but can be helpful identifying all type 2 vWD variants. The ristocetin-induced platelet agglutination identifies the ability of vWF to attract platelets in the presence of the antibiotic ristocetin and an abnormal result is typically indicative of vWD type 2B. The only test available to identify vWD type 2N is to individually test the binding capacity factor VIII has in the presence of vWF. Type 3 vWD is diagnosed by exclusion criteria along with vWF levels less than 5% of normal. Finally, the collagen binding assay is a test which measures the ability of vWF to connect to

collagen particles and is beneficial when determining patients with either type 1 or type 2 vWD variants of all subtypes (Pagon, Adam, & Ardinger, 2014).

Genetic Testing

When detailed laboratory analysis combined with physical examination and history yields a diagnosis of vWD, genetic testing is recommended in first degree relatives either with or without a history of spontaneous or uncontrollable bleeding. Ideally, the International Society on Thrombosis and Haemostasis (ISTH) recommends genetic testing on predisposed individuals prior to onset of uncontrollable bleeding to identify either type or variant of vWD. Also, the ISTH does not recommend laboratory testing until the patient is a minimum of 6 months of age. Patients with type 3 vWD are recommended to undergo phenotypic analysis prior to attempts to conceive children as the pregnancy and risk for hemorrhage pose a serious risk to both mother and child (Laffen et al., 2014). According to Dr. David Lillicrap (2014), "given the severe phenotype of type 3 vWD, genetic prenatal diagnosis of this variant provides results for families and their physicians to make informed decisions about family planning and obstetric management issues." Seemingly as the severity, either identified by subtype or clinical presentation, increases so too does the necessity for genetic testing and subsequent family planning.

Treatment

For those affected by an acute bleeding episode secondary to an underlying pathology of vWD or those looking for prophylaxis prior to surgery, many options are available of varying efficacies. Identifying the individuals subtype and variant of vWD is of the utmost importance in

determining the proper treatment method designed to achieve hemostasis. Typically, treatment options are considered either non-concentrate or concentrate containing therapies.

Desmopressin

First opined to be a treatment option for vWD in 1977, desmopressin or DDAVP is a derivative of the human body's anti-diuretic hormone or ADH. Desmopressin has the ability to raise intrinsic levels of vWF through agonistic activity on V2 vasopressin receptors. This agonistic activity signals endothelial cells to increase production and release of both vWF and factor VIII thereby raising intrinsic levels by as much as 2 to 3 times normal. However, clinical results vary which is thought to be the result of short acting multimers. Initially, these multimers achieve hemostasis but severe bleeding may re-occur following administration (Neff & Sidonio, 2014).

Clinicians generally recommend a test dose to determine an individual's response to desmopressin with subsequent doses to follow if hemostasis is achieved. In order to assess patient responsiveness to desmopressin, intrinsic levels of vWF can be measured at 60 minutes and 4 hours post administration. Desmopressin can be useful in treating vWD subtypes 1, 2A, 2M and 2N but is not recommended in type 2B related to the potential for worsening thrombocytopenia post-administration. Also, desmopressin is not effective in type 3 vWD as these patients produce less than 5% of normal vWF from endothelial cells. Desmopressin is approved for the following routes of administration: intravenous, subcutaneous and intranasal (Laffen et al., 2014).

Even though the response of desmopressin can be unreliable, DDAVP continues to be used both prophylactically and acutely for dental procedures, minor surgeries and child birth.

Standard dosing regimens include an intravenous dose or subcutaneous dose of 0.3mcg/kg given over 30 minutes with an intranasal dosage recommendation of 150 mcg to 300 mcg. Side effects reported include flushing, hypotension, hypertension, nausea, headache, hyponatremia, volume overload, seizures and tachyphylaxis (Neff & Sidonio, 2014). Since desmopressin is a derivative of the anti-diuretic hormone, the potential fluid volume overload and accompanying hypertension can be mitigated by limiting fluid intake in the 24 hours post administration period to an amount of 1 liter or less. Serial sodium levels should also be noted, particularly in children under the age of 2 or if multiple doses of desmopressin are administered to persons of any age (James & Goodeve, 2011).

Estrogen Derivatives

Typically reserved for women of childbearing age, oral contraceptives increase intrinsic production of vWF from endothelial cells. Along with increasing vWF production and release, the control of menstrual bleeding is also of benefit to the patient with vWD. However, as is the case with most therapies, estrogen derivatives are not useful in the treatment of type 3 vWD or the acute management of bleeding episode (Neff & Sidonio, 2014).

vWF concentrations

Fortunately, for patients with severe forms of vWD such as type 2N and type 3, there are treatments available to raise intrinsic vWF levels. These medications are specifically advantageous if major hemorrhage occurs or to be used on a prophylactic basis prior to surgery. Currently there are multiple vWF concentrates being manufactured and operate under the trade names Alphanate, Humate-P, Haemate-P and Wilate. These medications contain both vWF and factor VIII which, as previously stated, work synergistically to form a platelet plug in the clotting

cascade. However, each therapy contains a different ratio of vWF to factor VIII and are designed to be used in specific situations either prophylactically or to achieve hemostasis during acute bleeding episodes (Neff & Sidonio, 2014).

