Von Willebrand disease

Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: Identifying the need for personalized treatment

H. C. A. M. Hazendonk1 | J. M. Heijdra1 | N. C. B. de Jager2 | H. C. Veerman1 | J. Boender3 | I. van Moort1 | R. A. A. Mathôt2 | K. Meijer4 | B. A. P. Laros-van Gorkom5 | J. Eikenboom6 | K. Fijnvandraat7 | F. W. G. Leebeek3 | M. H. Cnossen1

1Department of Paediatric Haematology, Erasmus University Medical Centre - Sophia Children’s Hospital Rotterdam, Rotterdam, Netherlands
2Hospital Pharmacy - Clinical Pharmacology, Academic Medical Centre Amsterdam, Amsterdam, Netherlands
3Department of Haematology, Erasmus University Medical Centre Rotterdam, Rotterdam, Netherlands
4Department of Haematology, University of Groningen, University Medical Centre Groningen, Groningen, Netherlands
5Department of Haematology, Radboud University Medical Centre, Nijmegen, Netherlands
6Department of Thrombosis and Haemostasis, Leiden University Medical Centre, Leiden, Netherlands
7Department of Paediatric Haematology, Academic Medical Centre Amsterdam, Amsterdam, Netherlands

Introduction: Patients with Von Willebrand disease (VWD) are regularly treated with VWF-containing concentrates in case of acute bleeding, trauma and dental or surgical procedures.

Aim: In this multicentre retrospective study, current perioperative management with a von Willebrand factor (VWF)/Factor VIII (FVIII) concentrate (Haemate® P) in patients with VWD was evaluated.

Patients/Methods: Patients with VWD undergoing minor or major surgery between 2000 and 2015, requiring treatment with a VWF/FVIII concentrate (Haemate® P), were included. Achieved VWF activity (VWF:Act) and FVIII during FVIII-based treatment regimens were compared to predefined target levels in national guidelines.

Results: In total, 103 patients with VWD (148 surgeries) were included: 54 type 1 (73 surgeries), 43 type 2 (67 surgeries) and 6 type 3 (8 surgeries). Overall, treatment resulted in high VWF:Act and FVIII levels, defined as ≥0.20 IU/mL above predefined levels. In patients with type 1 VWD, respectively, 65% and 91% of trough VWF:Act and FVIII levels were higher than target levels. In patients with type 2 and type 3 VWD, respectively, 53% and 57% of trough VWF:Act and 72% and 73% of trough FVIII levels were higher than target level. Furthermore, FVIII accumulation over time was observed, while VWF:Act showed a declining trend, leading to significantly higher levels of FVIII than VWF:Act.

Conclusion: High VWF:Act and accumulation of FVIII were observed after perioperative FVIII-based replacement therapy in patients with VWD, both underlining the necessity of personalization of dosing regimens to optimize perioperative treatment.

Keywords
individualized medicine, surgery, therapy, von Willebrand Disease, von Willebrand factor (MESH entry database)
INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder with an estimated prevalence of approximately 1% with clinically relevant bleeding in 0.01%. It is caused by a quantitative or qualitative defect of von Willebrand factor (VWF) and is characterized by mucocutaneous bleeding and bleeding after trauma or surgery. In more severe VWD, there also may be a concomitant factor VIII (FVIII) deficiency, as VWF prevents FVIII from proteolysis. Generally, patients with VWD are treated with desmopressin (DDAVP) or VWF-containing concentrates when acute bleeding or trauma occurs, or to prevent bleeding in the surgical setting. The aim of treatment is to correct the VWF deficiency, and also to correct a FVIII deficiency, if this is present. In patients who do not respond adequately to DDAVP or have contra-indications for its use, treatment usually consists of combined VWF/FVIII factor concentrates amongst which the ratios of VWF activity (VWF:Act) over FVIII may differ.

Although clinical symptoms are generally milder than in haemophilia, dosing of perioperative treatment in VWD is more challenging due to variation in VWD types and mutations, and interpatient variability of residual endothelial VWF production, VWF secretion and clearance, as well as heterogeneity in type of factor concentrates with different ratios of VWF:Act/FVIII and VWF:Act/VWF antigen (VWF:Ag). Previous studies have, however, reported that surgical procedures can be performed safely in patients with VWD and that treatment with VWF-containing concentrates is efficacious.

In many countries, specific target levels are defined in national guidelines to safeguard haemostasis during surgery. These target values are based on expert opinion and limited observational research (Figure 1). Currently, calculation of the required doses of VWF and/or FVIII is based on body weight. In the Netherlands, dosing is FVIII level-based, due to the fact that FVIII is considered crucial in preventing surgical bleeding by its role in thrombin generation and consolidation of the fibrin plug. However, momentarily VWF levels are increasingly monitored as rapid availability of VWF activity assay results is becoming mainstream. This may facilitate a more VWF-based dosing regimen in the near future. Furthermore, it is increasingly common to label factor concentrates according to both FVIII and VWF content.

