Adenotonsillectomy in Children With von Willebrand Disease

Gregory C. Allen, MD; Derek R. Armfield, MD; Franklin A. Bontempo, MD; Lawrence A. Kingsley, DrPH; Nira A. Goldstein, MD; J. Christopher Post, MD

Objective: To review the effectiveness of a perioperative management protocol and our experience with a large population of patients with von Willebrand disease (vWD) who require adenotonsillar surgery (T&A).

Design: A retrospective review of the medical records of all patients having the diagnosis of vWD who underwent T&A between January 1, 1992, and July 31, 1996.

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

Interventions: Patients having a preoperative diagnosis of vWD received a single intravenous dose of desmopressin acetate, 0.3 µg/kg, approximately 20 minutes before the induction of anesthesia. Beginning January 15, 1994, a standard management protocol involving the postoperative administration of fluids and electrolytes was followed.

Main Outcome Measures: Operative blood loss and the incidence of postoperative bleeding and of hyponatremia.

Results: Of approximately 4800 patients who underwent T&A during the study period, 69 patients had a diagnosis of vWD. All 67 patients identified preoperatively received desmopressin; 2 were identified by postoperative workup as a result of excessive surgical bleeding. Minimal immediate postoperative bleeding was noted in 7 patients (10%), but none required intervention. Delayed bleeding occurred in 9 patients (13%); all were readmitted to the hospital for observation, 4 (6%) requiring operative cauterization. Substantial postoperative hyponatremia occurred in 3 patients, and 1 patient had seizure activity. Symptomatic hyponatremia has been avoided since a protocol of fluid and electrolyte administration was instituted.

Conclusions: Although T&A can be performed safely in patients with vWD, it is not without an increased risk of postoperative hemorrhage. The administration of desmopressin has been reported to reduce the risk of bleeding, but it is not without risk. A protocol for fluid and electrolyte management is recommended.


Von Willebrand disease (vWD) is an autosomal dominant inherited bleeding disorder primarily characterized by mucocutaneous bleeding, menometrorrhagia, excessive bleeding after trauma, postoperative bleeding, gastrointestinal bleeding, and occasionally petechiae and hemarthrosis. The disorder encompasses a family of molecular defects with several subtypes affecting 0.8% to more than 2% of the population. Clinical problems arise from either a quantitative or a qualitative defect in von Willebrand factor (vWF); this results in a hybrid hemostatic defect of abnormal platelet aggregation and decreased levels of factor VIII coagulant activity, leading to a prolonged bleeding time and activated partial thromboplastin time (aPTT).

In 1977, Mannucci et al2 first described the use of 1-deamino-8-D-arginine vasopressin (desmopressin acetate) in patients with mild hemophilia and vWD. Desmopressin is a synthetic analogue of naturally occurring antidiuretic hormone. Its actions include antidiuretic activity, and it stimulates the release of vWF and factor VIII from endothelial cells. Several published small series and case reports2-11 have addressed the efficacy and safety of using desmopressin therapy in pediatric patients undergoing adenotonsillar surgery. We now report a retrospective review of our experience with 69 pediatric patients with vWD undergoing adenotonsillar procedures (tonsillectomy, adenoidectomy, or both) at Children’s Hospital of Pittsburgh, Pittsburgh, Pa.
PATIENTS AND METHODS

The typical treatment protocol for patients undergoing adenotonsillar procedures includes a preoperative history and physical examination with emphasis on past bleeding and family history. All patients undergo laboratory screening that includes hemoglobin level, hematocrit, prothrombin time, and aPTT. Bleeding time was obtained only if the patient had a medical or family history of abnormal bleeding. If these laboratory values are abnormal, the tests are repeated. Patients with persistent abnormalities underwent further coagulation testing. Hematologic evaluation consisted of an extensive battery to determine the presence of a hereditary or acquired coagulopathy. Patients were determined to have vWD if they had 1 or more abnormal values of either factor VIII coagulant, vWF antigen, ristocetin cofactor aggregation, or aPTT, along with a family or patient bleeding history or 2 or more abnormal laboratory values in the absence of a family or bleeding history. Once the diagnosis of vWD was made, vWF antigen multimer electrophoresis was performed to further exclude vWD type IIB and platelet-type vWD, and a desmopressin challenge test was performed. Patients were given desmopressin acetate, 0.3 µg/kg, in isotonic sodium chloride solution, 50 mL intravenously; bleeding time and coagulation studies were performed before and 30 minutes after infusion. If an acceptable response to the desmopressin challenge test was demonstrated, the patient went on to surgery. Desmopressin (0.3 µg/kg) was administered 20 to 30 minutes preoperatively. Operative techniques were based on individual surgeon preferences and consisted primarily of the curettage of adenoids, followed by suction electrocautery and electrocautery removal of tonsils. Postoperative bleeding was defined as any bleeding that was mentioned in the medical record.

