Recombinant von Willebrand factor for perioperative bleeding management in pediatric patient with allergy to plasma-derived von Willebrand factor

Thuy Tran¹, Justin Arnall¹, Brendan Kleiboer¹, and Ashley Hinson²

¹Atrium Health
²Levine Children’s Hospital

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Abstract

Von Willebrand disease (VWD) is a hereditary bleeding disorder characterized by a deficiency of von Willebrand factor (VWF). In pediatrics, plasma-derived VWF (pdVWF) is the standard for factor replacement when indicated. Alternatives are needed for kids who are refractory or intolerant to pdVWF. There is limited data on the safety and efficacy of recombinant VWF in the pediatric population, and none regarding the switch from pdVWF to rVWF due to intolerance. Herein, we describe the safe and effective use of rVWF in a pediatric patient with history of anaphylaxis to pdVWF, who underwent elective orthopedic surgery.

Introduction

Von Willebrand factor (VWF) is a large multimeric procoagulant plasma protein. It plays an essential role in primary hemostasis by functioning as an adhesion molecule, binding platelets to the exposed subendothelium at a site of injury, and binding between platelets to form a platelet plug. VWF also acts as a carrier protein for Factor VIII (FVIII), protecting it from proteolytic degradation. Von Willebrand disease (VWD) is characterized by a qualitative or quantitative defect of VWF that results in prolonged bleeding due to the inability to form a stable platelet plug.[1] Common bleeding risks in VWD include mucosal bleeding such as nosebleeds, gum bleeding, easy bruising, and increased bleeding with procedures or surgeries.[2]

In the setting of acute bleeding and peri-procedural bleeding prevention, the goal of treatment in VWD is to achieve hemostasis by correcting the deficient quantity of VWF or by replacing the abnormally functioning VWF. Treatment primarily includes the use of desmopressin or factor concentrates, and antifibrinolytics as adjunctive therapy. Desmopressin (DDAVP) is an antidiuretic hormone that works by promoting the release of endogenous VWF from endothelial cell storage. Antifibrinolytic agents promote stability of platelet plugs by reducing fibrinolysis.

Factor concentrates provide exogenous factor replacement to increase the VWF activity level into the normal range.[3] While both pdVWF and rVWF are equally efficacious and have similar safety profile there are some notable differences between the two classes (Table 1).

Plasma-derived VWF is preferred for patients under the age of 18 because its use in children is FDA approved, has more supportive data, and more provider experience. However, pediatric patients who are refractory to, or have history of anaphylaxis to pdVWF, have limited treatment options. Prior to rVWF coming to market, children with history of anaphylaxis to pdVWF would undergo pdVWF desensitization;[4] whereas adult patients have the rVWF as another treatment option. There is still very limited data on the use of rVWF in children,[5] particularly in the setting of anaphylaxis. Herein, we present a case report of a pediatric patient
with VWD Type 1 and history of anaphylaxis to Humate-P who received Vonicog alpha prior to elective orthopedic surgery.

Case Report

An 8-year-old Caucasian male presented at our hemophilia treatment center for assessment of bleeding management for elective orthopedic surgery (left tibia epiphysiodesis) to correct right tibial anterolateral bowing and limb length discrepancy (left tibia greater than right). The patient has a strong family history of VWD (mother and older brother) and was diagnosed with mild VWD type 1 at 2 years old (VWF:Act = 30 iu/mL; FVIII = 63%; VWF:Ag = 28 iu/dL). He has occasional nosebleeds several times per year that have occasionally required intranasal DDAVP but are never longer than a few minutes in length. He had undergone several procedures in the past including meatoplasty, dental fillings and extractions; each successfully managed with intranasal DDAVP and/or oral aminocaproic acid.

