Efficacy and safety of factor VIII/von Willebrand factor concentrate (Haemate-P®) in preventing bleeding during surgery or invasive procedures in patients with von Willebrand's disease

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Background and Objectives. To evaluate the efficacy and safety of the factor VIII/von Willebrand factor concentrate Haemate-P® as replacement therapy in patients with von Willebrand's disease (VWD) undergoing surgical or invasive procedures.

Design and Methods. Between January 1996 and October 2002, 26 patients (12 males and 14 females, median age 41.5 years, range 9-80 years), followed at three Italian Hemophilia Centers (Trento, Verona and Parma), with VWD type 1 (19 cases) and VWD type 2B (7 cases), underwent 43 surgical or invasive procedures: major surgery (14 cases), minor surgery (11 cases), dental extractions (11 cases), invasive diagnostic procedures (7 cases). Replacement therapy with factor VIII/von Willebrand factor concentrate (Haemate-P®) was administered in the surgical setting as perioperative prophylaxis against excessive bleeding.

Results. The mean total dose (range) of Haemate-P® used for major surgery was 284.1 IU VWF:RCo/kg (range 125.0-976.4), for minor surgery it was 120.8 IU VWF:RCo/kg (range 42.9-173.3), for dental extractions it was 38.4 IU VWF:RCo/kg (range 23.5-100.0) and for invasive procedures it was 87.3 VWF:RCo/kg (range 27.3-160.0). We recorded one bleeding episode 3 days after multiple dental extractions in a patient with severe periodontal disease; this bleeding was controlled with 2 further administrations of concentrate. We did not observe thrombotic episodes or other side effects following infusion of the concentrate.

Interpretation and Conclusions. In conclusion, Haemate-P® was effective and safe in preventing excessive bleeding after major and minor surgery or invasive procedures in VWD patients.

Key words: factor VIII/von Willebrand factor concentrate, Haemate-P®, surgery, von Willebrand's disease.

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Von Willebrand's disease (VWD), the most frequent hereditary bleeding disorder in humans,[1,2] is characterized by a quantitative (type 1 and 3) or qualitative (type 2) defect of von Willebrand factor (VWF). Although desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), a synthetic analog of vasopressin, is the first choice for the treatment or prevention of bleeding events in most type 1 and some type 2 cases of VWD,[3,4] the remaining patients must be treated with factor VIII (FVIII) concentrates containing VWF.[5-8] Haemate-P® (Aventis Behring GmbH, Marburg, Germany) is one of the most widely used and studied FVIII/VWF concentrates.[9-13] It is a virally inactivated concentrate and has a multimeric pattern similar to that of VWF in normal plasma[14] and a standardized ratio of nearly 2.5 IU ristocetin-cofactor activity (VWF:RCo) to 1 IU FVIII:C.[11] Several trials[12,13,15,16] have documented the hemostatic efficacy of this concentrate, administered either by intermittent bolus injection[12] or by continuous infusion,[15] in VWD patients. The main aim of this study, which retrospectively collects the experience of three Italian hemophilia centers, was to assess the clinical efficacy of Haemate-P® in preventing excessive bleeding after major and minor surgery or invasive procedures in VWD patients.

Design and Methods

Patients

This study is a retrospective collection of clinical data from patients with congenital von Willebrand's disease undergoing surgical or invasive procedures and treated with Haemate-P® in order to prevent excessive bleeding. Between January 1996 and December 2002, 26 patients (12 males and 14 females, median age 41.5 years, range 9-80 years), followed at 3 hemophilia centers in northern Italy (Trento, Verona and Parma), with VWD type 1 (19 cases) and VWD type 2B (7 cases), underwent 43 surgical or invasive procedures. Table 1 reports the baseline characteristics of the patients divided according to the type of VWD. Five out of the 26 patients (19.2%) were responsive to DDAVP therapy. However, factor concentrate replacement was necessary in these patients because of the entity of their surgery. Table 2 lists the type of invasive or surgical intervention performed. Interventions were classified as major surgery, minor surgery, dental extractions and invasive procedures.

All patients were treated with intermittent bolus

Table 1. Baseline characteristics of VWD patients according to VWD types.

Characteristics	*VWD type*	
	Type 1	*Type 2B*
No. of patients	19	7
Sex (M/F)	9/10	3/4
Age (years)	43.7 (17-80)	35.1 (9-58)
FVIII:C (IU/dL)	23.1 (6-78)	56.0 (33-67)
VWF:Ag (IU/dL)	13.4 (0-52)	28.2 (14-76)
VWF:RCo (IU/dL)	14.7 (0-36)	10.1 (4-32)
Bleeding time (min)	14.3 (8-22)	19.4 (9-30)

Results are expressed as mean (range). FVIII:C: factor VIII coagulant activity; VWF:Ag : von Willebrand factor antigen; VWF:RCo: von Willebrand factor: ristocetin cofactor. Normal ranges: FVIII:C: 50-150 IU/dL; VWF:Ag: 60-150 IU/dL; VWF:RCo: 50-150 IU/dL; bleeding time: 2-6 minutes.

