American Journal of Hematology 70:64–71 (2002)

Acquired von Willebrand Disease—Hemostatic Management of Major Orthopedic Surgery With High-Dose Immunoglobulin, Desmopressin, and Continuous Factor Concentrate Infusion

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Acquired von Willebrand disease (aVWD) is a rare bleeding disorder that mimics congenital VWD in previously healthy individuals; it is most frequently associated with monoclonal gammopathy. Hemostatic therapy of aVWD is challenging due to the extremely shortened half-life of endogenous and exogenous VWF. High-dose intravenous immunoglobulin (ivIG) is recommended as the treatment of choice, usually rapidly normalizing coagulation; but in case of failure, alternative treatment options are not well explored. We report successful major orthopedic surgery in a 61-year-old woman with multiple myeloma IgG lambda and aVWD. IvIG alone failed to correct hemostasis. However, ivIG pretreatment improved the VWF ristocetin cofactor (VWF:RCo) half-life from only 1.5 hr to more than 4 hr, allowing desmopressin infusions twice daily to maintain sufficient VWF:RCo levels. Because of diminishing desmopressin effect, we attempted for the first time in aVWD a continuous VWF/FVIII infusion (Haemate HS®, 2.1–2.7 FVIII U/kg/hr or 51–64 U/kg/day, respectively 4.6–6.0 VWF:RCo U/kg/hr or 110–145 U/kg/day) to reach constant factor levels. The steady-state clearance was 2.4 mL/kg/hr for FVIII:C and 13.5 mL/kg/hr for VWF:RCo. During surgery, VWF:RCo, FVIII:C, and PFA-100 closure time were normalized. Until day 5, VWF:RCo was kept above 50%, from day 6 to 10 at least 30% activity were attained. FVIII:C levels were always >70%. The clinical course was uneventful without bleeding. Two weeks after hip surgery the patient was discharged from the hospital without complaints. The therapy described can be recommended as safe and feasible for further evaluation in aVWD patients who are hyporesponsive to ivIG treatment alone. Continuous VWF/FVIII infusion can improve substitution therapy in aVWD. Am. J. Hematol. 70:64–71, 2002. © 2002 Wiley-Liss, Inc.

Key words: acquired von Willebrand disease; desmopressin; high-dose immunoglobulin; von Willebrand factor; continuous infusion; surgery

INTRODUCTION

Acquired von Willebrand disease (aVWD) is a rare but probably underestimated bleeding disorder that mimics the congenital form of VWD (cVWD) in terms of laboratory findings and clinical presentation [1]. The acquired defect of the von Willebrand factor (VWF) causes an impaired primary hemostasis with prolonged bleeding time and reduced platelet adhesion. Additionally, a coagulopathy with reduced factor VIII procoagulant activity (FVIII:C) develops, because VWF protects FVIII from premature degradation. In contrast to cVWD, patients with aVWD typically show a late onset of bleeding events in life with negative personal and family histories [2]. aVWD is most frequently reported in association with monoclonal gammopathy of undetermined signifi-

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Received for publication 22 June 2001; Accepted 15 November 2001

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.10074

cance, multiple myeloma, Waldenström macroglobulinemia, autoimmune diseases, and myeloproliferative disorders [2]. In most cases of aVWD, the VWF is produced in normal quantity and multimeric composition; however, it prematurely disappears from the circulation [1]. This may be caused by an antibody against VWF, by adsorption of VWF to malignant cells or activated platelets, and by proteolytic or mechanical degradation [1]. The multimeric patterns of VWF most commonly resemble type II A cVWD with decreased proportion of large VWF multimers [2].

In some cases of aVWD the bleeding disorder can be cured by causative treatment of the underlying disease, i.e., surgery, radiation, chemotherapy, or immunosuppression [1]. However, in the majority of patients, therapeutic interventions are restricted to supportive measures aiming to control acute hemorrhage or to prevent bleeding complications. Possible treatment options include desmopressin, factor VIII/VWF concentrates, high-dose intravenous immunoglobulin, corticosteroids, plasma exchange, immunoadsorption [3], and activated factor VII [4].