A retrospective medical records review was performed of children who had the diagnosis of vWD who underwent adenotonsillar procedures at Children's Hospital of Pittsburgh between January 1, 1992, and July 31, 1996. Children diagnosed as having other coagulopathies were excluded. An adenotonsillar procedure is defined as either a tonsillectomy, adenoidectomy, or adenotonsillectomy. Medical records evaluation consisted of the following: demographics, history, preoperative blood work, coagulation studies, desmopressin challenge test, operative details, postoperative course, serum sodium levels, and the occurrence of bleeding or other complications. If bleeding occurred within 24 hours of surgery, it was considered immediate, and any bleeding thereafter was considered delayed. The postoperative bleeding rate in the remainder of the group was assessed by a review of medical records data and monthly morbidity information for 1996. Statistical analyses of data were performed using commercial software (SSPS for Windows, Release 8.0.0; SPSS Inc, Chicago, Ill).

RESULTS

Of 4769 patients who underwent adenotonsillar procedures during the study period, 69 (1.4%) were diagnosed as having vWD. One patient underwent adenoidectomy and later, tonsillectomy; therefore, a total of 70 procedures are reported. Preoperative laboratory evaluation identified 66 patients, 2 were identified postoperatively after excessive surgical bleeding, and 1 was referred because of the diagnosis of vWD. Thirty were male. Ages ranged from 18 months to 17.3 years, with a mean of 7.3 years. The age distribution is shown in the Figure. There were 56 whites and 13 African Americans in the study population. Fourteen (20%) had a history of excessive bleeding with minor trauma; 31 (45%) had previous surgery, but only 2 bled excessively with that procedure. None had a previous transfusion. The results of the preoperative laboratory evaluation showed a mean aPTT of 35.7 seconds (range, 25.7-80.2 seconds; reference range, 20-30 seconds) and a mean bleeding time of 9.4 minutes (range, 2.5 to >15.0 minutes; reference range, 1.5-7.0 minutes [age <11 years] or 3.0-9.0 minutes [age ≥11 years]). Fifty-nine patients had a desmopressin challenge test; the results are presented in Table 1.

The operative procedures performed include 19 adenoidectomies (27%), 11 tonsillectomies (16%), and 40 adenotonsillectomies (57%). The mean operative time was 38.5 minutes (range, 5-87 minutes), and the mean estimated blood loss was 44.6 mL (range, 0-200 mL). The initial hospital stay was 1 night for 59 patients, 2 nights for 7 patients, and more than 3 nights for 4 patients. Immediate postoperative bleeding occurred in 7 patients. This included any blood-tinged secretions from the nose or mouth in the first 24 hours. No patient required intervention, but 2 of these patients went on to have delayed bleeding on days 5 and 7.

Delayed postoperative bleeding occurred in 9 patients (13%) beginning on days 5 to 12 (mean, 7.7 days), and all were admitted to the hospital for observation. Four patients (6%) required cautereization in the operating room; no transfusions were required. No patient with delayed bleeding had undergone only adenoidectomy. Delayed postoperative bleeding was not predicted by bleeding history, family history, age, sex, or race. Table 2 presents data regarding desmopressin challenge testing between the 2 groups. Several factors in the response to
the desmopressin challenge test were significant or approached statistical significance with respect to delayed postoperative bleeding: ristocetin cofactor (P = .03), factor VIII coagulant (P = .07), and vWF antigen (P = .09). During 1996, delayed postoperative bleeding occurred in 38 (3.6%) of 1060 patients without coagulopathies who had adenotonsillar surgery. The rate of delayed postoperative bleeding was statistically significant between those patients with vWD and those without (P = .001).