VWF/FVIII concentrates can be classified into three different groups according to VWF:Act/FVIII and VWF:Act/VWF:Ag ratios. Firstly, products with a VWF:Act/FVIII ratio of approximately 1 (with low or high VWF:Act/VWF:Ag ratio). Secondly, with a VWF:Act/FVIII ratio of >1 (with high VWF:Act/VWF:Ag ratio) and lastly, VWF concentrates with a VWF:Act/FVIII ratio of >10 (with also high VWF:Act/VWF:Ag ratio). In case the last concentrates are used perioperatively, patients with low circulating FVIII levels should receive this concentrate intravenously 6-8 hours before surgery, to allow endogenous FVIII to rise to haemostatically adequate levels. Therefore, in emergency situations, a priming dose of FVIII in addition to VWF concentrate is often required. Because FVIII production and secretion are normal in patients with VWD, infusion of exogenous VWF, which stabilizes and increases endogenous FVIII levels, together with exogenous FVIII, may lead to very high levels of FVIII (>2.70 IU/mL). This is, of course, a possible risk factor for thrombosis. It has been demonstrated that repetitive dosing of concentrates with a VWF:Act/FVIII ratio >1 will result in less accumulation of FVIII than concentrates with a ratio of approximately 1. Worldwide, the most frequently used VWF/FVIII concentrate is Haemate®, a plasma-derived virus-inactivated VWF/FVIII concentrate with a VWF:RCO/FVIII ratio of 2.45.

Choice of perioperative treatment is dependent on type and severity of VWD, while dosing of replacement therapy is dependent on type and extent of the surgical procedure. In addition, treatment may differ due to interindividual differences in pharmacokinetic (PK) parameters such as clearance and half-life of both exogenous and endogenous VWF and FVIII. Studies report that perioperative VWF/FVIII concentrate consumption indeed varies substantially, from 27 to 146 VWF:Act IU/kg/day. As achieved FVIII and FVIII levels have rarely been evaluated and reported in relation to efficacy, we aimed to evaluate current perioperative management with VWF/FVIII concentrate in patients with VWD in relation to target levels as stated in national guidelines. This was done by assessing the extent to which predefined VWF:Act and FVIII target levels were actually achieved as well as by analysis of predictors of higher or lower VWF:Act and FVIII levels than targeted. Insight in these factors will help realize more efficacious and individualized treatment in VWD. In addition, collection of these data will help construct population PK models for patients with VWD in the near future.

MATERIALS AND METHODS

This multicentre retrospective observational cohort study was conducted in five Academic Haemophilia Treatment Centres in the Netherlands (Erasmus University Medical Centre Rotterdam (n = 51); Academic Medical Centre Amsterdam (n = 15); University Medical Centre Groningen (n = 14); Leiden University Medical Centre (n = 12) and Radboud university medical centre (n = 11). This study was not subject to the Medical Research Involving Human Subjects Act, as retrospective, anonymized data were analyzed and therefore, according to Dutch law, review by the Ethical Committee and informed consent were not required.

Subject selection

Patients with a clinical and laboratory diagnosis of VWD (historically lowest levels of VWF:Ag ≤0.30 IU/mL and/or VWF:Act ≤0.30 IU/mL and/or FVIII ≤0.40 IU/mL) were included. Patients who underwent a minor or major surgical procedure as defined by Koshy et al., under replacement therapy with a plasma-derived VWF/FVIII concentrate between January 1st 2000 and January 1st 2015, were eligible. Only patients treated with Haemate®, the most widely used concentrate for treatment of VWD in the Netherlands, were included. Monitoring of minimally two VWF:Act and FVIII levels was
obligatory for inclusion. Patients with other known haemostatic disorders and patients lacking accurate documentation were excluded.

2.2 | Study objective

The study objective was to evaluate current perioperative management with a specific VWF/FVIII factor concentrate (Haemate® P) in patients with VWD by specification of concentrate administration and analysis of subsequently achieved peak and trough levels of VWF:Act and FVIII in comparison with target VWF and FVIII levels as prescribed by national guidelines (Figure 1). In this study, both potential predictors of low and high levels of VWF:Act and FVIII as well as variables associated with VWF/FVIII concentrate consumption were collected and evaluated.

2.3 | Laboratory assessment

VWF:Act and FVIII were generally monitored daily during hospitalization. Immediately before surgery, peak levels were assessed and in the days after surgery trough levels were measured once or twice daily. In all cases, perioperative dosing was based on FVIII levels, as VWF:Act results were generally not or not rapidly available. FVIII was measured by one-stage clotting assays in all participating centres. In various centres, different VWF activity (VWF:Act) assays were performed according to local protocol.

2.4 | Data collection

Patient, surgical and treatment characteristics during the hospitalization period were collected retrospectively. Patient characteristics included age, body weight, gender, type of VWD, baseline VWF:Ag, VWF:Act and FVIII (historically lowest level), ABO blood group and VWF gene mutation if available. Surgical characteristics consisted of procedure severity as classified by surgical risk score, duration of surgery, perioperative blood loss and postsurgical bleeding complications. Bleeding complications were assessed according to definition by the International Society of Thrombosis and Haemostasis and defined as necessity of second surgical intervention, haemoglobin decrease ≥1.24 mmol/L and/or requiring red blood cell transfusion, or bleeding prolonging patient hospitalization. A clinically relevant bleeding complication was defined as a bleeding complication requiring a second surgical intervention and/or red blood cell transfusion. Treatment characteristics included timing and dosing of VWF/FVIII concentrate administration and achieved VWF:Act and FVIII during and after surgical procedure, mode of infusion (continuous or bolus infusion) of VWF/FVIII concentrate and co-medication with effect on haemostasis (desmopressin, tranexamic acid, low molecular weight heparin, non-steroidal anti-inflammatory drugs) as well as duration of hospitalization. Duration of hospitalization was defined as day of discharge minus day of surgical procedure and initiation of replacement therapy with VWF/FVIII concentrate.

