Treatment of von Willebrand disease with FVIII/VWF concentrates

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von Willebrand disease (VWD) is the most frequent inherited bleeding disorder and is the result of a deficiency and/or abnormality of von Willebrand factor (VWF). VWD is a heterogeneous disease and is usually classified into three main types according to quantitative (Type 1 and 3) or qualitative (types 2A, 2B, 2M, and 2N) abnormalities[1].

VWF is synthesised by endothelial cells and megakaryocytes and plays two major functions in haemostasis[2]. First, it is essential for platelet-subendothelium adhesion and platelet-to-platelet interactions as well as platelet aggregation in vessels in which rapid blood flow results in elevated shear stress. Adhesion is promoted by the interaction of a region of the A1 domain of the VWF with glycoprotein Ib (GpIb) on platelet membrane. Furthermore GpIb and VWF are also necessary for platelet-to-platelet cohesion[3]. The interaction between GpIb and VWF can be mimicked in platelet-rich plasma by the addition of the antibiotic ristocetin, which promotes the binding of VWF to GpIb of formalin-fixed platelets (Ristocetin cofactor activity of VWF, VWF:RCo). Aggregation of platelets within the growing haemostatic plug is promoted by the interaction with a second receptor on platelets, the GpIIb/IIIa (or integrin $\alpha_{IIb}\beta_3$) which after activation binds to VWF and fibrinogen, recruiting more platelets into a stable plug. Both these binding activities of VWF are highest in the largest VWF multimers.

Second, VWF is a specific carrier of factor VIII (FVIII) in plasma. VWF protects FVIII from proteolytic degradation, prolonging its half life in circulation and efficiently localising it at the site of vascular injury. Each monomer of VWF has one binding domain, located in the first 272 amino acids of the mature subunit (D' domain) able to bind one FVIII molecule; *in vivo*, however, only 1-2% of available monomers are occupied by FVIII[4]. This explains why high molecular weight multimers are not essential for the carrier function of FVIII, although one would expect that molecules of the highest molecular weight should be more effective in localising FVIII at the site of vascular injury. In any case, the reduction in plasma VWF level observed in VWD is usually associated with a concordant change in FVIII plasma concentration. An interesting exception is present in carriers of null alleles, in whom typically circulating FVIII coagulant (FVIII:C) level is twice than VWF level[5].

In general, in patients with VWD the goal of therapy is to correct the dual defect of haemostasis, the abnormal endothelium-platelet adhesion and platelet-platelet cohesion caused by the deficiency or abnormality of VWF, and the abnormal intrinsic coagulation pathway due to reduced circulating level of FVIII. Most FVIII/VWF concentrates are labelled with their FVIII:C and VWF:RCo content and these tests appear crucial in monitoring the safety and efficacy of replacement therapy in VWD.

It is generally believed that FVIII level is the best predictor of soft tissue or surgical bleeding, while VWF:RCo normalisation, which reflects the correction of VWF platelet-dependent functions, is a reliable indicator of an appropriate treatment of mucosal bleeding. Although these conclusions are mainly based on historical and anecdotal reports, often with ill-defined treatment criteria, clinical experiences still support this general belief. Recently, it has been demonstrated that in type 1 and type 3 VWD carriers the severity of bleeding history correlates with the level of FVIII and VWF in plasma[7,8].

There are two treatments of choice in VWD, i.e. desmopressin and transfusion therapy with plasma-derived FVIII/VWF products. A test-infusion with desmopressin should be given to all patients with clinically relevant VWD and FVIII/VWF≥10 U/dL, especially if elective treatment is planned. However, even patients with VWF levels <10 U/dL associated with increased VWF clearance may benefit from desmopressin[9]. Monitoring of VWF and FVIII:C or bleeding time (and possibly PFA-100), along with

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platelet count at least after 1 and 4 hours, is highly recommended. This prolonged schedule of testing is necessary to unravel patients with increased VWF clearance, who usually have a very large FVIII/VWF increment post-infusion, but with rapid return to baseline after 4 hours. The appreciation of increased clearance pattern may guide therapeutic decision, including time-interval between infusions or requirement of substitutive treatment. Patients with FVIII:C and VWF levels greater than 50 U/dL after desmopressin are the best candidates to desmopressin treatment. These patients are usually those with type 1 VWD.