The serum sodium level was measured 109 times in 53 patients. Mild hyponatremia (serum sodium level, 130-135 mmol/L) occurred in 27 patients (51%), but serum sodium levels less than 130 mmol/L were observed on only 3 occasions (3%). The calculated maintenance volume of intravenous fluids was compared with that actually received; patients with hyponatremia received significantly more of the calculated intravenous fluids than those without hyponatremia (P = .008). Younger age was not found to be a significant predictor of hyponatremia in these patients (P = .16). Before routine monitoring of postoperative serum sodium levels and judicious use of intravenous fluids, a 23-month-old girl had a generalized tonic-clonic seizure lasting 3 minutes on the morning of postoperative day 1. Her serum sodium level at this time was 123 mmol/L; this was slowly corrected during the next 24 hours, and she had no further seizures or sequelae. She had received 500 mL of Ringer’s lactate solution intraoperatively and 5% dextrose in 25% isotonic sodium chloride solution, 50 mL/h (calculated maintenance requirement), for 20 hours when the seizure occurred.

**COMMENT**

In 1926, Erich von Willebrand characterized a bleeding disorder in a 5-year-old Finnish girl and 66 affected family members. Distinctly different from the previously described hemophilia disorders, it was apparently inherited in an autosomal dominant pattern and was marked by primarily mucocutaneous bleeding. In addition, he noted that although the bleeding time was prolonged, the platelet count was normal. Today, it is known that the disorder that bears his name encompasses a family of molecular defects affecting 0.8% to more than 2% of the population, usually in an autosomal dominant familial inheritance pattern.

**Table 1. Results of Desmopressin Challenge Testing in 69 Children With von Willebrand Disease**

<table>
<thead>
<tr>
<th>Test</th>
<th>Before desmopressin challenge</th>
<th>After desmopressin challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated PTT, s (20-30)</td>
<td>32.9</td>
<td>28.3</td>
</tr>
<tr>
<td>VIII:c, ratio (0.5-1.5)</td>
<td>0.9</td>
<td>2.0</td>
</tr>
<tr>
<td>vWF:Ag, ratio (0.5-2.0)</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Ristocetin cofactor, ratio (0.45-1.25)</td>
<td>0.31</td>
<td>1.13</td>
</tr>
<tr>
<td>Bleeding time, min (1.5-7.0)</td>
<td>10.2</td>
<td>7.3</td>
</tr>
</tbody>
</table>

*Data are given as means, and all are statistically significant (P < .05). PTT indicates partial thromboplastin time; VIII:c, factor VIII coagulant activity; and vWF:Ag, von Willebrand factor antigen. Numbers in parentheses represent reference range.*

**Table 2. Results of Desmopressin Challenge Testing in 9 Patients With and 60 Patients Without Delayed Postoperative Bleeding**

<table>
<thead>
<tr>
<th>Test</th>
<th>With delayed bleeding</th>
<th>Without delayed bleeding</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated PTT, s (20-30)</td>
<td>34.2</td>
<td>32.8</td>
<td>.33</td>
</tr>
<tr>
<td>VIII:c, ratio (0.5-1.5)</td>
<td>0.6</td>
<td>0.9</td>
<td>.03</td>
</tr>
<tr>
<td>vWF:Ag, ratio (0.5-2.0)</td>
<td>0.4</td>
<td>0.6</td>
<td>.08</td>
</tr>
<tr>
<td>Ristocetin cofactor, ratio (0.45-1.25)</td>
<td>0.52</td>
<td>0.62</td>
<td>.15</td>
</tr>
<tr>
<td>Bleeding time, min (1.5-7.0)</td>
<td>12.0</td>
<td>9.8</td>
<td>.58</td>
</tr>
</tbody>
</table>

*Data are given as means. PTT indicates partial thromboplastin time; VIII:c, factor VIII coagulant activity; and vWF:Ag, von Willebrand factor antigen.*

von Willebrand factor is a 2050–amino acid, 270-kd protein coded on the short arm of chromosome 12. It dimerizes with strong disulfide bonds and then forms polymers up to 20 000 kd, with the largest of these multimers being the most active. This protein has 2 primary functions: it acts as an intermediary that binds to platelets, enabling them to bind to vascular endothelium; and it acts as a carrier for factor VIII, slowing its degradation, and thus helping to maintain an effective circulating concentration. Consequently, patients with vWD typically have prolonged bleeding times and aPTTs.