FIGURE 1 Target VWF:Act and FVIII in VWD patients in the perioperative setting. According to National guidelines. Guidelines describe a standard perioperative dosing regimen of patients with VWD undergoing minor or major surgery. A loading dose of VWF/FVIII factor concentrate of 50 IU/kg FVIII (30-50 IU/kg in case of minor surgery) followed by maintenance doses of 15-25 IU/kg FVIII twice daily, depending on FVIII measurements. Both VWF:Act and FVIII are targeted at trough and/or steady-state levels.
2.5 | National guideline and evaluation of perioperative VWF/FVIII concentrate management

National guidelines prescribe a FVIII-based regimen with a loading dose of VWF/FVIII concentrate (ratio of 2.4:1) of 50 IU/kg FVIII for major surgery and 30-50 IU/kg FVIII for minor surgical interventions followed by maintenance doses of 15-25 IU/kg FVIII twice daily with regular monitoring of VWF:Act and FVIII, although no definition of regular monitoring is given. Frequency and timing of monitoring is left to the expertise of the treating physician and depends on VWD type, type and severity of surgery and bleeding phenotype. Dosing is adjusted according to VWF:Act and FVIII target levels specified in guidelines and depicted in Figure 1. In general, patients are treated 7-10 days in case of a major surgical procedure and 4-7 days in case of a minor surgical procedure. This is in accordance with the UKHDCO and Nordic guidelines. Perioperative dosing was left to discretion of treating physician. When patients were prescribed thromboprophylaxis, in the majority of patients low molecular weight heparin was used. Thromboprophylaxis was given at the discretion of the treating physician, taking type of surgery, duration of hospitalization and patient risk factors for thrombosis, such as age, body mass index, history of thrombosis and genetic predisposition for thrombosis into account.

Perioperative management with VWF/FVIII concentrate after first peak values was evaluated by comparing achieved VWF:Act and FVIII trough and steady-state levels to target VWF:Act and FVIII levels. Trough levels were defined as measurements prior to bolus infusion or measurements at least 12 hours after infusion, when no subsequent factor concentrate infusion was given. Redundantly, no peak levels after bolus infusion were included in these analyses. Steady-state samples were defined as VWF and FVIII levels sampled when concentrate substitution is expected to equal elimination of VWF/FVIII concentrate when administered by continuous infusion. In general, it is assumed that steady state will be reached after a loading dose has been administered and continuous infusion has started.

Analysis of predictors of low and high levels of VWF:Act/FVIII could only be performed in patients with type 1 and type 2 VWD, due to limited numbers of patients with type 3 VWD. A stepwise backward and forward logistic regression analysis was performed with low levels defined as VWF:Act or FVIII below predefined target levels stated by guidelines, and high levels as all VWF:Act or FVIII levels above the predefined target level with a deviation of ±0.20 IU/mL. Potential predictors for low and high VWF:Act or FVIII levels in the analysis were severity of surgical procedure, blood group O vs non-O, body weight, age, mode of infusion and treatment centre.

2.6 | Statistical analysis

Descriptive data are presented as numbers with percentages for categorical variables and as medians with an interquartile range (IQR) for continuous variables, as data were not normally distributed. The non-parametric Mann-Whitney U test was used to compare VWF/FVIII concentrate consumption between surgical procedures of different severity. If a patient was subjected to two or more surgeries, calculations were only performed for the first surgical procedure. Potential predictors of lower and higher VWF:Act/FVIII levels than aimed for were analyzed by stepwise backward and forward logistic regression analysis with elimination of variables with P > .10. A linear regression analysis was performed to calculate if FVIII accumulation occurred after repetitive dosing of VWF/FVIII concentrate, whereby regression coefficients were compared between both VWF:Act and FVIII. Data management and statistical analysis were performed with IBM SPSS statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA). A P-value of <.05 was considered statistically significant.

3 | RESULTS

The study population consisted of 103 patients undergoing a total of 148 surgical procedures; 54 patients with type 1 VWD (73 surgical procedures), 43 patients with type 2 VWD undergoing 67 procedures in total: 24 type 2A patients (34 procedures), 7 type 2B patients (8 procedures), 3 type 2N patient (8 procedures) and 9 type 2M patients (17 procedures) and 6 patients with type 3 VWD (8 surgical procedures) (Table 1). Half of patients had blood group O (51%). Median historical lowest measured VWF:Ag level and VWF:Act level were 0.30 and 0.22 IU/mL for patients with type 1 VWD; 0.29 and 0.10 IU/mL for type 2 VWD and 0.05 and <0.10 IU/mL (lower than detection limit) for patients with type 3 VWD. Median historical lowest measured FVIII level was 0.54 IU/mL for type 1, 0.42 IU/mL for type 2 and 0.03 IU/mL for patients with type 3 VWD. Some patients in the study population underwent multiple surgical procedures (Table 1). Procedures were mainly orthopaedic (n = 36; 24%), general (n = 26; 18%) and gynaecological (n = 24; 16%). No differences in number and type of surgical procedures between VWD types were observed. Almost all patients received replacement therapy by bolus infusion (90%). Median duration of hospitalization was 6 days (Table 1). Eleven (29%) and 52 (47%) patients with respectively a minor and major surgical procedure received thromboprophylaxis with low molecular weight heparin. In 51 surgical procedures, patients received tranexamic acid.

