Otolaryngologic Surgery in Children With von Willebrand Disease

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**Objective:** To assess the efficacy, safety, and complications of otolaryngologic surgery in children with von Willebrand disease (vWD) undergoing surgery.

**Design:** A prospective, controlled study of 41 children with vWD who underwent surgery between June 1, 1999, and January 31, 2001.

**Setting:** A tertiary care, university-based children’s hospital.

**Interventions:** All children had a preoperative diagnosis of vWD. The patients were treated with either a protocol that includes the use of desmopressin acetate and tranexamic acid (37 children) or factor VIII concentrate in children with a positive history of seizures (4 children).

**Main Outcome Measures:** Immediate and delayed postoperative bleeding, hyponatremia, seizures, and urine output.

**Results:** Two adenotonsillectomy patients (5%) had an immediate postoperative hemorrhage. Delayed postoperative bleeding was not detected in our patients. Severe hyponatremia occurred in 2 patients (1 of them with clinical manifestations).

**Conclusions:** Our management of children with vWD was efficacious in otolaryngologic surgery. One child had important adverse effects with the use of desmopressin (seizure). Thus, the use of desmopressin should be weighed and closely monitored.


**With prevalence estimates ranging from 3 to 4 per 100,000 population to as high as 1.3% of the population, von Willebrand disease (vWD) is the most common inherited bleeding disorder in humans.**

It is caused by a quantitative or qualitative defect of von Willebrand factor (vWF). von Willebrand factor is a large multimeric glycoprotein with 2 important roles: it mediates platelet adhesion and thrombus formation at sites of vascular injury, and it serves as a carrier for procoagulant factor VIII (FVIII) in circulating blood.

von Willebrand disease is a heterogeneous disorder with different subtypes. A revised classification introduced in 1994 by Sadler identifies 3 primary categories. Type 1 vWD refers to a partial quantitative deficiency of vWF and has an autosomal dominant inheritance; type 2 (which includes subtypes 2A, 2B, 2M, and 2N) refers to qualitative deficiencies of vWF and is also, generally, inherited in a dominant manner; and type 3 vWD is characterized by a complete deficiency of vWF and is generally inherited in an autosomal recessive manner.

von Willebrand disease is clinically characterized by mucocutaneous hemorrhages (epistaxis, gastrointestinal bleeding, and menorrhagia) and postoperative bleeding that can lead to catastrophic surgical outcome. The diagnosis is based on clinical history and results of screening tests of hemostasis. Although types 2 and 3 vWD are relatively easy to diagnose, the diagnosis of type 1 vWD may be more difficult. Diagnosis of definite type 1 vWD is made in patients with significant mucocutaneous bleeding, a positive family history of type 1 vWD, and laboratory test results compatible with type 1 vWD. In many patients not all of these criteria are found, and thus these patients are included in a category called possible vWD. These patients may be at risk of bleeding after otolaryngologic surgery because of the rich vascularity of the head and neck region. Therefore, the hematologist and the surgeon must keep this possibility in mind, and empiric treatment should be considered in patients that have a possible type 1 vWD.

In our experience, there were some cases of significant bleeding after otolaryngologic surgery in children, and afterward these children were diagnosed as having vWD. Bearing these patients in mind, we decided to study all patients with a slight prolongation of activated partial thromboplastin time (aPTT) or a personal history of bleeding. After the diagnosis of vWD was made, we used a pro-
that simulates primary hemostasis after injury of a small vessel of the aperture is defined as closure time. All blood samples were aspirated at high shear rates through the capillary and phosphate, is present on the membrane. During the test, the blood comes into contact with the collagen and the agonist. Platelets adhere and aggregate until a platelet plug occludes the aperture. The laboratory variables and diagnostic steps used for vWD are summarized in Table 1. Closure time was evaluated on whole citrate blood using a high shear-inducing device that simulates primary hemostasis after injury of a small vessel (PFA-100; Dade Behring Inc, Deerfield, France). Disposible test cartridges contain a reservoir for whole blood and a small capillary mounted by a collagen-coated membrane with a central aperture. A platelet agonist, either epinephrine or adenosine diphosphate, is present on the membrane. During the test, the blood sample is aspirated at high shear rates through the capillary and comes into contact with the collagen and the agonist. Platelets adhere and aggregate until a platelet plug occludes the aperture. The time required to stop the blood flow and to obtain occlusion of the aperture is defined as closure time. All blood samples were tested with both types of cartridges.