Treatment with vWF concentrate is the gold standard of care for the 20% – 30% of patients who do not respond to desmopressin or do not produce intrinsic factor VIII. A prospective study was performed by Mannucci and associates (2002) over 5 years involving 87 patients with vWD undergoing treatment either prophylactically or for the treatment of an acute hemorrhage. This was the first study involving vWD patients and their response to vWF concentrate. Skin bleeding times were the laboratory test of choice for the researchers along with factor VIII assays. Patients of all subtypes and variants were tested in this study including 15 type 1 patients, 29 type 2A patients, 5 type 2B patients, and 32 type 3 patients along with both genders being represented. The researchers observed and treated 87 acute bleeding episodes with vWF concentrate, generally needing only a single bolus dose to achieve hemostasis, the exception being type 3 vWD patients who have little to no intrinsic factor VIII. The dose given for acute hemorrhagic episodes was 40 IU/kg with common bleeding sites being within the gastrointestinal/genitourinary systems or within the nasal cavity. Ultimately, all acute bleeds achieved hemostasis with the use of vWF concentrates. The research team also used vWF concentrate for surgical prophylaxis in 71 patients over the 5 year study. Initial surgical prophylaxis dose was 60 IU/kg followed by subsequent 40 IU/kg doses if bleeding persisted. Success of vWF was measured via actual blood loss versus expected blood loss based on procedure and in all cases the actual blood loss was less than the documented expected value. The vWF concentrate demonstrated both safety and efficacy as only mild side effects were

reported with no major complications secondary to the infusions. Blood loss was adequately controlled in all subjects (Mannucci et al., 2002).

A systematic review was performed by Dr. Erik Berntorp at Malmo University Hospital in Sweden and found to produce similar results. Looking at data from patients non-responsive to desmopressin, Dr. Berntorp found 90% of patients had corrected bleeding times with doses of vWF concentrate. Further research allowed Dr. Berntorp (2009) and his research team to conclude, vWF "effectively reduced the risk of bleeding complications in vWD patients undergoing elective surgery" (p. S14). This systematic analysis further reinforces the efficacy of vWF concentrate (Berntorp, 2009).

To reinforce the data further, exploration involving vWF concentrate dosing was studied by Auerswald and Kreuz (2009). Based on the findings, the researchers recommended dosages based on bleeding severity and concluded: for major bleeding and trauma a loading dose of 40 – 60 IU/kg be given intravenously followed by a maintenance dose of 40 – 50 IU/kg for 3 days keeping vWF levels greater than 50% and for minor bleeding events a dose of 40 – 50 IU/kg be given intravenously for either 1 or 2 doses depending on individual response (Auerswald & Kreuz, 2009).

As previously stated, the medication appears to be extremely safe with minimal side effects reported. Initially, viral complications were considered, but no viral infection pathology has been noted in the literature. Other complications include: anaphylactic type reactions, transient hyperthermia, vWF inhibitory antibodies, hemolysis, thromboembolic complications and hypervolemia. Thromboembolic events represent less than 1% of reported side effects (Berntorp, 2009).

Tranexamic acid

Tranexamic acid is an anti-fibrinolytic agent which opposes the disintegration of thrombus formation. A lysine derivative, tranexamic acid prevents plasmin from binding with fibrin thus inhibiting the breakdown of a previously made platelet plug or blood clot. This therapy is typically adjunctive with desmopressin and has been approved for dental procedures and minor surgery. Available routes of administration include local infiltrations, mouthwash, oral and intravenous (Neff & Sidonio, 2014). Tranexamic acid is specifically useful in oral surgery and dental procedures to combat the natural proteolytic enzymes present in the oral cavity (Federici et al., 2000). General dosing guidelines recommend 650mg orally prior to surgery for prophylaxis or 1300 mg every 8 hours for 5 days for females using it with the occurrence of menstruation. Intravenous dosing for tranexamic acid generally involves 10mg/kg over 15 minutes (Neff & Sidonio, 2014).

Cryoprecipitate

Cryoprecipitate is a plasma derived blood product containing vWF, factor I, VIII, XIII, and fibrinogen (Nagelhout & Plaus, 2014). Generalized use is falling out of favor related to the presence of acute viral pathology post-infusion. The use of cryoprecipitate is reserved for when vWF concentrates are unavailable. Each unit of cryoprecipitate contains toughly 80 – 100 units of factor VIII (Neff & Sidonio, 2014).