Transfusion therapy with blood products containing FVIII/VWF is at the moment the treatment of choice in the patients who are unresponsive to desmopressin. Early studies indicated that cryoprecipitate administered every 12-24 hours normalised plasma FVIII levels, shortened the bleeding time and stopped or prevented clinical bleeding in VWD - reviewed in[10]. Based on these observations cryoprecipitate has been the mainstay of VWD therapy for many years. However, virucidal methods cannot be applied to cryoprecipitate, so that this product carries a small but definite risk of transmitting blood-borne infections. Therefore, virus-inactivated concentrates, originally developed for the treatment of haemophilia A, play an important role in the current management of VWD patients unresponsive to desmopressin. Table I summarises the FVIII/VWF concentrates available for VWD treatment in Italy. Many of the intermediate-purity concentrates contain also significant amounts of VWF. However, as estimated by the VWF:RCo/VWF:Ag ratio, the presence of functional VWF may vary among them. Also the ratio of VWF activity to FVIII:C varies, so that significantly different levels of the two moieties are achieved post-infusion. Nowadays, most concentrates are labelled for their FVIII and VWF:RCo content so that adequate replacement treatment can be designed. In fact, if the activity of FVIII is relatively higher than VWF, repeated doses may lead to inappropriate high levels of FVIII that may predispose to venous thrombosis. High levels of post-infusion FVIII:C obtained with repeated infusions have been associated with episodes of deep vein thrombosis in VWD patients receiving repeated infusions of FVIII/VWF concentrates following surgery. Nearly all concentrates appear able to correct FVIII and VWF deficiency, while some, but not all concentrates appear to be effective in shortening the bleeding time (BT). Using VWF concentrates is more cumbersome and offer no practical advantage especially in planned surgery, since with these products FVIII:C increase occurs some hours later and initial supplementation with a separate FVIII concentrate may be necessary, especially in patients with type 3 VWD. Several retrospective and prospective studies have demonstrated a high rate of success in surgery, with a median dose of VWF:RCo/kg ranging from 51-82 IU in studies dosed according to VWF:RCo (Table II). Among the VIII/VWF concentrates actually available, Haemate® P (CSL Behring, Marburg, Germany), a pasteurised plasma-derived concentrate, presents the highest content of VWF activity (2,400 IU VWF:RCo/1,000 IU FVIII:C) and it is characterised by the relatively high proportion of high molecular weight VWF multimers when compared with other commercially available FVIII/VWF concentrates[11,12].

Replacement therapy is still empirical and the declared content of FVIII and VWF should be used as a guideline. The goal of treatment in patients undergoing major surgery is to maintain FVIII plasma levels around 80-100 IU/dL for at least a couple of days and above 50 IU/dL for an additional 5-7 days thereafter. A loading dose of 50 U/kg of VWF is usually given in severe cases 1 hour before surgery, followed by similar daily doses for the next two days. Furthermore, a FVIII increase lasting for up to 24 hours and much higher than predicted is observed because of the stabilising effect of exogenous VWF on endogenous FVIII, which is synthesised at a normal rate in these patients. Since FVIII:C reliably predicts delayed bleeding, daily monitoring of FVIII:C during the first 5-7 days after major surgery is advised. VWF level monitoring is not strictly required. In high-risk surgery, heparin prophylaxis should be considered, especially when high FVIII:C levels are obtained after infusion. Monitoring of BT or PFA-100 and/or VWF function is not strictly required, apart from mucosal bleeding or if bleeding continues despite adequate FVIII levels. A recent study has shown that a safe and efficacious use of an intermediate purity concentrate (Haemate® P) dosing based on pharmacokinetics of VWF:RCo could be obtained in a cohort of 28 patients with various types of VWD undergoing elective surgery[13]. Successful

Table I - FVIII/VWF concentrates available in Italy for VWD treatment.