Methods

Between June 1, 1999, and January 31, 2001, we prospectively studied 41 children with type 1 vWD who underwent an otolaryngologic surgical procedure at La Paz Hospital, Autonomous University, Madrid, Spain. The mean age of the children was 5.2 years (range, 16 months to 13 years). One patient had a mild deficiency of factor XI, and 3 had a mild deficiency of factor XII. Thirty-five children had an abnormal closure time, 5 patients had an abnormal bleeding time, and 1 patient had normal findings on exploration of primary hemostasis. Types and numbers of surgical procedures performed in our patients are as follows: adenoidectomy, 13 (32%); adenoidectomy and myringotomy, 9 (22%); adenotonsillectomy, 10 (24%); adenotonsillectomy and myringotomy, 6 (15%); tonsillectomy, 2 (5%); and endoscopic sinus surgery, 1 (2%).

All patients who undergo otolaryngologic surgery at our center are asked about personal and family bleeding history. A physical examination is also performed. Screening tests such as prothrombin time, aPTT, fibrinogen level, and platelet count are performed in all children before the surgical procedure. If the patient had a positive history for personal or family bleeding and/or if there were an abnormality on screening test results, the patient was referred to the hematologist to investigate bleeding risk at surgery. Because vWD is the most common inherited bleeding disorder in humans, all children with a personal or family mucocutaneous bleeding history are tested for type 1 vWD. In 4 of these patients, a FVIII concentrate that is rich in vWF (Hemate P; Aventis Behring, Barcelona, Spain) was administered intravenously (10 mg/kg every 8 hours at a rate of 1 mL/min) in inpatients and orally in outpatients until day 7 after surgery. Postoperative hemorrhage was defined as any bleeding that required medical intervention. Serum sodium levels and hemostatic variables were measured daily. Operative techniques were based on individual surgeon preferences. Fluids during the postoperative period were managed on the basis of particular criteria of each anesthesiologist, although trends are toward fluid restriction.

All data were statistically analyzed using SPSS statistical software (SPSS Inc, Chicago, Ill). The paired t test was used as the parametric test. When the number of cases was too small for parametric tests, the Wilcoxon test was used. All statistical tests were considered bilateral and received the same level of significance (P = .05).

Results

Preoperative laboratory evaluation identified 40 patients with type 1 vWD, and 1 child was referred to our center with the diagnosis of type 1 vWD. In 4 of these patients, a FVIII concentrate that is rich in vWF (Hemate P) was administered because of a positive history of seizures. A desmopressin challenge test was performed in the remaining 37 patients, with a significant good response (Table 2).

Two adenotonsillectomy patients (5%) of the group treated with desmopressin (both with possible vWD) had an immediate postoperative hemorrhage (one from the adenoidectomy and the other from the tonsillectomy area). Both cases received FVIII concentrate rich in vWF when bleeding was detected. In addition to this, these 2 patients needed a new surgical intervention to stop the bleeding. None of them required transfusion of packed red blood cells. In the group treated with FVIII concentrate, no postoperative bleeding was noted. There was no de-
layed postoperative bleeding in our series. No variable of the desmopressin challenge testing was related to the appearance of hemorrhage (Table 3).

All cases had a significant decrease of serum sodium levels after treatment with desmopressin: 138.0 ± 2.2 mEq/L before vs 135 ± 3.4 mEq/L after (P < .001). Mild hyponatremia (serum sodium level, 130-135 mEq/L) was detected in all patients who received desmopressin for more than 1 day (24 patients) and in 3 of 13 patients who received just 1 dose. Severe hyponatremia (serum sodium level <125 mEq/L) occurred in 2 patients. Both had received 2 doses of desmopressin. One had no clinical manifestation. The other patient with severe hyponatremia had seizures and a serum sodium level of 121 mEq/L. He did not have further seizures or sequelae after correction of serum sodium level.

The 2 other patients (5%) had a strong anti-diuretic effect of desmopressin with a decrease in urinary output, but it was dealt with by close monitoring of fluid intake and stopping the desmopressin administration.