Anesthetic Considerations

One of the primary duties of the anesthesia professional is optimizing the patient's status intraoperatively by understanding basic and advanced methods of controlling surgical blood loss. The anesthetist must adapt a plan of care for each individual with vWD and tailor that plan based

on the proposed surgical intervention both major and minor, elective or emergent. Anesthetic considerations will be presented for multiple patient populations including obstetrics, pediatrics, dental prophylaxis, regional anesthesia and the trauma patient.

Obstetric Considerations

The benefits of neuraxial anesthesia in the obstetric population include a decreased or eliminated need for opioids and related side effects for mother and baby, faster recovery time, decreased mortality, decreased surgical blood loss and improved patient satisfaction (Choi & Brull, 2009). However, deciding to perform spinal or epidural anesthesia in the vWD patient poses inherent risks and theoretically can lead to dangerous and even fatal complications. Fortunately, pregnant vWD patients tend to exhibit a remission of symptoms and inherent vWF levels increase with the peak occurring during the third trimester (Butwick & Carvalho, 2007). Choi and Brull (2009) performed a case review involving 10 research studies with 74 vWD undergoing spinal/epidural anesthesia for labor analgesia and found no complications reported. All subtypes were represented including 71 type 1, 2 type 2, and 1 type 3 vWD patient. The patients' vWF levels were drawn prior to initiating spinal or epidural anesthesia and all levels were within normal limits with the exception of 10 patients. Patients with abnormal vWF were treated with either desmopressin or synthetic vWF concentrates and regional anesthesia proceeded without complications (Choi & Brull, 2009).

Spinal hematoma secondary to spinal or epidural anesthesia is an extremely rare complication but must be considered in the patient with vWD or other inherent bleeding disorders. The risk of spinal hematoma is 1 in 200,000 or 0.0005% even in the presence of inherited coagulopathy. Spinal or epidural anesthesia is considered to be safe in the vWD patient if based on coagulation studies especially inherent vWF levels. Careful monitoring of vWF must

be performed to ensure patient safety and each patient should have a unique plan of care developed (Butwick & Carvalho, 2007). A desmopressin challenge test, which involves a loading dose of desmopressin and subsequent aPTT and factor VIII levels being drawn, can be performed to further assist the provider in determining the safety and efficacy of the regional anesthetic technique (Cata et al., 2009). In the presence of vWD, postpartum hemorrhage risk is nullified if inherent vWF and factor VIII levels are 30 – 40 % of normal which is typical in the third trimester even in the most severe forms of vWD. Other techniques to minimize risk for spinal hematoma include removing the epidural catheter immediately in the postpartum period. After delivery of baby, the vWD patient's inherent factor VIII and vWF levels will begin to decrease, thus hastening the necessity to remove the epidural catheter (Butwick & Carvalho, 2007).

Spinal and epidural anesthesia in the vWD patient poses unique risks that must be understood by the anesthetist providing labor analgesia. However, in the presence of vWF levels within normal limits, the use of these regional anesthetic techniques appears safe and efficacious. If vWF levels are not normalized, the use of spinal or epidural anesthesia can proceed following the administration of either desmopressin or vWF concentrate if vWF levels are normalized post treatment. If levels have not normalized, neuraxial anesthesia should be deferred. Each labor and delivery plan for the vWD patient must take bleeding risk into account and the patient and provider can optimize the labor and delivery plan based on this information.

Pediatric Considerations

Specialized and individualized care must be provided for the pediatric vWD disease patient. Generally, advanced manifestations of vWD are not seen until teenage years related to

inherent vWF levels being increased in the neonate similar to the obstetric population (James & Goodeve, 2011).

Preoperative surgical recommendations for the pediatric patient undergoing various procedures include the consultation of a hematologist specializing in the pediatric population (Berlucchi et al., 2002). The most common symptoms observed in the pediatric population with von Willebrand disease are easy bruising and bleeding within the oral cavity (Witmer et al., 2009). Coagulation tests performed focus primarily on inherent vWF and factor VIII levels. If the patient is greater than 2 years of age, a loading dose of desmopressin 0.3mcg/kg is recommended 30 – 45 minutes prior to surgical incision to control bleeding and maintain hemostasis in types 1 and specific variants of type 2 as previously discussed (Berlucchi et al., 2002). Determinants observed to predict post-operative bleeding in the pediatric vWD patients include inherent vWF levels, desmopressin trial response, age, and estimated blood loss of the initial surgery. Synthetic factor VIII can also be administered and as extensively covered previously, there are minimal safety concerns with this medication. Typically, hesitation of administering factor VIII results from monetary concerns (Witmer et al., 2009). During the immediate postoperative period, serial serum sodium levels should be drawn to assess for hyponatremia resulting from fluid overload. Hyponatremia can manifest as intractable seizures which, if not identified and promptly treated, can be fatal. The pediatric patient should be admitted at a minimum of overnight and closely observed for hemorrhage both external and internal. Other recommendations to control postoperative hemorrhage include oral tranexamic acid for 7 to 10 days (Berlucchi et al., 2002). Aminocaproic acid can be a useful antifibrinolytic agent as it prevents the degradation and lysis of clot formation, but does not contribute to the initial maintenance of hemostasis (Witmer et al., 2009). The patient should be evaluated by the

surgeon weekly for 1 month and then routine follow up with the pediatric hematologist to monitor vWF and factor VIII levels (Berlucchi et al., 2002).