More than 20 subtypes of vWD have been described, but 4 major types are recognized based on a quantitative or a qualitative defect. Type I vWD is the most common, representing 70% to 80% of cases and evidenced by a relatively mild to moderate decrease in normal-functioning vWF. Type II disease represents about 20% of cases of vWD and typically involves qualitative defects in vWF, as determined by a variation in multimer formation patterns seen on electrophoresis. Many subtypes exist within type II disease, with types IIA and IIB representing 95%. If abnormal multimer formation is found, suggesting type II vWD, ristocetin-induced platelet aggregation testing is performed at both normal (1.2 mg) and low (0.3 mg) strengths. In type IIA disease, there is little or no platelet aggregation at low-strength ristocetin, whereas in type IIB disease, ristocetin at low strength causes platelet aggregation and may lead to marked and sudden thrombocytopenia. Clinically, this differentiation is extremely important because the administration of desmopressin may be beneficial in the treatment of types I and IIA disease (about 95% of cases of vWD) but is contraindicated in type IIB, where it may cause thrombocytopenia, subsequent prolongation of the bleeding time, and increased surgical bleeding. Patients with minimal or undetectable amounts of structurally normal vWF are categorized as having type III. Type III represents a homozygous defect, which may account for its rare occurrence and severe clinical implications. Desmopressin is not beneficial for this type because no vWF is pres-
ent to be released by the vascular endothelial cell. A fourth type of vWD is designated platelet type or pseudo-vWD. This rare type of vWD is actually an intrinsic platelet defect due to alteration of the platelet glycoprotein Ib-IX complex receptor for vWF. The result is increased affinity of the receptor for high-molecular-weight vWF multimers that appears clinically and in the laboratory like vWD type IIb.14,15 As in type IIb, desmopressin is contraindicated in patients with platelet-type vWD. Table 3 summarizes the various types of vWD and the various tests commonly used in their diagnosis. As the molecular defects responsible for each subtype of vWD are elucidated, simplified mutational classification schemes will likely emerge.

Whereas other compounds like epiinephrine and insulin are known to increase levels of factor VIII and vWF in healthy subjects, patients with hemophilia A, and those with vWD, desmopressin can be administered with relatively few adverse effects.2,3,16,17 Consequently, desmopressin therapy has enjoyed widespread use in patients with bleeding disorders since first described by Mannucci et al2 in 1977. Although the exact mechanism of action of desmopressin is not clear, it is thought to stimulate the release of vWF from its storage sites in vascular endothelium. Because of limited storage of vWF within the vascular endothelium, prolonged use or too-frequent desmopressin dosing leads to a progressively diminished clinical response.3,18 Whereas the use of desmopressin greatly reduces the need for blood product administration, it is not without risks or contraindications. Desmopressin is a synthetic analogue of naturally occurring antidiuretic hormone and, thus, simulates the resorption of free water in the kidney. The most important adverse effect of desmopressin use is hyponatremia, which can be a cause of seizures.19,21 Predisposing factors reported in the literature20,21 include young age, weight less than 10 kg, the administration of hypertonic intravenous fluids, liberal fluid replacement, emesis, multiple doses of desmopressin, and an increased release of endogenous antidiuretic hormone during stress. Other observed effects of desmopressin therapy include headache, flushing, angioedema, hypotension, and mild tachycardia.

For patients with vWD, desmopressin is typically useful in patients with types I and II A disease, but those with type IIIA disease have a variable response and require infusion testing.2,9,12,22 Because they have essentially no vWF in the vascular endothelium, patients with type III disease do not respond well to desmopressin. When desmopressin use is not indicated, or when it is not effective in controlling postoperative bleeding, plasma-derived factor VIII concentrate (Humate-P; Centeon L.L.C., King of Prussia, Pa) can be given. This antihemophilic factor is a pasteurized, intermediate-purity factor VIII concentrate that contains not only high levels of factor VIII but also a full range of hemostatically active vWF multimers. Although used widely in the past for patients with vWD, cryoprecipitate is not recommended because of the risk of viral transmission.