Table 2. Results of Desmopressin Challenge Testing in the 37 Patients Treated With This Protocol

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Desmopressin Challenge Before</th>
<th>Desmopressin Challenge After</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT, s</td>
<td>24-32.5</td>
<td>35.2 ± 2.2</td>
<td>29.4 ± 2.4</td>
</tr>
<tr>
<td>FVIII:c, IU/mL</td>
<td>0.5-1.5</td>
<td>0.62 ± 0.29</td>
<td>2.74 ± 0.78</td>
</tr>
<tr>
<td>vWF:Ag, IU/mL</td>
<td>0.5-1.75</td>
<td>0.58 ± 0.16</td>
<td>1.42 ± 0.27</td>
</tr>
<tr>
<td>vWD:RCo, IU/mL</td>
<td>0.5-1.5</td>
<td>0.49 ± 0.12</td>
<td>1.33 ± 0.16</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD and all are statistically significant (P < .001). aPTT indicates activated partial thromboplastin time; FVIII:c, factor VIII coagulant; vWF:Ag, von Willebrand factor antigen; and vWD:RCo, von Willebrand disease ristocetin cofactor.

Table 3. Results of Desmopressin Challenge Testing in 2 Patients With and 35 Without Immediate Postoperative Bleeding

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Bleeding With</th>
<th>Bleeding Without</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT, s</td>
<td>24-32.5</td>
<td>32.8 ± 0.2</td>
<td>35.4 ± 2.2</td>
<td>.08</td>
</tr>
<tr>
<td>FVIII:c, IU/mL</td>
<td>0.5-1.5</td>
<td>0.62 ± 0.13</td>
<td>0.83 ± 0.29</td>
<td>.33</td>
</tr>
<tr>
<td>vWF:Ag, IU/mL</td>
<td>0.5-1.75</td>
<td>0.61 ± 0.02</td>
<td>0.58 ± 0.17</td>
<td>.97</td>
</tr>
<tr>
<td>vWD:RCo, IU/mL</td>
<td>0.5-1.5</td>
<td>0.58 ± 0.14</td>
<td>0.49 ± 0.12</td>
<td>.40</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. aPTT indicates activated partial thromboplastin time; FVIII:c, factor VIII coagulant; vWF:Ag, von Willebrand factor antigen; and vWD:RCo, von Willebrand disease ristocetin cofactor.

The high prevalence of vWD indicates that mild forms of the disease may manifest during surgical procedures with increased bleeding. Also, in patients with a diagnosis of vWD, the surgical procedure might be dangerous without correct management. The main goals in the treatment of vWD are to correct the coagulation defect, which is the result of low levels of FVIII coagulant activity, and to correct the defect in primary hemostasis, which is reflected in bleeding time or closure time abnormalities.

Desmopressin is a synthetic derivative of the antidiuretic hormone l-arginine vasopressin. Desmopressin has little effect on the vasopressin 1 receptor, so it has no vasoconstrictive effect. However, desmopressin is a strong agonist for the vasopressin 2 receptor, and therefore it regulates water reabsorption in the kidney.

The mechanisms of action of desmopressin are not well understood, but shortening of aPTT and bleeding time indicates the global hemostatic effect of desmopressin. It has been proposed that its effect is due to the release of FVIII-vWF complex and tissue plasminogen activator (tPA), activation of blood cell–mediated hemostasis, and generation of platelet microparticles that may increase the procoagulant surface action on platelets.10 Recently, it has been suggested that desmopressin liberates tPA, vWF, and FVIII predominantly via systemic mechanisms, possibly mediated by cytokine release.11

Despite the generalized use of desmopressin in different clinical settings since the report by Mannucci et al.,12 it has been proposed recently that desmopressin is not a panacea for children with vWD.13 This observation is based on the adverse effects of desmopressin. Adverse effects immediately following desmopressin infusion, such as facial flushing, headache, a slight drop in systolic blood pressure, and a small increase in pulse rate, are mild and transient. The potent anti-diuretic action of desmopressin can be harmful in patients younger than 18 months because of the possibility of water intoxication and electrolyte imbalance.

Hyponatremia and seizures due to desmopressin administration have been observed in children.14,15 Usually in the postoperative period large amounts of hypotonic intravenous fluids are administered, but in patients undergoing desmopressin treatment, fluid intake should be restricted, electrolytes monitored, and urine output controlled every 6 hours for 24 hours.10 In our series, we observed mild hyponatremia in all patients who received more than 1 dose of desmopressin. Two patients (5%) had severe hyponatremia with levels below 125 mEq/L. One of them had cerebral convulsion associated with hyponatremia despite electrolyte control. A strong anti-diuretic effect of desmopressin was observed in 2 patients (5%), with a significant decrease in urine output. We agree with Sutor13 that the anti-diuretic action of desmopressin increases the risk-benefit ratio in children, and its use must be weighed and closely monitored.