The symptomatic treatment in aVWD is typically complicated by the extremely shortened half-life of endogenous and exogenous VWF, requiring more frequent administrations and excessive factor concentrate dosages. Furthermore, individual responses to treatment are difficult to predict. Several authors recommend high-dose intravenous immunoglobulin as the treatment of choice for aVWD associated with IgG gammopathy, because they observed a rapid and long-lasting normalization of VWF activities and a delayed clearance of infused VWF [5–9].

Recently, continuous infusion of factor concentrates has been recognized as improvement of therapy in hemophiliacs and patients with cVWD [10,11]. Factor stability and biological activity are preserved [12]. Dose requirements are reduced up to 50% compared with intermittent bolus injections [13–15]. However, experiences with continuous factor VIII/VWF infusion in aVWD have not been reported until now.

Controlled clinical trials investigating different treatment regimens in patients with aVWD undergoing emergency or elective surgery are not available, thus, treatment recommendations have to be based on small patient series, case reports, and personal experiences.

We report herein the successful total hip replacement without bleeding complications in a 61-year-old woman with multiple myeloma and aVWD. Although high-dose intravenous immunoglobulin alone was not sufficient, additional administration of desmopressin and, for the first time in aVWD, subsequent continuous VWF/FVIII concentrate infusion allowed safe major surgery.

CASE HISTORY

A 61-year-old woman was referred to the University Hospital for elective total hip replacement because of progressive pain of the left hip with reduced mobility. The radiologic findings were typical for a severe osteoarthritic destruction of the hip. Ten years ago, a total hip endoprosthesis had already been implanted on the other side because of arthrosis. Histopathological examinations that time had shown a completely normal bone marrow.

Five years ago, the diagnosis of an IgG lambda plasmacytoma with associated acquired von Willebrand disease had been established when the patient presented with a hemorrhagic erysipelas of the right lower leg. Immunofixation electrophoresis of serum proteins showed a monoclonal IgG lambda. Urine samples were negative for paraproteins or free light chains. Bone marrow aspiration revealed a diffuse infiltration by small, mostly multinucleated plasma cells (about 20% of the bone marrow cells). Skeletal X ray showed no osteolytic lesions. According to the criteria of Durie and Salmon the multiple myeloma was classified as stage IA. At that time coagulation assays showed a prolonged Mielke bleeding time (>15 min; reference value, 3–8 min), a reduced factor VIII:C level (48%), and a VWF:RCo activity of 20%. A control bone marrow aspiration, laboratory, and radiologic evaluation prior to hip surgery showed no significant disease progression (see Table I).

TABLE I. Baseline Laboratory Findings (Blood Chemistry and Coagulation)

Parameter	Five years ago	PreOP	Reference value
IgG	16.7	17.4	7–16 g/L
IgA	0.39	0.21	0.7–4.0 g/L
IgM	0.48	0.20	0.4–2.3 g/L
Kappa light chains	0.05	0.25	2.0–4.4 g/L
Lambda light chains	4.10	4.27	1.1–2.4 g/L
Kappa/Lambda ratio	0.12	0.06	1.4–2.7
Total serum protein	79	82	66–83 g/L
Hemoglobin	120	115	120–160 g/L
Platelets	230	350	150–350 g/L
Calcium	2.3	2.36	2.1–2.6 mmol/L
Creatinine	1.0	1.1	0.7–1.1 mg/dL
Quick	91	98	70–100%
APTT	38–39	42–46	28–38 sec
F VIII:C	48	19	70–140%
VWF:RCo	20	9	50–150%
VWF:Ag	n.d.	44	50–160%
CBA	n.d.	0.36	0.8–2.0 ×
Ristocetin-induced platelet aggregation	n.d.	Absent	> 70%
PFA 100 capillary closure time	n.d.	Koll/ADP > 300 Koll/Epi > 300	62–104 sec 82–170 sec

The diagnosis of aVWD was based on the following criteria: (1) presence of an underlying disease commonly associated with aVWD; (2) laboratory evidence for a deficiency or dysfunction of circulating VWF; (3) pathologic VWF multimeric pattern in plasma and normal platelet VWF; (4) negative family history of bleeding; and (5) late onset of bleeding events in the personal history. A tonsillectomy 1950, an endometrial curettage 1978, and the contralateral total hip replacement in 1990 had been uneventful. A history of spontaneous skin or mucosal bleeding and other clinical bleeding signs were denied.