Product	Purification	Viral inactivation	Specific activity# (U/mg protein)	VWF:RCo/Ag (ratio)	VWF:RCo/ FVIII:C (ratio)	Other proteins
Alphanate (Grifols, Los Angeles, USA)	Affinity chromatography (heparin)	Solvent/detergent + 72 h at 80 °C	>100	0.94	1.21	Albumin +
Fanhdi (Grifols, Barcelona, Spain)	Affinity chromatography (heparin)	Solvent/detergent + 72 h at 80 °C	>100	0.83	1.48	Albumin +
Haemate® P (CSL Behring, Marburg, Germany)	Multiple precipitation	Pasteurisation 10 h at 60 °C	40±6	0.96	2.54	Albumin +
Immunate (Baxter, Wien, Austria)	Ion exchange chromatography	Detergent + vapour heat 10 h at 60 °C, 1 h at 80 °C	100±50	0.47	1.10	Albumin +
Wilfactin (LFB, France)	Aluminium hydroxide gel adsorption ion exchange + Affinity chromatography	Solvent/detergent; dry heat; 72 h at 80 °C; 35 nm nanofiltration	≥50*	0.95	>10	Albumin +

Specific activity measured as FVIII before the addition of albumin as stabiliser.
* Specific activity measured as VWF:RCo.

Table II - Summary of clinical studies reporting the use of FVIII/VWF concentrates for surgery in von Willebrand disease.

Author	Concentrate	Type of surgery	Study	Outcome
Goudemand Haemophilia 1998	LFB-VHP-VWF	Minor 48 pt Major 36 pt	Retrospective	No haemorrhagic complications
Dobrkovska Haemophilia 1998	Humate-P	97 pt	Retrospective	Excellent/good 99%
Lillicrap Thromb Haemost 2002	Humate-P	73 surgical procedures	Prospective	Excellent/good 99%
Federici Haemophilia 2002	Fahndi	14 surgical procedures	Retrospective.	Excellent/good clinical effect in 93%
Mannucci Blood 2002	Alphanate	39 pt, 71 surgical or invasive procedures	Prospective	Good clinical response
Franchini Haematologica 2003	Haemate-P	26 pt, 43 procedures	Retrospective	Excellent/good 98%
Thompson Haemophilia 2004	Humate-P	39 pt, 42 procedures	Prospective	Excellent/good 100%
Michiels Blood Coagul Fibrinolysis 2004	Haemate-P	26 pt	Prospective	Good clinical response
Federici Haematologica 2007	Haemate-P	56 pt, 73 surgical procedures	Retrospective	Excellent/good 97%
Lethagen J Thromb Haemost 2007	Haemate-P	29 pt, 27 surgical procedures	Prospective	Excellent/good 96.3%

haemostasis with a loading dose of 62.4 IU VWF:RCo/kg (app. 32-35 IU FVIII:C/kg) was obtained following the results with a pharmacokinetic profile. For patients undergoing minor surgery or invasive procedures (e.g. dental extractions) a FVIII:C level around 30-50 IU/dL for at least 12-24 hours is required. In some instances (e.g. patients with shortened VWF survival after desmopressin), treatment with VWF/VWF-containing products may be advisable as an adjunctive treatment in high-risk situations. Recombinant FVIII or concentrates obtained by immunoaffinity chromatography (FVIII>2,000 IU/mg) and devoid of VWF should be the preferred choice in type 3 VWD patients with homozygous gene deletions or nonsense mutations, who develop alloantibodies against transfused VWF with the risk of life-threatening anaphylaxis.

Conclusions

FVIII/VWF concentrates are the treatment of choice for patients with type 3 and type 2B von Willebrand disease and severe/intermediate patients who are not responsive to desmopressin. Replacement therapy is also required for patients responsive to desmopressin who are undergoing major surgery, procedures with high bleeding risk, or those in which even minor bleeding should be avoided (e.g. neurosurgery). Furthermore, treatment with FVIII/VWF products should be considered for patients in whom desmopressin may be contraindicated, such as patients with overt cardiovascular disease or very young children (<2 years). Commercially available FVIII/VWF products feature a variable content of FVIII and VWF and a heterogeneous multimer pattern. However, high post-infusion levels of FVIII and VWF are consistently obtained with almost all plasma-derived FVIII/VWF concentrates. Products labelled for VWF content and with a VWF/FVIII ratio ≥1 should be preferred. Several retrospective and prospective studies have demonstrated the efficacy of these products in stopping spontaneous bleeding and in the prevention of bleeding during surgery.

Keywords: von Willebrand disease, von Willebrand factor, inherited bleeding disorders, FVIII/VWF concentrates.

Conflicts of interest disclosure

The Author declares he has no conflicts of interest.

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