Table 2. Description of invasive or surgical interventions included in the study.

Invasive or surgical intervention	*No. of procedures*
Major surgery (n = 14)	
Hysterectomy	1
Adnexectomy	2
Laryngectomy	1
Tympanoplasty	2
Partial colectomy	1
Hip arthroplasty	1
Knee arthroplasty	2
Aorto-femoral bypass graft	1
Reduction of pelvic fracture	1
Disc hernia	1
Excision of acoustic neurinoma	1
Minor surgery (n = 11)	
Perianal fistulectomy	2
Hemorrhoidectomy	2
Appendectomy	2
Removal of tendinous cyst of hand	1
Removal of Bartholin's cyst	1
Drainage of perianal abscess	1
Exeresis of nevus	2
Dental extractions (n = 11)	
Multiple dental extractions	11
Invasive procedures (n = 7)	
Gastroscopy with sclerosis of bleeding duodenal ulcer	2
Angiography for colonic angiodystrophy	1
Amniocentesis at 16 weeks of pregnancy	1
Aortic-arteriography	1
Chemo-embolization for hepatocellular carcinoma	1
Explorative puncture	1
Total	43

injection of factor concentrate during the peri-operative period in order to prevent bleeding. The dosing regimens of Haemate-P® used for the different interventions were those approved by the Italian Association of Hemophilia Centers (AICE).[2] The dosage of Haemate-P® was expressed as VWF:RCo units, which were derived from the analysis of the lots used for the present study (average ratio VWF:RCo/FVIII:C of 2.2). The pre-operative dose was administered 1 hour before the operation; 8 out of the 14 patients undergoing major surgery received an additional concentrate administration after the operation, whereas all the other patients were managed with a single daily infusion. We recorded the levels of von Willebrand factor antigen (VWF:Ag), von Willebrand factor: ristocetin cofactor (VWF:RCo) and factor VIII coagulant activity (FVIII:C) before infusion of the factor concentrate (pre-operative, baseline levels) and 1 hour post-infusion. In patients who underwent major surgery, these coagulation parameters were also monitored once daily, before the factor concentrate infusion, during the post-operative period. The *in vivo* recovery of VWF:RCo activity was determined from peak VWF:RCo levels (1 hour post-infusion) and was expressed as a percentage increase per unit of Haemate-P® per kilogram of body weight (%/IU/Kg). We also documented any bleeding episodes and adverse drug reactions possibly occurring in association with the treatment. Treatment outcome was rated as excellent (achievement of normal hemostasis), good (mildly abnormal hemostasis not requiring additional therapy), or poor (hemostasis less than expected) as a measure of overall efficacy. No patient was treated during the study period with desmopressin, antifibrinolytic agents, other FVIII/VWF concentrates or transfusion therapy (plasma or platelet concentrates).

Laboratory tests

VWF:Ag was measured by a commercial automated enzyme-linked immunosorbent assay on a mini Vidas analyzer (BioMerieux, Mercy L'Etoile, France). VWF:Rco activity was assayed on a Behring Coagulation Timer (BCT, Dade Behring), using proprietary reagents. FVIII:C activity was determined using a one stage clotting assay with the relative

Table 3. Use of Haemate-P® according to type of intervention.

Intervention	*Total dose*		*Pre-operative dose*	*Days of treatment*	*Mean daily dose*
	IU VWF:RCo	*IU VWF:RCo/kg*	*IU VWF:RCo/kg*		*IU VWF:RCo/kg/day*
Major surgery (n = 14)	25692.3 (10000-83000)	284.1 (125.0-976.4)	61.2 (47.5-81.1)	9.7 (5-23)	39.3 (25.0-52.5)
Minor surgery (n = 11)	10457.1 (3000-18500)	120.8 (42.9-173.3)	49.8 (42.9-61.5)	4.2 (2-7)	28.7 (21.4-34.8)
Dental extractions (n = 11)	2500.0 (1500-4500)	38.4 (23.5-100.0)	35.2 (23.5-46.1)	1.6 (1-5)	24.0 (23.5-25.0)
Invasive procedures (n = 7)	6833.3 (1500-12000)	87.3 (27.3-160.0)	43.6 (27.3-53.3)	2.7 (1-5)	32.3 (27.3-37.0)
Total (n = 43)	12791.9 (15000-83000)	183.2 (23.5-976.4)	48.8 (27.3-81.1)	5.7 (1-23)	31.5 (21.4-52.5)

Results are expressed as mean (range).

deficient plasma and Pathromptin SL (micronized silica + calcium chloride solution, Dade Behring) on the BCT.

Statistical analysis

Statistical analysis of the results was carried out using Student's t test, and a p value <0.05 was considered statistically significant.