MATERIALS AND METHODS

Blood Sampling and Processing

Blood for the coagulation assays was collected by clean venipuncture from forearm veins in 0.106 M trisodium citrate (blood/citrate 9:1) using the Monovette® system (Sarstedt, Nümbrecht, Germany) and immediately processed. Platelet-poor plasma (PPP) was prepared by centrifugation (10 min at 2,000 *g*, 21°C) and assayed on the same day or stored in small aliquots in polypropylene tubes (Eppendorf Reagiergefäße, Eppendorf, Germany) at −80°C until analysis. Platelet-rich plasma (PRP) for aggregometry studies was obtained by centrifugation for 10 min at 160 *g*, 21°C. For the full blood counts, blood was collected in EDTA tubes (Sarstedt Monovette®).

Coagulation Assays

Prothrombin time (Quick) and APTT were performed using the reagents Innovin® and Actin FS® (Dade Behring, Marburg, Germany), respectively. Thrombin time was measured with BC-Thrombin Reagenz (Dade Behring). Factor VIII procoagulant activity (FVIII:C) was determined in a one-stage clotting assay with FVIII-deficient plasma (Sigma, Deisenhofen, Germany). Von Willebrand factor antigen (VWF:Ag) was measured using the STA LIATEST® VWF microlatex assay (Roche Diagnostics, Mannheim, Germany). These assays were performed on an AMAX 400® analysis system (Amelung, Germany). Ristocetin cofactor activity (VWF:RCo) was determined on a Behring Coagulation System (BCS®, Dade Behring) using a turbidimetric method (von-Willebrand-Reagenz, Dade Behring). Collagen binding activity (CBA) was determined by ELISA (Immunozym® VWF:CBA, Immuno, Austria).

The platelet function analyzer (PFA-100®, Dade Behring) was employed to evaluate platelet function under high shear stress simulating primary hemostasis. Citrated whole blood (0.106 M, 1/10) is aspirated through a capillary and the central aperture of a membrane coated with collagen and either ADP or epinephrine (collagen/ADP and collagen/epinephrine cartridges). A platelet plug forms, ultimately occluding the aperture. The time until blood flow stops is recorded (capillary closure time). This non-invasive test proved to be superior to skin bleeding time for diagnosis of VWD and useful for therapeutic monitoring [16,17].

Von Willebrand factor multimeric patterns in plasma and platelets were analyzed by sodium dodecyl sulfate (SDS) gel electrophoresis based on the method described by Ruggeri and Zimmerman [18]. The von Willebrand protein was electrophoresed overnight in SDS agarose gels of low and intermediate resolution. The multimeric pattern was detected and visualized by western blotting onto nitrocellulose filters and use of the luminol technique (chemiluminescence), which is of similar sensitivity and resolution as autoradiography [19]. Classification of the multimeric pattern was done according to Sadler et al. [20].

Platelet aggregometry was performed on an APACT-2 aggregometer (LAbor, Ahrensburg, Germany) according to the light-transmission principle. Aggregation was induced by ADP (10 μM final concentration), collagen (10 μg/mL), arachidonic acid (1 μM), and ristocetin (1.5 mg/mL, all reagents from DiaMed, Switzerland), and the response was recorded over 10 min.

Inhibitor studies were done by mixing patient and standard human plasma (SHP, Dade Behring, vol/vol 1/4, 1/1, and 4/1). The plasma mixtures as well as patient and standard plasma alone were incubated for 1 hr at 37°C and assayed for FVIII:C and VWF:RCo activity.

Treatment Regimens

Desmopressin (Minirin®, Ferring, Kiel, Germany) was given as an intravenous infusion in 100 mL isotonic saline over 30 min at the standard dose of 0.3 μg/kg body weight (bw). To evaluate the response to desmopressin, blood samples for coagulation assays were taken before the infusion and at least 1, 2, and 6 hr later.

High-dose intravenous immunoglobulin (ivIG, Intraglobin F®, Biotest Pharma, Dreieich, Germany) were initially administered at a daily dose of 1 g/kg bw on three consecutive days. For a second ivIG course, a reduced daily dose of 0.5 g/kg bw for 3 days was used.