With roughly 400,000 adenotonsillar procedures performed annually in the United States, it is one of the most common cases performed in the pediatric population. The relative risk of post-operative hemorrhage in the healthy pediatric population is 1.5% to 5% and drastically increased in the patient with vWD. As extensive laboratory testing is generally not performed in the pediatric patient, vWD can potentially be discovered in the postoperative period if unexpected or continual hemorrhaging persists after surgical intervention. Further complicating matters for the pediatric vWD patient, proteolytic enzymes proliferate the saliva making achieving hemostasis challenging (Witmer et al., 2009).

In a comprehensive study involving pediatric patients with vWD, Witmer and associates (2009) studied 41 cases of adenotonsillar surgery. Preoperative surgical interventions included a 0.3mcg/kg dose of desmopressin 30 minutes prior to incision and aminocaproic acid was initiated the night prior to surgery and continued for 5 days. Of the 41 pediatrics studied, 38 required subsequent re-dosing of desmopressin to control tonsillar hemorrhage. Postoperative hemorrhage requiring further surgical intervention was reported in 7 out of the 41 patients with 5 of those patients requiring immediate surgical intervention. Transfusion of packed red blood cells was reported in 2 patients with an average hemoglobin decrease of 4.8 g/dl in these patients. Based on this expansive study, postoperative hemorrhage in the vWD pediatric patient undergoing adenotonsillar procedures is roughly 17% to 44% accounting for a high risk surgical procedure. Witmer and associates (2002) recommend adenotonsillar type procedures in the pediatric vWD patient only be performed as a last resort intervention for acute tonsillitis or obstructive sleep apnea with multiple, documented apneic periods. Furthermore,

recommendations were made to avoid aminocaproic acid in this patient population as nausea is a common side effect and acute vomiting appeared to be a contributing factor to postoperative hemorrhage. In the pediatric patient with known vWD, the use of vWF concentrates and laboratory analysis of inherent vWF levels and factor VIII levels is recommended to optimize surgical condition (Witmer et al., 2009).

Regional Anesthesia

As with the obstetric patient population, many similarities exist in the management of regional anesthesia techniques in the non-obstetric patient with vWD. The choice of whether to proceed with regional anesthesia in the vWD patient primarily focuses on laboratory results particularly inherent vWF and factor VIII levels. Other analysis can include vWF antigen levels, APTT, PT/INR, platelets, and the consultation of a hematologist or oncologist. An inherent vWF level greater than 50% is preferred but hemorrhagic complications from regional anesthesia techniques is considered to be minimal if inherent vWF levels are greater than 30%. The risk of acute hemorrhage, particularly spinal hematoma, drastically increases when inherent vWF levels are less than 10% (Stedford & Pittman, 2000).

The advantages of neuraxial anesthetic practices in the non-obstetric patient can be highly beneficial over general anesthesia and include increased postoperative pain control, decrease gastrointestinal complications, improved and hastened rehabilitation, and diminished surgical mortality. Pharmacological intervention prior to regional anesthesia must heavily focus on inherent vWF levels and treat according to subtype or variant of vWD. Either desmopressin or vWF concentrates are the preferred pre-treatment prior to regional anesthesia and associated interventions. If epidural catheters are placed, removal of the catheter is recommended as soon

as clinically possible to prevent bleeding diathesis from occurring or worsening if already present (Choi & Brull, 2009).

Generally, peripheral nerve blocks are safer and preferred in contrast with neuraxial anesthesia with indwelling catheter placement in the vWD patient. However, epidurals when used for postoperative pain management, allow the surgeon and multidisciplinary team to avoid anti-platelet drugs commonly used to treat pain such as non-steroidal anti-inflammatory drugs and aspirin. Researchers Hara, Kishi, and Sata (2009) recommend vWF levels be greater than 50% but prefer vWF levels to be 100% or greater with maintenance of previously stated levels for the length of time the catheter is in place. Furthermore, the aforementioned research team provided guidelines for the ability of the anesthesia professional to place epidural/spinal catheters which include: the patient has a documented positive response to desmopressin, a loading dose of desmopressin 0.3mcg/kg is given 30 – 45 minutes prior to catheter placement and a thorough and documented consent is obtained by the anesthesia professional. The prompt removal of the catheter is necessary with 24 hour observation post removal to assess the vWD patient for severe and potentially catastrophic complications especially epidural or spinal hematoma. Therefore, under specific circumstances with documented laboratory analysis, regional anesthesia can be an option for anesthetic management in the patient with vWD (Hara, Kishi, & Sata, 2009).