3.1 | Actual VWF:Act and FVIII levels compared to predefined target levels

No differences were observed in achieved VWF:Act and FVIII levels between patients with type 1, type 2 and type 3 VWD (Figure 2) after replacement therapy. In all VWD types, most perioperative VWF:Act and FVIII levels were well above predefined target levels. Postoperatively, accumulation of FVIII was observed after repetitive dosing of VWF/FVIII concentrate, resulting in increased FVIII in comparison with VWF:Act (P < .01) (Figure 3). No differences in FVIII accumulation were observed between type 1 and type 2 (data not shown). Thirteen (8%) FVIII trough levels were above 2.70 IU/mL.
In the 54 patients with type 1 VWD, in the first 36 hours after surgery, median trough VWF:Act was 1.48 IU/mL (IQR 1.03-1.87). Eighty-four percent of trough and steady-state levels were above predefined target level, with a median deviation of 0.80 IU/mL (IQR 0.38-1.11). Seventy levels were below target level (median deviation: 0.24 IU/mL [IQR 0.03-0.38]). All these patients underwent a major surgical procedure and received an additional bolus infusion with VWF/FVIII concentrate to correct lower levels. With regard to FVIII, median trough and steady state was 1.46 IU/mL (IQR 1.14-1.82) in this time period. Ninety-two per cent of measured levels were above predefined target level, with a median deviation of 0.70 IU/mL (IQR 0.42-1.07). Only in five patients (9%) FVIII was below the predefined target level. All received additional treatment: in four patients this consisted of VWF/FVIII concentrate and in one patient of intravenous desmopressin. In the period from 36 hours until 72 hours after surgery, all trough and steady-state FVIII levels were above FVIII target level (median FVIII 1.80 IU/mL [IQR 1.35-2.11]).

### TABLE 1 General characteristics of study population

| Patients | Total | Type 1 | Type 2 | Type 3 |
|----------|-------|--------|--------|--------|
| No. of patients | 103 (100) | 54 (100) | 43 (100) | 6 (100) |
| Female gender | 69 (67) | 38 (70) | 27 (63) | 4 (67) |
| Age (years) | 51 [36-62] | 52 [40-61] | 53 [36-66] | 22 [16-33] |
| Height (cm) | 175 [167-180] | 173 [166-179] | 175 [165-183] | 179 [168-180] |
| Body weight (kg) | 77 [65-85] | 79 [68-89] | 75 [62-83] | 74 [65.7-78.5] |
| Body mass index (kg/m²) | 24.9 [22.7-28.1] | 25.4 [23.6-29.1] | 24.2 [21.7-25.7] | 22.5 [21.2-26.2] |
| Blood group O | 51 (50) | 32 (59) | 16 (37) | 3 (50) |
| Baseline VWF/FVIII levels | | | | |
| Antigen (IU/mL) | 0.28 [0.21-0.38] | 0.30 [0.22-0.38] | 0.29 [0.22-0.39] | 0.05 [0.01-0.06] |
| Activity (IU/mL) | 0.14 [0.10-0.25] | 0.22 [0.13-0.30] | 0.10 [0.05-0.15] | 0.10 [0.04-0.10] |
| FVIII (IU/mL) | 0.44 [0.28-0.60] | 0.54 [0.34-0.69] | 0.42 [0.24-0.57] | 0.03 [0.02-0.08] |
| Surgery | | | | |
| No. of surgical procedures | 148 (100) | 73 (100) | 67 (100) | 8 (100) |
| Total number of patients undergoing | | | | |
| 1 procedure | 75 (73) | 41 (76) | 29 (67) | 5 (83) |
| 2 procedures | 16 (15) | 7 (13) | 9 (21) | 0 (0) |
| 3 procedures | 10 (10) | 6 (11) | 3 (7) | 1 (17) |
| ≥4 procedures | 2 (2) | 0 (0) | 2 (5) | 0 (0) |
| Severity of surgical procedure | | | | |
| Minor | 38 (26) | 13 (18) | 18 (27) | 7 (88) |
| Major | 110 (74) | 60 (82) | 49 (73) | 1 (12) |
| Treatment | | | | |
| Duration hospitalization (days) | 6 [4-8] | 6 [4-8] | 6 [3-9] | 7 [3-8] |
| Type of infusion | | | | |
| Bolus infusion | 133 (90) | 64 (88) | 62 (93) | 7 (88) |
| No. of complications | | | | |
| Bleeding | 20 (14) | 12 (16) | 8 (12) | 0 (0) |
| Re-operation | 1 (5) | 0 (0) | 1 (11) | 0 (0) |
| Hemoglobin drop ≥1.24 mmol/L and/or RBCTF | 19 (95) | 12 (100) | 7 (89) | 0 (0) |
| Prolonged hospitalization | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Thrombosis | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