Factor VIII/VWF concentrate (Haemate HS®, Aventis Behring, Marburg, Germany) was reconstituted according to the manufacturer's instructions. For continuous intravenous infusion, the stock solu-

tion was diluted with isotonic saline to achieve a final concentration of 20 IU FVIII/mL. The diluted factor concentrate was delivered by an infusion pump (perfusor secura®, B. Braun, Melsungen, Germany) without bacterial filter via a peripheral vein or perioperatively via a central venous line. For the prevention of thrombophlebitis the solution contained a small amount of unfractionated sodium heparin (approximately 4 IU/mL).

During surgery VWF:RCo and FVIII:C were aimed to be 100%. During the first 5 postoperative days the hemostatic therapy was adapted to achieve a VWF:RCo activity of at least 50%. The following days until the 10th postoperative day the minimal VWF:RCo level was aimed to be 30%.

Treatment Monitoring

The hemostatic therapy was monitored by the determination of APTT, FVIII:C, and VWF:RCo at least once daily in the morning. In the perisurgical period the PFA-100® capillary closure time was also measured. Additional plasma samples for the coagulation assays were routinely collected in the afternoon or evening and assayed on the following morning. Daily physical examination, full blood count, and measurement of C-reactive protein were performed in order to control for signs of bleeding or infection.

Hip Surgery and Mobilization

A cemented total hip arthroplasty was implanted (BiContact®, Aesculap, Tuttlingen, Germany). Rehabilitation included daily physiotherapy and the use of crutches for 4 weeks with full weight bearing. To prevent thromboembolism during substitution therapy, a prophylactic anticoagulation with dalteparin (Fragmin P®) 5,000 antiXaU/day subcutaneously was commenced postoperatively without bleeding complications.

RESULTS

Baseline Values and Responses to Hemostatic Treatment

Baseline laboratory findings are displayed in Table I. The results of the coagulation assays were consistent with a VWD. Ristocetin-induced platelet aggregation was absent excluding a platelet-type VWD and VWD IIB. The platelet response to the other tested stimuli was normal. Mixing studies for the detection of plasma inhibitors against VWF:RCo or FVIII:C were negative. The VWF multimeric analysis revealed a loss of the large multimers in plasma similar to type IIA cVWD [20] corresponding with a strongly reduced CBA (17% compared to 0.36×VWF:Ag; reference value, 0.8–2). Platelet VWF content and distribution were normal.

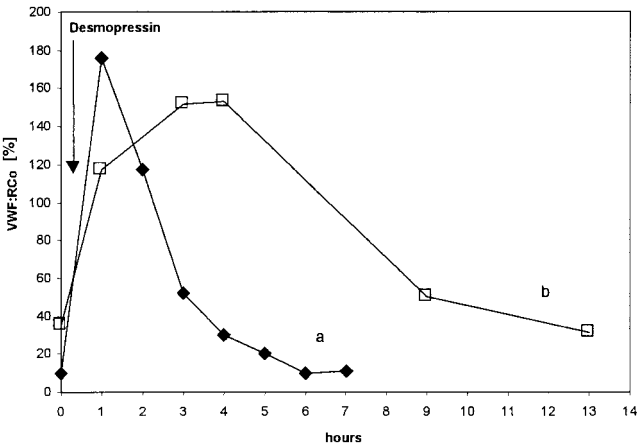

Fig. 1. Time course of ristocetin cofactor activity of von Willebrand factor (VWF:RCo) after intravenous desmopressin (Minirin®) without (curve a) and with high-dose immunoglobulin pretreatment (curve b).

One month before surgery we performed a desmopressin test infusion to evaluate the individual response. Figure 1 (curve a) shows the time course of VWF:RCo activity. Desmopressin caused a steep increase of VWF:RCo from about 10% to almost 180% followed by a rapid decline with an apparent half-life of only about 1.5 hr. After 6 hr VWF:RCo activity had reached the baseline value again.

An initial three-day course of ivIG (1g/kg bw on days 1–3) produced a moderate increase of VWF:RCo and FVIII:C with maximum values on day 6 (VWF:RCo 50%, FVIII:C 93%). Surprisingly, the activities then rapidly decreased again (on day 8: VWF:RCo 22%, FVIII:C 64%), reaching the baseline levels already on day 10 (VWF:RCo 9%, FVIII:C 34%). As this effect was believed not to be sufficient for safe surgery, the hip replacement was postponed.