Few series and several case reports2-7 address the problem of adenotonsillar surgery in patients with vWD. Table 4 lists some of the previous publications and our data. Although these studies vary in their approach to patients with vWD, patients with this disorder are clearly at increased risk for postoperative bleeding, regardless of the perioperative management.

We report our experience in 69 patients diagnosed as having vWD during 4½ years. Delayed postoperative bleeding occurred in 9 patients (13%), and this is significantly higher than our rate of delayed postoperative bleeding (3.6%) at Children’s Hospital of Pittsburgh for 1996. All patients who underwent surgery during this time had acceptable correction of their coagulopathy following intravenous desmopressin administration. Postoperative bleeding was not predicted by history. Initial factor VIII coagulant levels were significantly lower (P = .03) in patients with delayed postoperative bleeding; in addition, initial vWF antigen levels approached statistical significance (P = .08). Several factors in the response to desmopressin challenge were significant or approached statistical significance with respect to delayed postoperative bleeding: ristocetin cofactor (P = .03), factor VIII

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Table 3. Characteristics of von Willebrand Disease Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency, %</th>
<th>vWF:Ag Test</th>
<th>RIPA Test</th>
<th>vWF:RCoF</th>
<th>Multimer Analysis</th>
<th>Desmopressin Acetate Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>70-80</td>
<td>↓</td>
<td>↓ or Nl</td>
<td>↓</td>
<td>All ↓</td>
<td>Good</td>
</tr>
<tr>
<td>II A</td>
<td>10-15</td>
<td>↓ or Nl</td>
<td>↓ or Nl</td>
<td>↓</td>
<td>Large, med ↓</td>
<td>Fair to good</td>
</tr>
<tr>
<td>II B</td>
<td>&lt;5</td>
<td>↑↑</td>
<td>↑↑ or Nl</td>
<td>↑</td>
<td>Largest absent Nl</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>III</td>
<td>Rare</td>
<td>↓ ↓</td>
<td>↓ ↓</td>
<td>↓ ↓</td>
<td>Largest absent Nl</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Platelet</td>
<td>Rare</td>
<td>↓ ↓</td>
<td>↓ ↓</td>
<td>↓ ↓</td>
<td>Down-pointing arrow, slightly increased level or reaction; and 2 up-pointing arrows, markedly increased level or reaction.</td>
<td></td>
</tr>
</tbody>
</table>

* vWF:Ag indicates von Willebrand factor antigen; RIPA, ristocetin-induced platelet aggregation; vWF:RCoF, ratio of von Willebrand factor to ristocetin cofactor; Nl, normal; med, medium; down-pointing arrow, slightly decreased level or reaction; 2 down-pointing arrows, markedly decreased level or reaction; and up-pointing arrow, slightly increased level or reaction; and 2 up-pointing arrows, markedly increased level or reaction.

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Table 4. Case Series of Adenotonsillar Procedures (T&A) in Patients With von Willebrand Disease (vWD)

<table>
<thead>
<tr>
<th>Study</th>
<th>T&amp;A and Delayed Bleeding, No. (%)</th>
<th>Perioperative Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derkay et al,3 1996</td>
<td>12 (2 16)</td>
<td>Desmopressin acetate plus aminocaproic acid or tranexamic acid</td>
</tr>
<tr>
<td>Conlon et al,4 1996</td>
<td>3 (1 33)</td>
<td>Factor VIII</td>
</tr>
<tr>
<td>Prinsley et al,6 1993</td>
<td>3 (1 33)</td>
<td>Factor VIII</td>
</tr>
<tr>
<td>Present study</td>
<td>69 (9 13)</td>
<td>Desmopressin</td>
</tr>
</tbody>
</table>
von Willebrand disease is a disorder frequently encountered by otolaryngologists, and its appropriate management is of utmost importance. Young children who present for adenotonsillar surgery may not have been previously challenged surgically, and therefore a high index of suspicion for a coagulopathy must be maintained. Adenotonsillar surgery can be safely performed in patients with vWD, but it is not without an increased risk of delayed postoperative bleeding. As expected, patients with more severe vWD or those with less complete correction after desmopressin challenge are at a higher risk for postoperative bleeding. Desmopressin appears to be effective in correcting the coagulopathy that is present in these patients, but its use is not without risk as well.

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CONCLUSIONS

REFERENCES