Results

Table 1 reports the presenting features and laboratory data of the patients, divided according to the type of their VWD. Of the 43 interventions, 14 were classified as major surgery, 11 as minor surgery, 11 as multiple dental extractions and 7 as invasive procedures (Table 2). The mean pre-infusion FVIII:C, VWF:Ag and VWF:RCo levels were 30.0 IU/dL (range 6-78 IU/dL), 17.0 IU/dL (range 0-76 IU/dL), 12.4 IU/dL (range 0-36 IU/dL), respectively. The mean plasma levels of FVIII:C, VWF:Ag and VWF:RCo activity one hour after the pre-operative factor concentrate infusion were, respectively, 112.7 IU/dL (range 62-226 IU/dL), 166.6 IU/dL (range 90-299 IU/dL) and 134.7 UI/dL (range 78-265 IU/dL). The mean *in vivo* incremental recovery of VWF:RCo was 2.0%/IU/kg (range 1.4-2.7%/IU/kg). Table 3 shows the treatment by type of procedure. Overall, the patients undergoing major surgery received higher loading and maintenance doses, more infusions (mean number of infusions, 10.3 vs. 2.9) and were treated for more days than subjects undergoing minor surgery, dental extractions or invasive procedures. The pre-operative post-infusion FVIII:C, VWF:Ag and VWF:RCo levels were directly proportional to the mean pre-operative factor concentrate infusion. Thus, the patients undergoing major surgery demonstrated the highest peaks of FVIII:C, VWF:Ag and vWF:RCo levels after the pre-operative infusion. We did not observe significant differences between patients with type 1 VWD and those with type 2B regarding the mean post-infusion FVIII:C, VWF:Ag, VWF:RCo levels and VWF:RCo recovery or the total dose of factor concentrate infused. Similarly, ABO blood group did not significantly influence any of the parameters reported above. The daily post-operative pre-infusion monitoring of FVIII:C, VWF:Ag and VWF:RCo levels in patients who had undergone major surgery showed mean values constantly above 80 IU/dL (104.2 UI/dL [range 56-185 UI/dL] for FVIII:C, 87.1 UI/dL [range 52-166 UI/dL] for VWF:Ag and 83.4 UI/dL [range 50-140 UI/dL] for VWF:RCo).

Red blood cell transfusions (mean 2.6 units, range 2-5 units) were required in five (11.6%) interventions. All these interventions were major surgery and the average volume of transfused blood was equivalent to that transfused to hemostatically normal people undergoing the same operations.

The administration of Haemate-P® was well tolerated and no adverse drug reactions or thrombotic episodes were observed following concentrate infusion. Prophylaxis was rated as excellent/good in all procedures but one. One patient with VWD type 1 and severe periodontal disease, who underwent multiple dental extractions with a single pre-operative infusion of factor concentrate, developed a hemorrhagic complication 3 days after the dental procedure: the bleeding was successfully controlled with additional administration of concentrate for another 2 days.

Discussion

Nearly twenty percent of patients with von Willebrand's disease are unresponsive to desmopressin and must be treated with plasma-derived

products containing both factor VIII and von Willebrand factor in order to control bleeding episodes or to prevent surgical bleeding.[2] In spite of the fact that von Willebrand's disease is the most prevalent inherited bleeding disorder,[1] relatively few data are available in the literature describing the management of patients with VWD undergoing surgery.[6,7,12,13,16] In this retrospective study we reported the experience of 3 Italian hemophilia centers with the use of high purity FVIII/VWF concentrate Haemate-P® in patients undergoing surgery or invasive procedures. The FVIII/VWF concentrate infusion, at a mean pre-operative dose of 48.8 IU/kg, provided adequate hemostasis during the procedures as documented by the 1 hour post-infusion levels and daily monitoring (for patients undergoing major surgery) of FVIII:C, VWF:RCo and VWF:Ag. Patients undergoing major surgery had higher preoperative levels of these parameters, but had also received higher mean pre-operative and total doses of concentrate and were treated for more days than the other groups of patients. However, all patients reached pre-operative post-infusion levels of the analyzed coagulation parameters that were considered hemostatic for the type of intervention.[3] Moreover, we monitored (after the pre-operative concentrate infusion in all patients and during the post-operative period in patients undergoing major surgery) the levels of VWF:RCo, which is the current standard method for determining VWF activity.[16] We did not record any bleeding episodes in patients undergoing major surgery. The only hemorrhagic complication was documented in a patient who had multiple dental extractions. This episode was attributed to the severe periodontal disease of this patient rather than to the pre-operative dose of factor concentrate, which was adequate to reach hemostatic levels of FVIII:C, VWF:RCo and VWF:Ag. Thus, the replacement therapy with Haemate-P showed a good to excellent clinical efficacy in 98% of cases. The high mean pre-operative dose of factor concentrate used in patients undergoing oral surgery was explained by the fact that all these patients underwent multiple dental extractions. However, the mean total and daily dose, number of infusions and days of treatment were significantly lower than those of the patients undergoing the other procedures. A similar trend was also observed for invasive procedures compared with minor surgery.

Another important feature of our study was that patients were not receiving any other concomitant treatments (e.g. DDAVP, antifibrinolytic amino acids) in association with FVIII/VWF concentrate, so we could evaluate the hemostatic efficacy of Hemate-P® exactly, without the influence of other external factors.

In conclusion, our retrospective analysis confirms the safety and efficacy of Haemate-P® as prophylaxis against bleeding after elective surgery or invasive procedures in VWD patients unresponsive to DDAVP.

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