Ten days after the first course a second pretreatment with high-dose ivIG (reduced daily dose 0.5 g/kg bw) over 3 days was started. The effect on the time course of the VWF:RCo response to desmopressin was studied on the third treatment day, the day of the hip surgery (Fig. 1, curve b). Starting from a moderately increased pre-infusion level (35%), the VWF:RCo activity rose to more than 150% with a seemingly delayed peak compared with desmopressin alone. The PFA-100® capillary closure time was normalized (coll/ADP, 118 sec; coll/epi, 114 sec). The observed delay in the peak values may have been due to the surgical intervention and blood and fluid substitution. However, as can be deduced from Figure 1, the half-life of VWF:RCo was

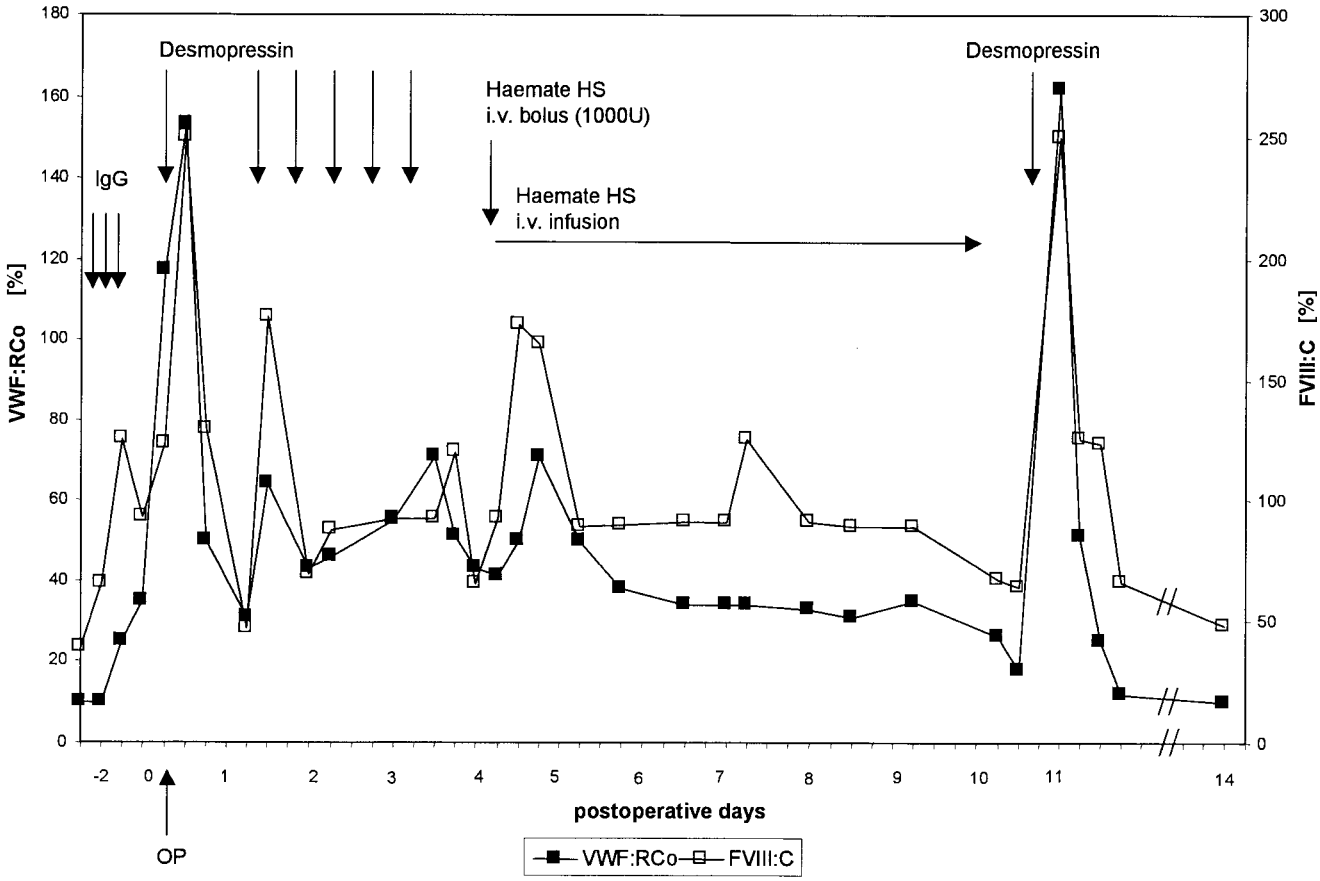

Fig. 2. Time courses of Factor VIII procoagulant activity (FVIII:C, right *y* axis) and ristocetin cofactor activity (VWF:RCo, left *y* axis) during the hospital stay. IgG means administration of high-dose intravenous immunoglobulin prior surgery. The vertical arrows mark the application of single doses of IgG, desmopressin, or Haemate HS® factor concentrate. The horizontal arrow marks continuous infusion.