No., number (percentages); Median, [IQR = Inter quartile range 25%-75%]; cm, centimetre; kg, kilogram; kg/m², kilogram per square meter; VWF, von Willebrand factor; IU/mL, international units per millilitre; mmol/L, millimol per litre; RBCTF, red blood cell transfusion.  
24 type 2A, 7 type 2B, 3 type 2N and 9 type 2M patients.  
Historically lowest measured VWF/FVIII levels.  
VWF: Act measurements were lower than the limit of detection 0.10 IU/mL in a number of VWD type 3 patients.
FIGURE 2 Achieved VWF:Act and FVIII in the perioperative period. The red lines indicate predefined target VWF:Act and FVIII according to national guidelines. Preoperative peak VWF:Act and FVIII levels are shown <0 hours. Postoperative trough and steady-state VWF:Act and FVIII measurements are shown after surgery. Start of surgical procedure was defined as t = 0 hours. (A) Achieved VWF:Act and (B) Achieved FVIII levels. No differences in achieved VWF:Act and FVIII are observed between types of VWD.

FIGURE 3 Accumulation of FVIII after repetitive dosing of VWF/FVIII concentrate. Accumulation of FVIII was present after repetitive dosing of VWF/FVIII concentrates, resulting in increased FVIII in comparison with VWF:Act (P < .01) (F = 6.90 DFn = 1, DFd = 209); Haemate® P.
Overall, no differences in achieved VWF:Act and FVIII were observed for minor versus major surgical procedures, blood group non-O versus O, adults versus children and between modes of infusion (data not shown). Moreover, high VWF:Act and FVIII levels (defined as >0.20 IU/mL above target) were predominant as illustrated by the fact that 65% of trough and steady-state VWF:Act levels, and 91% of FVIII values were above target.

In the 43 patients with type 2 and 6 patients with type 3 VWD, 62% and 71% of trough VWF:Act levels were above predefined target level in the first 36 hours after surgery (not significantly different from type 1 VWD). Median VWF:Act in this period was 1.07 IU/mL [IQR 0.68-1.50] and 1.30 IU/mL [IQR 0.82-1.68], respectively. Eighty-six per cent and 89% of trough FVIII were above target in the first 36 hours with a median deviation of 0.40 IU/mL [IQR 0.26-0.85] and 0.47 IU/mL [IQR 0.28-0.71], respectively, for patients with type 2 and type 3 VWD. In addition, all FVIII were above target after 36 hours of hospitalization for both minor and major surgical procedures. High VWF:Act and FVIII (≥0.20 IU/mL) were present in 53% and 57% of VWF:Act and in 72% and 73% of FVIII for patients with type 2 and type 3 VWD, respectively.

### 3.2 | Bleeding complications

Overall, occurrence of bleeding complications was not associated with a low trough VWF:Act and/or low FVIII ($P = .95$ and 0.25 respectively). Exception was one patient, undergoing a craniotomy with excessive blood loss with need for blood cell transfusions and presenting with lower trough VWF:Act (0.40 IU/mL) and FVIII (0.60 IU/mL) levels (Table 2). Clinically relevant bleeding only occurred in 5 (3.4%) surgical procedures, as four surgical procedures required red blood cell transfusion post surgery and only one a second surgical intervention (Table 2). Despite excessive FVIII levels, no thrombotic complications were reported. Of the 18 patients reaching very high (≥2.70 IU/mL) FVIII levels, 61% received thromboprophylaxis with low molecular weight heparin.

### 3.3 | Treatment

Two patients with type 1 VWD received only desmopressin prior to surgery to achieve VWF:Act and FVIII target levels. After surgery, trough VWF:Act and FVIII were 0.56/0.55 and 0.59/0.48 IU/mL, respectively. Consecutively, the treating physician administered VWF/FVIII concentrate on following postoperative days. Four patients with type 1 VWD received desmopressin as well as Haemate®P before start of surgery. In the postoperative period, desmopressin was administered in 7 patients with type 1 VWD and 1 type 2A VWD patient.

In patients with type 1 and type 2 VWD, median loading dose for minor and major surgical procedures did not differ (Figure 4). In patients with type 1 VWD, maintenance dose on day 1 (0-24 hours) after surgery differed between minor and major procedures with a significantly higher dose in cases of minor surgery (33 and 26 IU/kg respectively, $P = .048$). No differences between minor and major
surgical procedures were observed for loading and maintenance doses in type 2 VWD. Loading dose and maintenance doses did not differ between patients with type 1 and type 2 VWD, as median for loading doses was 36 IU/kg [IQR 27-49] and 43 IU/kg [IQR 37-52], \( P = .12 \), and median maintenance doses ranged from 22-27 IU/kg to 21-35 IU/kg. Patients who underwent a minor procedure were generally treated with VWF/FVIII concentrate for a median duration of 48 hours. Median duration of hospitalization for patients undergoing a minor or major surgical procedure did not differ significantly (respectively, 4 [IQR 4-8] versus 6 [IQR 4-8] days, \( P = .88 \)).

### 3.4 Predictors of low and high VWF:Act and FVIII levels

It was only possible to evaluate predictors in patients with type 1 and type 2 VWD, due to a limited number of type 3 patients. This was performed for both VWF:Act and FVIII by both stepwise backward logistic regression analysis as well as stepwise forward logistic regression analysis. In type 1 VWD, in the total postoperative period, only blood group O was predictive of high VWF:Act levels (VWF:Act levels ≥0.20 IU/mL above target) (OR 2.9; 95%CI [1.3-6.6]); not of high FVIII levels. No other predictors were found for low and high VWF:Act and FVIII levels in both patients with type 1 and type 2 VWD.