Antifibrinolytic agents such as tranexamic acid have been used to control bleeding due to excessive fibrinolysis in situations such as systemic states of hyperfibrinolysis, states of localized increased fibrinolysis, and conditions of defective hemostasis in the presence of normal active fibrinolysis (eg, patients with hemophilia).10,13,16,17 The use of tranexamic acid could be efficacious to prevent and control bleeding in the patients with vWD and otolaryngologic surgery, since saliva contains natural activators but...
not inhibitors of fibrinolysis,18,19 and desmopressin produces the release of tPA.10 Minor complaints, such as nasal stuffiness, abdominal discomfort, nausea, vomiting, diarrhea, conjunctival suffusion, and rash, have been noted in patients who receive tranexamic acid, but the serious systemic thrombotic complications described are related to the underlying clinical state and not to the administration of tranexamic acid.17 In the children we studied, we observed 1 patient (2.4%) with nausea and vomiting probably associated with tranexamic acid administration.

The otolaryngologist who performs procedures in patients with vWD has to keep in mind not only the management of the most common complications after adenotonsillar procedures but also the armamentarium available to combat perioperative bleeding. The main condition before surgery is an adequate effect of the therapy and the accomplishment of the habitual recommendations before these procedures (ie, to avoid all antplatelet drugs and no fever and/or infections 1 week before surgery). In addition, these patients are encouraged to avoid intramuscular injections and rectal medications and to have scrupulous dental hygiene.

During the operation, the aim is to improve surgical hemostasis. Multiple opinions with respect to the ideal method to remove the adenotonsillar tissue in these patients have been published. Therefore, careful classic dissection with pilars suture, bipolar electrocautery, or laser dissection have been proposed, although no clear benefits have been demonstrated by any method. Thus, the main objective remains, in all cases, to perform an atraumatic dissection avoiding incisional bleeding.

Few series and several case reports15-19,25 have addressed the efficacy and safety of different protocols in the management of vWD in pediatric patients undergoing adenotonsillar surgery. In Table 4 some of the previous publications about this topic are detailed. Although these studies vary in their approach to patients with vWD, in all but one,19 patients with this disorder are clearly at increased risk for postoperative bleeding, regardless of the perioperative management. No logical explanations have been found regarding the differing results of this work,19 although the low number of cases studied could be responsible for these results. Our study shows a global incidence of immediate postoperative bleeding of 5% (2/41 patients) and 0% of delayed hemorrhage after surgery. However, in the previous series published, most hemorrhages occur after the first 24 hours.13,21,24,25 This finding can be explained by the pharmacologic properties of tranexamic acid,17 which is administered during the first postoperative week.

In conclusion, our management protocol (using desmopressin and tranexamic acid) for children with vWD has proved to be efficacious in otolaryngologic surgery. Two children had significant hypotremia, 1 of them with seizures, with the use of desmopressin. Thus, the use of desmopressin has to be weighed and closely monitored.

Accepted for publication June 27, 2002.

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Table 4. Case Series of Adenotonsillar Procedures in Patients With von Willebrand Disease

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Postoperative Bleeding, No. (%)</th>
<th>Perioperative Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al.,20 1999</td>
<td>69</td>
<td>9 (13)</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>Shah et al.,21 1998</td>
<td>5</td>
<td>0</td>
<td>Desmopressin and aminocaproic acid</td>
</tr>
<tr>
<td>Derkay et al.,21 1996</td>
<td>12</td>
<td>2 (16)</td>
<td>Desmopressin and aminocaproic acid or tranexamic acid</td>
</tr>
<tr>
<td>Conlon et al.,24 1996</td>
<td>3</td>
<td>1 (33)</td>
<td>Factor VIII</td>
</tr>
<tr>
<td>Prinsley et al.,23 1993</td>
<td>3</td>
<td>1 (33)</td>
<td>Factor VIII</td>
</tr>
</tbody>
</table>

*Delayed bleeding.

REFERENCES