clearly prolonged to more than 4 hr. After 13 hr the preinfusion level of VWF:RCo (31%) was reached, excluding a further ivIG induced VWF:RCo increase as the reason for the observed half-life.

Figure 2 summarizes the time course of VWF:RCo and FVIII:C levels and the therapeutic measures during the hospital stay. The second ivIG course caused a rise in VWF:RCo (35%) and FVIII:C (93%). Desmopressin was planned to be given twice daily. Erroneously, the first postoperative desmopressin dose in the late evening was omitted. Therefore, on the next morning the VWF:RCo was only 28% (FVIII:C 49%), fortunately without bleeding. The following days, the VWF release response progressively diminished (on day 2 no time course data available) with a maximum VWF:RCo of only 70% on day 4. Therefore, in the evening of day 4 a continuous VWF/FVIII infusion (Haemate HS®) was begun with a bolus of 1000 FVIII units followed by 200 FVIII units/hr (FVIII, 2.7 U/kg/hr; VWF:RCo, 6 U/kg/hr). On days 6–9 an infusion rate of 160 U/hr (FVIII, 2.1 U/kg/hr; VWF:RCo, 4.6 U/kg/hr) resulted in a largely constant VWF:RCo level of about 35% (FVIII:C about 90%). At this time the calculated clearances [clearance = infusion rate (U/kg/hr)/steady state concentration (U/mL)] were 2.4 mL/kg/hr for FVIII:C and 13.5 mL/kg/hr for VWF:RCo. On day 10 the VWF dose requirement tended to increase with falling VWF:RCo level despite constant infusion rate of 160 U/hr. On day 11 another desmopressin infusion was given which revealed a reconstituted VWF:RCo response (162%). The observed half-life of about 2.5 hr was again largely comparable with the initial test infusion result, indicating that the ivIG effect was wearing off. The hemostatic therapy was stopped on day 11 without delayed bleeding events.

Clinical Course

The therapy both with Haemate HS® and with desmopressin was well tolerated without adverse effects. Particularly, the patient did not suffer from thrombophlebitis. During hip surgery no unusual bleeding was noted, and the arthroplasty could be

performed without remarkable events. Due to a preoperatively lowered hemoglobin level (100 g/L) the patient received 3 erythrocyte concentrates during the intervention. For the first postoperative night the patient was monitored on an intensive care unit without bleeding signs. Also on the following days, no blood loss or local hematoma formation was detected, suggesting sufficient hemostasis.

The patient was discharged from the hospital 14 days after hip surgery without complaints. Wound healing was unremarkable. After rehabilitation the patient was able to ambulate without assistance. During the follow-up time of 22 months up to now, the patient presented free from pain and with unlimited walking ability. Radiographically, there have been no signs of loosening (no migration, no radiolucent lines) and no periarticular ossifications.

DISCUSSION

Hemostatic management of patients with aVWD is a challenging clinical problem and differs from hereditary forms of VWD. High-dose ivIG is commonly recommended as the treatment of choice in aVWD associated with monoclonal IgG gammopathies, because it mostly leads to an immediate and dramatic increase of FVIII:C, VWF:Ag, and VWF:RCo (attained activities 100–400%), normalizing coagulation for at least 2 weeks [5–7]. In a comparative pharmacodynamic study, ivIG was found to be the most effective treatment [8]. As outlined before, in our patient the ivIG treatment alone was disappointing. Although we noticed a progressive rise of FVIII:C and VWF:RCo, the response was delayed and only moderate and was regarded as insufficient for safe major surgery. Furthermore, the effect disappeared more rapidly than expected. Nevertheless, ivIG appeared to be a prerequisite to attain sufficient hemostasis. Extending the findings of van Genderen [9], we found that the ivIG pretreatment prolonged the half-life of endogenously released VWF, thus allowing desmopressin infusions twice daily to maintain sufficient VWF:RCo levels.