Dental Considerations

As one of the most common manifestations of vWD is bleeding in the oral cavity, dental procedures can provide challenges to healthcare professionals to maintain hemostasis. As previously stated, proteolytic enzymes proliferate in the saliva making the oral cavity a likely place for acute hemorrhage especially during dental procedures ranging from routine tooth

cleanings to comprehensive extractions related to dental caries. The most difficult location within the oral cavity to control bleeding is within the tongue, mandible and lip. The preferred clinical intervention used to treat bleeding in this location is oral tranexamic acid using a "swash and spit" method. Bleeding within the gingival tissue surrounding the individual tooth is generally controlled with direct pressure applied to the area. Other interventions, generally performed by the dental professional, include packing, splinting and the use of oxidized cellulose to assist in clot formation (Morimoto et al., 2005).

Interventions used prior to dental procedures are similar to those discussed for surgical procedures in previous sections. However, a few unique caveats exist when dealing with procedures involving the oral cavity. According to Morimoto and associates (2005), tranexamic acid is recommended prior to all dental procedures due to the antifibrinolytic activity and also the ability of tranexamic acid to oppose the lysis of clots within the oral cavity. These distinct mechanisms of action make tranexamic acid a vital and crucial medication for controlling intraoral bleeding in vWD patients (Morimoto et al., 2005). Another potential intervention to control oral bleeding is the use of fibrin glue to synergistically work with tranexamic acid to achieve hemostasis (Federici et al., 2000). Further recommendations proposed by Morimoto and associates (2005) include the following parameters based on subtype of vWD and include: 0.3 – 0.4 mcg/kg of desmopressin for patients with type 1 and 2A vWD undergoing surgical dental extractions with a total of three doses given intravenously, for vWD not responsive to desmopressin and all other types of vWD undergoing surgical dental extractions a minimum of two doses of vWF concentrate should be given intravenously and repeated four to six times as needed, and finally for routine extractions simple pressure applied to the gingival area should be adequate to achieve hemostasis.

Researchers at the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre and Department of Internal Medicine sought to determine the effects of local versus systemic methods to treat dental hemorrhage post intervention. A total of 64 participants were involved in the study spanning a 4 year period. The local interventions used were a combination of tranexamic acid and fibrin glue with the systemic interventions comprising either desmopressin or vWF concentrate. All surgical interventions were performed by the same surgeon and consisted of dental extractions and periodontal surgery. Of the 64 vWD patient participants, 32 received local therapy and 32 received systemic interventions. Systemic interventions of desmopressin and vWF concentrate were discussed at length in previous sections and doses were identical in this study. The researchers found no significant difference in outcomes based on the type of therapy received. Each group had one reported bleeding episode and both were treated with fibrin glue to achieve local hemostasis. The researchers concluded that a combination of tranexamic acid and fibrin glue was equally effective as desmopressin and vWF concentrate for controlling mucosal bleeding in vWD patients undergoing oral or periodontal surgery. The researchers also highlighted the significant cost reduction when using local therapy to achieve and maintain hemostasis (Federici et al, 2000).

Trauma

The trauma patient presents multiple challenges in hemostasis and this can be further complicated when a patient, unbeknownst to the healthcare professional, has a bleeding diathesis such as vWD. Severe complications are likely in the trauma patient and likelihood of fatality is drastically increased if the patient has vWD. Interventions the patient can perform to assist healthcare providers in treatment would be to wear an identification bracelet noting the presence of vWD and ideally detailing the specific subtype. This information can allow for a unique

treatment plan which can hasten hemostasis and prevent death. One of the most important interventions hematologists can execute is a thorough and detailed education on the potential severity of the disease. Seemingly innocent blunt trauma can prove fatal if not identified promptly which is why every patient with vWD must investigate any sign of internal bleeding (Slam et al., 2008).

Trauma patients with uncontrollable hemorrhage either internal or external are candidates for massive transfusions protocols. Patients with vWD require interventions, however, that are more specific to the disease and replacing inherent factors that are not present in the vWD patient. Slam and associates (2009) have developed a transfusion protocol for trauma patients with vWD that includes the following parameters placed in order of intervention: desmopressin 0.3mg/kg intravenously over 30 minutes, if head injury present or major trauma give 50 IU/kg of vWF concentrate intravenously, if either joint, soft tissue or muscle hemorrhage present give 25 IU/kg of vWF concentrate intravenously, if oral mucosa bleeding present give 50 IU/kg vWF concentrate intravenously with aminocaproic acid orally and finally cryoprecipitate can be added as a last resort (Slam et al., 2008). Treatment for victims of trauma with vWD present unique complications to healthcare and anesthesia providers alike and unfortunately carry a high risk of mortality. Treatment options are available, however knowledge or identification of the patient's condition must be recognized early to ensure highest chance for survival.

