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Advantage of recombinant von Willebrand factor for peri-operative management in paediatric acquired von Willebrand syndrome

Dear Editors,

A 2-year-old African American male child with pulmonary valve stenosis sustained a skull fracture and large epidural haemorrhage after a fall. He underwent multiple procedures over several days, all of which were complicated by postoperative bleeding. Past bleeding history was significant for bleeding with eruption of new teeth. Family history was negative for bleeding manifestations. Laboratory workup prior to a planned cranioplasty revealed normal prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, factor IX, factor XI and factor XIII (present by clot dissolution assay). Blood type was AB+. A von Willebrand factor (vWF) panel revealed elevated factor VIII (FVIII) of 333%, normal ristocetin cofactor activity (vWF:RCo) of 58% (normal range 50%-150%) with vWF antigen (vWF:Ag) of 178% (normal range 50%-150%; Table 1). The vWF:RCo/vWF:Ag ratio was abnormally decreased to 0.33, consistent with acquired von Willebrand syndrome (avWS), likely secondary to pulmonic stenosis. Plasma von Willebrand multimer analysis revealed the absence or decreased abundance of the highest molecular weight multimers (HMWMs), but no definitely increased abundance of lower molecular weight vWF multimers, more characteristic of avWS than a congenital vWF defect. Although his vWF:RCo level was within a low-normal range, most guidelines suggest attaining a goal activity level of 100 IU/dL[1] for surgical prophylaxis, particularly in major surgery.

Given the need for cranioplasty in the setting of avWS and significantly elevated factor VIII levels, there was concern about the use of traditional plasma-derived vWF concentrates (which all include FVIII in variable proportions) and potential for increased thrombotic risk. Although thrombotic events are rare occurrences in patients with bleeding disorders, the risk in von Willebrand disease (vWD) does seem to be increased compared to that seen in haemophilia.[2] Three of the four vWD patients with thrombotic events within a systematic review whose FVIII level was measured had levels in excess of 200%.[2] Given this, most guidelines recommend the following FVIII levels with replacement therapy and avoiding levels >100%-200%.[1,2] Thus, the decision was made to treat preoperatively with a recombinant vWF (rvWF) which does not contain FVIII (Vonvendi®; Shire, Dublin, Ireland) and may confer a lower risk of thromboembolic sequelae. The rvWF (80 IU/kg) was administered just prior to surgery. Adequate haemostasis was achieved with minimal blood loss. There was concern for an acute bleed due to a drop in haemoglobin on postoperative day 2, so he received an additional dose of 80 IU/kg of rvWF. This was later attributed to dilutional effects of intravenous fluid, and no evidence of bleeding was found by clinical assessment or imaging. The patient recovered well without complication.

Acquired von Willebrand syndrome is a rare entity with bleeding symptomatology similar to those seen in the inherited form of vWD. It is typically characterized by a negative family history, lack of prior bleeding symptoms and older age. It most commonly occurs in patients with lymphoproliferative or myeloproliferative disease (63%), cardiovascular disease (21%), solid tumours (5%) or autoimmune disorders (2%). Within cardiovascular disease, where loss of HMWM is caused by increased shear stress, it has been reported to occur with aortic stenosis, pulmonary stenosis, patent ductus arteriosus, ventricular and atrial septal defects and ventricular assist devices.[3] The Risk of bleeding in patients with cardiopulmonary disorders has been associated with a VWF:RCo/VWF:Ag ratio of <0.7.[4] There are no consistent guidelines for the treatment of aVWS likely due to its rarity. The efficacy of DDAVP is likely to be limited, and patients with cardiovascular disease have been reported to have the worst outcomes with its use with therapeutic responses only seen in 10%.[5] Additionally, DDAVP provided additional obstacles in our patient given the haemostatic challenges inherent to neurosurgery, his young age and risk of hyponatremia, and concern for further elevation of his FVIII.

Another complicating factor in our patient was his baseline elevation in FVIII, likely secondary to a combination of an acute phase reaction to ongoing inflammation, non-O blood type[6] and ethnicity.[7] Elevated plasma levels of FVIII have been associated with a dose-dependent increased thrombotic risk at levels >150 IU/dL.[8] At least one case has been reported of avWS with elevated FVIII (to levels similar to our patient) treated with plasma-derived FVIII/vWF concentrate who went on to develop an embolic stroke.[9] Given his severely elevated levels preoperatively, the use of a plasma-derived FVIII/vWF concentrate was deemed to pose an unacceptable risk in terms of thrombosis. Recombinant vWF, in addition to the advantage of the absence of FVIII, also includes ultralarge and high-molecular weight multimers which are likely to be beneficial in the treatment of avWS. Additionally, most plasma-derived FVIII/VWF concentrates typically have a vWF:RCo/vWF:Ag ratio of <1, as opposed to >1 in rvWF.[10] This is likely to be advantageous in a disease where the vWF:RCo/vWF:Ag ratio is by very definition decreased. This case illustrates an ideal scenario in which rvWF may provide distinct advantages over plasma-derived FVIII/vWF concentrates. This is, to our knowledge, the first report of the use of rvWF in a paediatric patient, as well as the first reported case in avWS, since its approval in 2015. As yet, it has only been approved for on-demand treatment, with prophylactic Phase 3 trials ongoing. Peri-operative treatment in this paediatric patient was efficacious, safe and tolerable. He did not develop any thrombotic complications, and no evidence of antibodies to vWF was observed.

TABLE 1 Laboratory values throughout clinical course

Assay (normal range)	Time							
	At diagnosis	Preop	12 h post 1st dose	30 h post 1st dose	40 h post 1st dose	10 h post 2nd dose	60 h post 2nd dose	9 d post 2nd dose
PTT (22.0-32.0 s)	27.1	21.4	27.7	31.6	41.9	25	25.6	27.3
Factor VIII (50%-150%)	333	514	363	266	309	332	299	411
vWF:RCo (50%-150%)	58	63	136	108	97	194	148	57
vWF:Ag (50%-100%)	178	190	364	218	215	320	221	202
vWF:RCo/vWF:Ag	0.33	0.33	0.37	0.50	0.45	0.61	0.67	0.28
Multimers	Absence or decreased abundance of highest molecular weight multimers, but no definitely increased abundance of lower molecular weight multimers						Absence or decreased abundance of highest molecular weight multimers, but no definitely increased abundance of lower molecular weight multimers	

DISCLOSURES

ACW has served as a consultant for Shire and serves as a co-investigator on a study funded by Shire. RJ has no conflicts to disclose. SWP has served as a consultant for Shire and CSL Behring.

AUTHOR CONTRIBUTIONS

ACW analysed the data and wrote the paper, RJ and SWP analysed the data and performed critical manuscript review and edits.

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