Desmopressin should be preferred to factor concentrates in VWD because it avoids the risk of viral infections (e.g., hepatitis, HIV) and is cost-saving. In our case, desmopressin saved 4 days of factor concentrate therapy, thereby compensating for the costs of the ivIG.

To our knowledge, we report here for the first time the use of continuous VWF/FVIII concentrate infusion in aVWD. Although continuous infusion has been introduced early in hemophilia and cVWD treatment [21], it has not yet become a standard procedure in substitution therapy. The continuous infusion avoids peak and trough levels leading to substantially reduced dose requirements and to fewer bleeding complications [13–15]. In aVWD this mode of application is of special interest since the short VWF half-life necessitates bolus injections as often as every 3–6 hr. In aVWD, the use of VWF-containing concentrates should be restricted to patients not sufficiently responding to ivIG and after depletion of the desmopressin effect. Our data suggest that the pretreatment with ivIG led to a substantially reduced daily VWF dose requirement. Compared with our earlier experiences in a comparable patient with aVWD, in the present case a dosage of maximal 4,800 FVIII units (10,500 VWF:RCo units) per day was sufficient, corresponding to a dosage reduction of at least 50% (unpublished data). Nevertheless, in our patient the calculated steady-state clearances for FVIII:C and VWF:RCo were 4–5 times higher than reported for cVWD [11]. Ten days after the ivIG course, the effect appeared to wear off since the dose requirement tended to increase.

We used Haemate HS® because it is recommended as the first-choice treatment [22,23]. It contains a high amount of VWF with preserved large VWF multimers showing a multimeric pattern similar to normal plasma capable to normalize bleeding time in cVWD [22,24,25].

The levels of FVIII:C and VWF:RCo in VWD required for secure hemostasis in case of major surgery are still under debate. Also, the optimal treatment duration is not clear. Most guidelines for treatment of cVWD recommend a VWF:RCo activity of at least 50% for the first 3 days or for the total treatment time of 5–10 days [11,22,23]. Others found postoperative FVIII:C levels of $>50\%$ sufficient for hemostasis in cVWD [26].

Since special therapeutic goals for aVWD are lacking, we applied target levels recommended in cVWD. During surgery, normalized VWF:RCo and FVIII:C levels were attained. Subsequently, the VWF:RCo level was kept above 50%. From day 5, a VWF:RCo level of 30–35% appeared sufficient to prevent bleeding. Corresponding FVIII:C levels were always in the normal range. As patients with VWD may suffer from delayed bleedings up to 10 days after surgery, we kept the patient on treatment for this time.

Normalization of skin bleeding time does not seem to be necessary for sufficient perisurgical hemostasis [27,28], and therefore it is not recommended for therapeutic monitoring. The PFA 100® closure time may be a valuable parameter because it is an automated, rapid, and non-invasive test, sensitive for VWF abnormalities and therapeutic interventions [17].

Hip surgery is complicated by deep vein thrombosis in 40–60% of patients in the absence of prophylaxis

and still in 10–15% of patients under low molecular weight heparins [29]. Because hemostatic therapy normalizing coagulation also restores the capability to develop thromboembolism [30], we administered a prophylactic anticoagulation following the high-risk regimen (dalteparin 5,000 antiXa units once daily) in addition to compression stockings.

In conclusion, we report the successful total hip replacement in a patient with aVWD due to multiple myeloma. The patient was hyporesponsive to ivIG treatment alone. But pretreatment with ivIG allowed repeated desmopressin infusions and subsequent continuous VWF/FVIII concentrate infusion to attain sufficient hemostasis. Continuous factor infusion improves substitution therapy in aVWD. The described management is recommended for further evaluation at least in aVWD patients undergoing elective major surgery. Optimal therapeutic target levels for VWF:RCo and FVIII:C as well as treatment duration in patients with aVWD need further investigation.

ACKNOWLEDGMENT

The von Willebrand factor multimeric analysis and determination of collagen binding activity was kindly performed by Prof. Ulrich Budde, Coagulation Laboratory, Hamburg, Germany.

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