### 4 DISCUSSION

This study is the largest so far evaluating perioperative management of patients with VWD in a resource-rich country. We present data that underline the complexity of VWF/FVIII concentrate dosing in this patient population, as illustrated by the fact that in patients with type 1 VWD, 65% of trough and steady-state VWF:Act and 91% of FVIII levels were ≥0.20 IU/mL above predefined target thresholds.
levels. In type 2 and type 3 VWD, respectively, 53% and 57% of VWF:Act and 72% and 73% of FVIII were ≥0.20 IU/mL above pre-defined target levels. In contrast to results in perioperative severe and moderate haemophilia A patients, only a small percentage of patients with VWD experienced low levels in the first 36 hours after surgery, as only 16% of VWF:Act levels in patients with type 1 VWD and 38% and 29% of VWF:Act levels in patients with type 2 and 3 VWD, respectively, and only 8%, 14% and 11% of FVIII levels in, respectively, type 1, type 2 and type 3 VWD were below prescribed target level. This is probably due to FVIII-based dosing performed according to the Dutch national guidelines applied in this study. Although both VWF:Act and FVIII were measured perioperatively, VWF:Act was not directly available in most cases and could not be used to monitor perioperative VWF/FVIII concentrate management. In our cohort, prevalence of clinically relevant bleeding complications was low (3.4%) and not associated with achieved VWF:Act and/or FVIII. This is supported by others and confirms that other causal factors for bleeding, counterintuitively, on day 1 (0-24 hours) after surgery, a significantly higher VWF/FVIII concentrate consumption was observed for minor surgical procedures when compared to major surgical procedures. This is probably explained by the fact that patients undergoing a minor surgical procedure received less frequent but higher dosed bolus infusions with a shorter period of time. This finding is supported by a previous study in 29 patients with type 1, 2A, 2M and 3 VWD in which no differences in concentrate consumption between patients undergoing minor or major surgical procedures were observed.

In this perioperative study, accumulation of FVIII was observed after repetitive dosing of VWF/FVIII concentrate, with median FVIII values increasing with time (Figure 3). Increasing FVIII levels, due to concomitant increase in both endogenous and exogenous FVIII, were significantly higher than VWF:Act levels (P < .01). This may be partly explained by findings by Kahlon et al who observed an intraoperative decrease and postoperative increase in VWF and FVIII levels in 30 individuals without a bleeding disorder undergoing surgery. In these healthy individuals, mean VWF:Act and FVIII levels were greater than 1.00 IU/mL at all intra- and postoperative time points. This physiological response to surgery may reflect an increased need of VWF in the perioperative period. Current guidelines are not in line with these physiological responses to surgery, as perioperative target VWF:Act and FVIII levels are >0.80 IU/mL (0-36 hours postoperatively) and >0.30/0.50 IU/mL (36-240 postoperatively) and thus below 1.00 IU/mL.

Although we observed high FVIII levels that confer a possible risk for thrombosis, no thrombo-embolic complications were observed. Previously, Wells et al. demonstrated that FVIII levels above 2.70 IU/mL are associated with a higher risk of thrombosis in nonsurgical patients. In our study, 8% of trough levels of FVIII were above 2.70 IU/mL. Also, observed postoperative VWF:Act and FVIII levels were increased for only a brief period of time and coincide with physiological levels in healthy individuals without a bleeding disorder. Mannucci et al. also reported this scarcity of thrombosis in perioperative VWD patients on replacement therapy. In our study, it must also be taken into account that almost half of patients undergoing a major surgical procedure received thromboprophylaxis with low molecular weight heparin.

As reported, plasma-derived VWF/FVIII concentrate in this study (Haemate P), has a VWF:Act/FVIII ratio of 2.4:1 and contains large amounts of high molecular-weight multimers, which are thought to be the most haemostatically potent multimers. Earlier, in vivo recovery (IVR) studies have demonstrated a median IVR of 2.0 for VWF:Act and FVIII, implying a rise of approximately 0.02 IU/mL in VWF:Act and FVIII for each infused IU/kg for VWF:Act or FVIII. Theoretically, for each infused IU/kg of FVIII an increase in approximately 0.05 IU/mL VWF:Act will be observed (2.4 × 0.02 IU/mL). Currently, it is common practice to apply IVR to dose and monitor replacement therapy. However, dosing based on body weight and IVR does not take interindividual differences in clearance and volume of distribution into account that are associated with half-life of VWF/FVIII concentrates. Personalized perioperative dosing based on IVR deducted from a preoperative PK profile is not possible, as PK profile is not representative for clearance during surgery as shown by Di Paola et al. In this study, only a weak correlation was shown between IVR values of VWF:Act obtained 1 week prior to surgery and IVR values obtained directly after surgery (n = 41; r = .41). Both the
changes of IVR following surgery and differences in half-life between VWD types demonstrate the complexity and importance of development of alternative dosing algorithms to individualize treatment for each patient with VWD. Hypothetically, VWD population PK models will be able to incorporate these differences between VWD types due to: mutational variation, differences in baseline values of endogenous VWF:Act and FVIII, higher FVIII levels with a longer half-life, differences in clearance of endogenous and exogenous VWF:Ag and VWF:Act and differences in composition of administered VWF/FVIII concentrates. Also, other known and unknown modifying factors that influence clearance and volume of distribution in an on-demand perioperative setting can be incorporated. The development of such models will lead to Bayesian adaptive dosing to predict VWF:Act and FVIII and effects of treatment more precisely. In the long run, we believe such an approach will optimize patient care and potentially reduce overall costs of treatment by reduction in the amount of total infused clotting factor concentrate. Therefore, PK-guided dosing forms a promising approach for more efficient and individualized replacement therapy in VWD with considerable clinical and economic impact due to the frequency of this bleeding disorder.