Case Study

In retrospect, the aforementioned case scenario was adequately managed and confirmed by the available literature presented in the Independent Project. The 6900 IU dose of vWF concentrate sufficiently controlled and maintained intraoperative hemostasis based on actual versus expected blood loss. As stated in the literature, the medication was both safe and

efficacious which is why it continues to by the gold standard treatment for vWD patients. Unfortunately, patients are not usually identified by the variant of vWD leaving providers in a potentially difficult position. Typically, patients are categorized by severity of symptoms and not subtype as advanced laboratory analysis can be cost prohibitive. Furthermore, patients are characterized as being either responsive to desmopressin or non-responsive to desmopressin. For patients who are not responsive to desmopressin, as was the scenario in the aforementioned case study, vWF concentrate therapy is the preferred treatment of choice. Further analysis of laboratory methods should be ascertained to streamline costs associated with identifying the subtype of vWD to assist medical and anesthesia providers in treatment modalities. Again, the case presented was adequately managed and the patient had a desirable outcome postoperatively.

Conclusion

Patients with vWD pose unique risks during the intraoperative period and treatment information specific to each individual must be understood by the anesthesia professional. The research and literature reviewed documented approved treatment options for each subtype of vWD along with the various safety and efficacy of each intervention. Within the realm of anesthesia, certain interventions, such as regional anesthetic techniques like spinal and epidural anesthesia, may pose an increased bleeding risk for patients with vWD leading to potential hemorrhagic complications. The management of various patient populations with vWD such as obstetrics and pediatrics each carry inherent risks which make the practice of anesthesia difficult. The treatment options focus on two mainstays and include desmopressin and vWF concentrates. Each of these medications have characteristics of benefit to the vWD patient. The overarching treatment continues to be vWF concentrates and is effective at treating all subtypes of vWD. Genetic testing continues to make phenomenal strides allowing for more accurate treatment plans

tailored to treat each individual vWD patient. The information provided within this Independent Project will allow anesthesia professionals to be familiar with the underlying pathology of vWD and, along with the current treatment recommendations, provide the vWD patient with the safest and most efficacious intraoperative experience possible.

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Appendix

The following PowerPoint presentation was presented at the spring North Dakota Association of Nurse Anesthetists meeting in Fargo, North Dakota on April 15th, 2016.

Von Willebrand Disease and Anesthesia

Jordan Idso, SRNA

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Von Willebrand Disease: A Historical Perspective

- First introduced in 1962 by Dr. Erik von Willebrand
- Originated in the Baltic Sea, discovered with the onset of menarche in females
- Initially termed pseudohemophilia as bleeding times were prolonged in the absence of thrombocytopenia
- vWD was identified to affect both males and females in contrast to hemophilia
- Continues to be the most common inherited coagulopathy occurring in 1% - 2% of the

(Pagon, Adam, & Ardinger, 2014).

Pathophysiology of vWF

- Characterized by a malfunctioning clotting factor specifically von Willebrand factor (vWF)
  - vWF is a large glycoprotein produced in the plasma, platelets, endothelial cells, and megakaryocytes
- vWF assists in platelet adhesion via 3 functions:
  - Attracting platelets to the site of injury
  - Initiating the transport of factor VIII to form fibrin clots
  - Protecting factor VIII from in vivo proteolysis (an internal degradation process)
- Patients with von Willebrand disease (vWD) also have abnormal communication with glycoprotein Ib receptors

(Mannucci et al., 2002)

Presentation & Classification

Clinical Presentation

- Depends on classification
- Typically mucocutaneous bleeding
- Delayed hemostasis post-injury
- Menorrhagia in females
- Prolonged epistaxis
- GI/GU bleeding
- Often asymptomatic

Classification

- vWD variants
  - Type1
  - Type 2A, 2B, 2M, 2N
  - Type 3
- Most severe forms
  - Type 2N and type 3
- As a general rule, severity of vWD increases with number (i.e. Type 3 is more severe than type 1)

(Pagon, Adam, & Ardinger, 2014).

Prevalence of vWD

- Demographics
  - Females more susceptible than males, prevalence is roughly 2:1
    - Data appears to be controversial
- Population
  - Affects roughly 1% - 2% of the world's population
  - Roughly 75% of patients are Caucasian
    - However, no one population is predisposed to vWD
  - The other 25% is represented by people of Middle East, Far East, and Native American descent

(Lillicrap, 2013)

Case Information

- Surgical Procedure
  - **Robotic hysterectomy**
    - Removal of malignant ovarian mass secondary to Cowden's syndrome
- Pertinent Patient Information
  - 31 year old, female
  - **138 kg**, 63 in
  - ASA 3
  - No known allergies