For this outpatient orthopedic procedure, intranasal DDAVP could not be used due to international recall and unavailability of the product. The decision to use a factor product instead of intravenous or subcutaneous desmopressin was made from logistical consideration for the patient. This patient would need to come to the hemophilia treatment center to receive any injectable therapy the morning of surgery. To avoid the need for additional factor should patient sub-optimally responded to desmopressin, and to avoid the need of water restriction post desmopressin, a plan was made for peri-operative exogenous factor administration. Prior to the left tibia epiphysiodesis surgery, the patient received 2984 units (50 iu/kg VWF) of pdVWF (Humate-P). He experienced chest tightness, lip swelling, tongue tingling, and desaturations requiring diphenhydramine, famotidine, and epinephrine immediately after the pdVWF infusion was complete. The surgery was canceled and rescheduled.

There are no records of the plasma response to pdVWF infusion, as this patient is factor naïve. An anti-VWF antibody is unlikely in type 1 VWD. If this was an anti-VWF antibody, then a lack of response should be evident. This patient was then assumed to have an IgE-mediated allergic reaction to pdVWF. Therefore, on the day of rescheduled surgery, considering the history of anaphylactic reaction to pdVWF, the patient was given Vonicog alpha 3040 units (50 iu/kg VWF) prior, with plan for 1 additional Vonicog alpha dose post-operative as needed. A pre-medication regimen of one dose of IV push diphenhydramine 25 mg, famotidine 20 mg, and oral acetaminophen 320 mg (5 mg/kg) prior to the pre-operative Vonicog alpha was given. He tolerated the Vonicog alpha well, with no notable post-infusion adverse effects; and he tolerated the procedure well without any complications. He did not require additional post-operative Vonicog alpha. The patient reported some mild skin bleeding on post-op day 3, that was managed with aminocaproic acid orally every 6 hours, but he did not require any additional Vonicog alpha post-op. Oral aminocaproic acid was started the night before both scheduled surgeries.

Discussion

Plasma-derived VWF has higher risk of causing severe allergic reactions than rVWF because it contains extraneous plasma proteins, as demonstrated in this patient case. Patients with VWD who have demonstrated severe anaphylaxis to one pdVWF product should be excluded from future use of all pdVWF products. Adult patients with intolerance to pdVWF have been successfully treated with rVWF.[5] Children with VWD and history of anaphylaxis to pdVWF can undergo pdVWF desensitization since rVWF is not yet FDA approved for use in pediatric population. There is no standard protocol or consensus for factor desensitization; the factor dose and method are institution-specific. Drawbacks to this approach with factor desensitization is that it may require more time and can be more costly, and still poses a risk of further potentially serious allergic reactions.[4,6]

Recombinant VWF is a more direct treatment for VWD than the traditional pdVWF concentrates by providing VWF to correct the deficiency without introducing additional FVIII that may lead to excessive accumulation of FVIII and increase risk for thrombosis. Recombinant VWF has been used off-label to successfully treat bleeds in pediatric patients who are refractory to pdVWF. This patient case offers support that rVWF is also safe and effective in preventing perioperative bleeding in pediatric patients and offers
another treatment option for those with allergies to pdVWF. Larger studies are needed to confirm the result of this case report. Further investigation is still needed to determine the safety and efficacy of the prophylactic use of rVWF in pediatric patients with severe disease, or who are refractory to standard therapies and pdVWF. These studies are ongoing.[7]

In conclusion, recombinant VWF is approved for on-demand and perioperative bleeding management in adults, but it remains to be determined if the use of rVWF is efficacious and safe in patients 18 years and younger. Furthermore, the safety of rVWF in children with hypersensitivity to pdVWF has not been determined. Notwithstanding the FDA’s current restrictions on the use of rVWF to only patients 18 years and older, the use of a recombinant product in pdVWF-naıve children should be considered as it confers no risk of pathogenic transmission, less risk of allergic reactions, and reduces excessive FVIII accumulation in VWD patients. This case reports the safe and effective switch to rVWF in the prevention of perioperative bleeding in a child with history of anaphylaxis to pdVWF.

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References:

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