5 | CONCLUSION

Although perioperative replacement therapy in patients with VWD is successful with few bleeding complications, it can be optimized as patients are currently overtreated with accumulation of FVIII as a consequence, fortunately without thrombotic complications. Due to the complexity of treatment in VWD, we hypothesize that population PK models, which incorporate known and unknown modifying factors of clearance and other PK parameters of VWF/FVIII concentrates, may be promising tools for personalization of replacement therapy in all patients with VWD.

ACKNOWLEDGEMENTS

This study is performed as part of the “OPTI-CLOT” and “WIN” studies. The “OPTI-CLOT” study group (Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrate in bleeding disorders), is an international multicentre consortium aiming to implement PK-guided dosing of clotting factor replacement therapy by initiating studies to prove the implications of PK-guided dosing, to construct perioperative and prophylactic PK population models and to evaluate the cost-effectiveness of a PK-guided approach. The “WIN” study group (Von Willebrand disease in the Netherlands study), is a national study aiming to identify phenotypic and genotypic differences in all types of von Willebrand disease. A complete list of the members of the “OPTI-CLOT” and “WIN” study groups is listed in Appendix S1. The authors would specifically like to thank YV. Sanders for aiding in study protocol development.

DISCLOSURES

All authors have completed the Competing Interest form and have no financial or personal relationships that could inappropriately influence the study. With regards to other projects and travel grants: JB has received an unrestricted research grant from CSL Behring. KM has received unrestricted research support from Bayer, Sanquin and Pfizer, speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS and Aspen and consulting fees from UniQure. BL has received unrestricted grants from Shire and CSL Behring. JE has received research funding from CSL Behring and honorarium for educational activity from Roche. KF has received unrestricted research grants for her institution from CSL Behring and Novo Nordisk and performed consultancy for Shire and Novo Nordisk. FL has received unrestricted research grants from CSL Behring and Shire. He is a consultant for Shire, UniQure and Novo Nordisk: fees go to the institution. MC has received unrestricted research grants for investigator-initiated studies on the treatment of VWD from CSL Behring and the Dutch “Innovatiefonds” and has received travel funding from Pfizer, Shire, Bayer, Novo Nordisk, Novartis, Roche and CSL Behring. The remaining authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

MC and HH were responsible for protocol development. HH and HV were responsible for the implementation of the study protocol, data collection and analysis. IM contributed to data collection. HH and HV are the main authors of the paper. JH and MF critically revised the paper. KM, BL, JE, and KF monitored patient inclusion. MC supervised the study, with FL giving critical guidance during the project. All authors substantially contributed to the writing and critically revised the manuscript, with approval of the final draft.

ORCID

J. M. Heijdra http://orcid.org/0000-0003-1069-8097
F. W. G. Leebeek http://orcid.org/0000-0001-5677-1371

REFERENCES

1. Rodeghiero F. Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand’s disease. Blood. 1987;69:454-459.
2. Sadler JE, Budde U, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006;4:2103-2114.
3. Lenting PJ, Pegon JN, Christophe OD, Denis CV. Factor VIII and von Willebrand factor—too sweet for their own good. Haemophilia. 2010;16(suppl 5):194-199.
4. Heijdra JM, Cossen MH, Leebeek FWG. Current and emerging options for the management of inherited von Willebrand disease. Drugs. 2017;77:1531-1547.
5. Sanders YV, Groeneveld D, Meijer K, et al. von Willebrand factor propeptide and the phenotypic classification of von Willebrand disease. Blood. 2015;125:3006-3013.
6. Miesbach W, Berntorp E. Interaction between VWF and FVIII in treating VWD. *Eur J Haematol.* 2015;95:449-454.

7. Lethagen S, Carlson M, Hillarp A. A comparative in vitro evaluation of six von Willebrand factor concentrates. *Haemophilia.* 2004;10:243-249.

8. Franchini M. Surgical prophylaxis in von Willebrand's disease: a difficult balance to manage. *Blood Transfus.* 2008;6(suppl 2):s33-s38.

9. Franchini M, Rossetti G, Tagliabue L, et al. Efficacy and safety of factor VIII/von Willebrand factor (Haemate-P) in preventing bleeding during surgery or invasive procedures in patients with von Willebrand disease. *Haemophilia.* 2003;8(suppl 3):1279-1283.

10. Barg K, Wiewiorski M, Anderson AE, et al. Total ankle replacement in patients with von Willebrand disease: mid-term results of 18 procedures. *Haemophilia.* 2015;21:e389-e401.