Pre-operative Evaluation

- Past Medical Hx
  - Hypertension, hyperlipidemia, anemia, Cowden's syndrome, colon/liver CA, GERD, **von Willebrand disease type 2**, and an uncorrected hiatal hernia
- Surgical hx
  - Tonsillectomy and adenoidectomy
  - Lap appendectomy/cholecystectomy
  - Hemicolectomy
- Pre-op VS
  - BP: 158/105, HR: 88, RR: 16, Oxy. sat. 98%, and temp. 98.1
- Pertinent labs
  - H:H 10.2/29, plt 180, K 3.3, creatinine 1.3, all other labs WNL
- Airway evaluation
  - Mallampati IV, short thryomental distance, limited neck ROM, and previous documentation of difficult airway

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Anesthetic Course

- Induction
  - Versed 2 mg
  - Fentanyl 150 mcg
  - Rocuronium 5 mg
  - Propofol 200 mg
  - Succinylcholine 200 mg
- Technique
  - Rapid sequence performed, airway secured with a video laryngoscope and 7.0 endotracheal tube
  - +BBS, +EtCo2 noted
- Vent Settings
  - PCV, insp pressure 22, rate 14, PEEP 5, tidal volumes 520 – 560 cc's achieved
- Maintenance
  - Desflurane 7% - 8%
  - Fentanyl 25 -50 mcg prn
  - Rocuronium 10 – 20 mg prn
    - Once twitches returned
  - Ofirmev 1 gram pre incision
  - **vWF concentrate 6900 IU pre incision over 10 minutes**
- Anti-emetics
  - Zofran 4 mg
  - Decadron 5 mg
- Reversal
  - Neostigmine 5 mg
  - Glyco 0.8 mg

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Intraoperative Issues

- Surgical course proceeded uneventfully
  - VSS throughout
- Total Anesthesia Time
  - 3 hours 3 minutes
- I/O
  - 2300 cc's of crystalloid
  - 200 cc's of urine output
- **Estimated Blood Loss (EBL)**
  - **150 cc's**

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PACU

- An awake extubation was performed uneventfully in the operating room
- Patient was initially placed on a non-rebreather at 10 liters per minute and once in the PACU converted to Bipap for roughly 2 hours
  - Bipap was planned and not due to distress or hypercapnia
- Pain level of 2/10
  - Treated with fentanyl and morphine PCA per PACU staff
- No PONV or intraoperative awareness reported
- Transferred to general floor after an uneventful PACU stay
  - Discharged to home 3 days later with no complications noted

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Preoperative Evaluation for vWD

Laboratory Analysis

- vWF:Ag. levels (50 – 200 IU/dl)
- Factor VIII:C levels (50 – 150 IU/dl)
  - Most specific
- Others
  - CBC, aPTT, platelet function assays, vWF multimer analysis, ristocetin-induced platelet agglutination, and collagen binding assays
- Obtain T/S for all procedures along with H/H and Coag's

Preoperative Screening

- Investigate level of bleeding risk via frequency of the previously mentioned symptoms
- Type of vWD is not often available related to the expense of testing
  - Severity is more often determined by frequency and duration of bleeding events

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Treatment options for vWD

- Desmopressin
- vWF concentrates
- Cryoprecipitate
- Tranexamic Acid
- Estrogen Derivatives

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Desmopressin (DDAVP)

- Introduced as a treatment option for vWD in 1977
  - Derivative of ADH
- Mechanism of action works to raise intrinsic vWF levels through agonistic activity on V2 vasopressin receptors
  - vWF along with factor VIII levels subsequently increase 2 to 3 times normal
  - Clinical results have demonstrated variability in patient outcomes related to short acting multimers
- Standard Dosing
  - **0.3mcg/kg IV given over 30 minutes**
  - 150 mcg to 300 mcg intranasal

(Neff & Sidonio, 2014).

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DDAVP

- Side effects
  - Flushing, hypotension, hypertension, N/V, headache, hyponatremia, volume overload, seizures, and tachyphylaxis
- Useful in treating the following variants:
  - Type 1
  - Type 2A, 2M, and 2N
- Used both prophylactically and acutely in dental procedures, child birth, and minor surgeries
- Pearls of Use
  - Test dose useful in determining individual response
    - Draw vWF levels at 60 minutes and 4 hours post administration
  - Draw serial Na levels for prolonged use
  - Limit fluid intake in the 24 hour period post administration

(Laffen et al., 2014)

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vWF Concentrates

- Considered the gold standard treatment for vWD
  - Useful in treating all variants of vWD
- Used under the trade names Alphanate, Humate-P, Haemate-P, and Wilate
  - Each medication contains varying concentrations of vWF and factor VIII
  - Standard dosing
    - 60 IU/kg bolus followed by 40 IU/kg doses as needed
- Favorable side effect profile
  - Anaphylactic reactions, hyperthermia, vWF inhibitory antibodies, hemolysis, thromboembolic complications (less than 1%), and hypervolemia

(Mannucci et al., 2002)

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vWF concentrate

Mannucci et al. (2002)