11. Zulfikar B, Koc B, Ak G, et al. Surgery in patients with von Willebrand disease. *Blood Coagul Fibrinolysis.* 2016;27:812-816.

12. Di Paola J, Lethagen S, Gill J, et al. Presurgical pharmacokinetic analysis of a von Willebrand factor/factor VIII (VWF/FVIII) concentrate in patients with von Willebrand disease (VWD) who have limited value in dosing for surgery. *Haemophilia.* 2011;17:752-758.

13. Lethagen S, Kyre PC, Castaman G, Haertel S, Mannucci PM, Group HPSS. von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost.* 2007;5:1420-1430.

14. Lethagen S. Haemostatic treatment in connection with surgery in patients with von Willebrand disease. *Haemophilia.* 1999;5(suppl 2):64-67.

15. Gill JC, Shapiro A, Valentino LA, et al. von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand disease. *Haemophilia.* 2011;17:895-905.

16. Mannucci PM, Kyre PA, Schulman S, Di Paola J, Schneppenheim R, Gill JC. Prophylactic efficacy and pharmacokinetically guided dosing of a von Willebrand factor/factor VIII concentrate in adults and children with von Willebrand disease undergoing elective surgery: a pooled and comparative analysis of data from USA and European Union clinical trials. *Blood Transfus.* 2013;11:1-8.

17. Castaman G. Treatment of von Willebrand disease with FVIII/VWF concentrates. *Blood Transfus.* 2011;9(suppl 2):s9-s13.

18. Leebeek FWG, Mauser-Bunschoten EP. Richtlijn Diagnostiek en behandeling van hemofilie en aanverwante hemoostasestoornissen. *Van Zuiden Communications BV.* 2009;1:197.

19. Laffan MA, Lester W, Donnell JS, Will A. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol.* 2014a;167:453-465. Wiley Online Library.

20. Goudemand J, Scharrer I, Berntorp E, et al. Pharmacokinetic studies on Wilfactin, a von Willebrand factor concentrate with a low factor VIII content treated with three virus-inactivation/removal methods. *J Thromb Haemost.* 2005;3:2219-2227.

21. Wells PS, Langlois NJ, Webster MA, Jaffey J, Anderson JA. Elevated factor VIII is a risk factor for idiopathic venous thromboembolism in Canada - is it necessary to define a new upper reference range for factor VIII? *Thromb Haemost.* 2005;93:842-846.

22. Makris M, Colvin B, Gupta V, Shields ML, Smith MP. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand’s disease. *Thromb Haemost.* 2002;88:387-388.

23. Berntorp E, Archey W, Auerwald G, et al. A systematic overview of the first pasteurised VWF/FVIII medicinal product, Haemate P/Humate -P: history and clinical performance. *Eur J Haematol Suppl.* 2008;70:3-35.

24. Windyga J, Dolan G, Altisent C, et al. Practical aspects of factor concentrate use in patients with von Willebrand disease undergoing invasive procedures: a European survey. *Haemophilia.* 2016;22:739-751.

25. Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. *Cooperative Study of Sickle Cell Diseases.* 1995;86:3676-3684.

26. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in surgical patients. *J Thromb Haemost.* 2010;8:202-204.

27. Laffan MA, Lester W, O’Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol.* 2014b;167:453-465.

28. Hillarp A, Landorph A, Andre Holme P, Petrinj P, Lassila R, Onundarson PT. Nordic guidelines for diagnosis and management of von Willebrand disease (VWD). 2012.

29. Hazendonk HC, Lock J, Mathot RA, et al. Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications. *J Thromb Haemost.* 2016;14:468-478.

30. Siboni SM, Biguzzi E, Solimeno LP, et al. Orthopaedic surgery in patients with von Willebrand disease. *Haemophilia.* 2014;20:133-140.

31. Kahlon A, Grabell J, Tuttle A, et al. Quantification of perioperative changes in von Willebrand factor and factor VIII during elective orthopaedic surgery in normal individuals. *Haemophilia.* 2013;19:758-764.

32. Mannucci PM. Venous thromboembolism in von Willebrand disease. *Thromb Haemost.* 2002;88:378-379.

33. Raquet E, Stokschlaeder M, Mueller-Cohrs J, Zollner S, Pragt I, Diekmann C, Utah Big. Utility of a high VWF: FVIII ratio in preventing FVIII accumulation: a study in VWF-deficient mice. *Blood Coagul Fibrinolysis.* 2015;26:515-521.

34. Morfini M. Pharmacokinetics of VWF/VIII concentrates is a very intricate matter. *Haemophilia.* 2011;17:846-848.

35. Gill JC, Ewenstein BM, Thompson AR, Mueller-Velten G, Schwartz BA, Humate P. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VVF:RCO) to measure potency and to guide therapy. *Haemophilia.* 2003;9:688-695.

36. Lillicrap D, Poon MC, Walker I, Xie F, Schwartz BA. Association of Hemophilia Clinic Directors of the United States Expert Panel on von Willebrand disease with factor VIII:VWF (Humate-P) and to guide therapy. *Haemophilia.* 2003;9:688-695.

37. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia.* 2008;14:171-232.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Hazendonk HCAM, Heijdra JM, de Jager NCB, et al. Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: Identifying the need for personalized treatment. *Haemophilia.* 2018;24:460-470. https://doi.org/10.1111/hae.13451