- 5 year, prospective study
- 87 patients
  - All subtypes represented
- Used for 71 cases of surgical prophylaxis and 87 situations involving acute hemorrhage
  - Skin bleeding time used for analysis
- Standard dosing applied
  - 60IU/kg bolus, 40IU/kg re-dose prn
- Acute bleeding episodes controlled with one bolus dose
- Surgical bleeding was controlled with vWF concentrate
  - Measured via expected surgical blood loss vs. actual blood loss
- No incidences of hemorrhage or side effects reported

Berntorp (2009)

- Systematic review investigating patients non-responsive to desmopressin treated with vWF concentrate
- Found 90% of patients had corrected bleeding times with a single bolus dose of vWF concentrate
- Concluded:
  - "effectively reduced the risk of bleeding complications in vWD patients undergoing elective surgery"

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vWF concentrate

- Auerswald and Kreuz (2009):
  - Suggested to following dosing regimens:
    - for major bleeding and trauma
      - loading dose of 40 – 60 IU/kg be given intravenously followed by a maintenance dose of 40 – 50 IU/kg for 3 days keeping vWF levels greater than 50%
    - For minor bleeding
      - a dose of 40 – 50 IU/kg be given intravenously for either 1 or 2 doses depending on individual response

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Tranexamic Acid (TXA)

- Lysine derivative, anti-fibrinolytic agent
  - Opposes the disintegration of thrombus formation
  - Typically used as an adjunct with desmopressin for vWD patients
  - Used in minor surgery and dental procedures
    - Combats natural proteolytic enzymes in the oral cavity
  - Standard dosing
    - 650mg orally for surgical prophylaxis
    - 1300mg orally every 8 hours for 5 days for menorrhagia
    - 10mg/kg IV bolus over 15 minutes (typically 1 gram given)

(Neff & Sidonio, 2014)

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Cryoprecipitate

- Plasma derived blood product
  - Contains vWF, factor I, VIII, XIII, and fibrinogen
    - 80 – 100 units of factor VIII
  - Reserved for when vWF concentrates unavailable
    - Falling out of favor related to acute viral pathology post-infusion

(Neff & Sidonio, 2014)

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Estrogen Derivatives

- Increase vWF production from endothelial cells
  - Reserved for vWD affected women of childbearing age
    - Effective in type 1 vWD
    - Not for use in the acute, hemorrhagic scenario
    - Not typically seen as an effective treatment option

(Neff & Sidonio, 2014)

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Genetic Testing

- Recommended in first degree relatives of a vWD patient with or without a history of spontaneous bleeding episodes
  - The International Society on Thrombosis and Haemostasis (ISTH) recommends all type 3 vWD patients undergo phenotypic analysis prior to conceiving children

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Practice Recommendations

- **Obstetrics**
  - Pregnancy tends to place vWD in remission making neuraxial anesthesia safe
    - Choi and Brull (2009) performed a case review involving 10 research studies with 74 vWD patients undergoing spinal/epidural anesthesia for labor analgesia and found no complications reported
  - However, vWF levels should be drawn prior to neuraxial anesthesia and should not proceed if levels are less than 30% to 40% of normal
    - Removing the epidural catheter immediately in the postpartum period is recommended
  - Typically, even in the most severe forms of vWD, inherent vWF are increased to 40% to 50% of normal in the pregnant patient

(Choi & Brull, 2009)

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Practice Recommendations

- **Regional Anesthesia**
  - Generally considered safe and efficacious
    - Especially if inherent vWF levels greater than 50% of normal
      - Bleeding risk is nullified at this level
  - Either desmopressin or vWF concentrates are the preferred pre-treatment prior to regional anesthesia if deemed clinically necessary
    - If catheters are placed, removal of the catheter is recommended as soon as clinically possible to prevent bleeding diathesis from occurring or worsening if already present

(Stedford & Pittman, 2000)

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Synopsis of vWD Treatment

- Desmopressin useful in the treatment of vWD
  - Type 1
  - Type 2A, 2M, and 2N
- **vWF concentrates are the GOLD standard**
  - Efficacious in the treatment of all vWD variants
- Adjuncts
  - TXA
  - Cryoprecipitate (falling out of favor)
  - Estrogen derivatives not commonly used

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Conclusion

- vWD places the surgical patient at an increased risk of intraoperative complications related to hemorrhage
  - Desmopressin and vWF concentrates are both effective as surgical prophylaxis for vWD patients
  - Unlike desmopressin, vWF concentrates are approved for all variants of vWD
- vWF concentrates effectively controlled surgical blood loss and maintained hemostasis in the vWD patient undergoing robotic hysterectomy
  - Evidence supports the use of vWF concentrates across multiple peer reviewed studies
  - vWF concentrates appear to have a favorable side effect profile
  - Effective in both the surgical arena as well as the management of acute hemorrhage

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Are There Any Questions?

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