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Quantification of perioperative changes in von Willebrand factor and factor VIII during elective orthopaedic surgery in normal individuals

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Summary

von Willebrand's disease (VWD) patients undergoing major surgery are prophylactically treated to promote haemostasis. There is variability in perioperative clinical practice; however, most guidelines suggest replacing the deficient factor to a level of 1.0 IU mL⁻¹ (or 100%). A review of the literature reveals a paucity of well constructed descriptive data quantifying the changes in coagulation that occur in response to surgical stress. The aim of this study was to quantify the changes in haemostatic variables occurring in response to elective orthopaedic surgery in normal individuals. Eligible subjects >18 years of age undergoing total hip or knee replacement were recruited. Blood samples were drawn at five time points: baseline, preoperatively, 30 min after surgical incision, 30 min postoperatively, postoperative day (POD) 1. Analyses included t-tests and repeated measures ANOVA. Overall 30 patients, 21 women and 9 men, with a mean age of 65 were included in the final analysis. All von Willebrand factor (VWF) variables were seen to significantly decrease intraoperatively and increase postoperatively. VWF multimers showed a statistically significant decrease in high molecular weight multimers intraoperatively and an increase postoperatively. On subgroup analysis, age, gender and anaesthesia type were significantly correlated with changes in VWF parameters. Data presented in the current study establish a physiological baseline for VWF parameters in the normal population and demonstrate mean VWF/factor VIII levels greater than 1.0 IU mL⁻¹ intraoperatively. As such, current management in VWD patients does not appear to mimic the normal physiological response to surgery.

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Author contributions

A. Kahlon and P James wrote the paper, designed and performed the research. J. Grabell and A. Tuttle performed the research. W. Hopman analysed the data. D. Engen contributed to the design of the research study and data collection. D. Lillicrap contributed to the design of the research study.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

Keywords

factor VIII; surgery; von Willebrand factor

Introduction

von Willebrand factor (VWF) is a large multimeric glycoprotein synthesized in endothelial cells and megakaryocytes. Initially, it is synthesized as a 2813 amino acid protein that undergoes extensive post translational processing including dimerization, multimerization and glycosylation. VWF is trafficked through the endoplasmic reticulum and Golgi apparatus, under the direction of the VWF propeptide (VWFpp), into storage granules. VWFpp is then cleaved, but remains non-covalently associated with the mature protein in the storage organelles, which include Weibel-Palade bodies in endothelial cells and in alpha granules in platelets [1].

VWF is released into the circulation in response to vascular injury as ultra-large multimers that are cleaved by the metalloprotease, ADAMTS-13 (a disintegrin-like and metalloprotease with thrombospondin motif-13) to regulate haemostasis. VWF functions in primary haemostasis, facilitating normal platelet adhesion, and in secondary haemostasis by acting as a carrier of factor VIII (FVIII), stabilizing FVIII in the circulation [1].

von Willebrand's disease (VWD) results from quantitative or qualitative abnormalities of VWF. Prevalence estimates are as high as 1% of the population, however, rates of symptomatic disease are closer to 1 in 1000 [2–4]. VWD is phenotypically diverse and is classified into three main types. Type 1 VWD is characterized by a partial quantitative deficiency of functionally intact VWF and accounts for approximately 70–80% of VWD patients. Type 2 VWD is characterized by qualitative defects in VWD and type 3 VWD results from a severe deficiency in VWF. Current therapeutic options for VWD include desmopressin, a synthetic analogue of the antidiuretic hormone vasopressin and transfusional therapies with plasma-derived concentrates containing FVIII and VWF. Desmopressin binds to V2 receptors on vascular endothelial cells resulting in the endogenous release of VWF and FVIII. Use of desmopressin is expected to increase plasma VWF and FVIII levels three to fivefold above basal levels within 30 min of administration. Transfusional therapies aim to exogenously supplement these factors and increase their levels in plasma. Infusions of desmopressin and transfusional therapies may be repeated every 12–24 h and 24 h, respectively, to maintain therapeutic levels of plasma VWF [5,6].

At present, VWD patients undergoing major surgery are prophylactically treated to promote haemostasis. Although a great deal of variability exists in the perioperative management of VWD patients, consensus exists that patients should be treated with the aim to correct the deficient factor to a level of 1.0 IU L^{-1} (or 100%). Recent studies have shown an association between elevated plasma VWF/FVIII levels and an increased tendency towards postoperative thrombotic events in patients undergoing such supplementation [7,8]. Studies have also demonstrated that VWF/FVIII behave as acute phase reactants and plasma VWF/FVIII levels rise under stress conditions, such as surgery and inflammatory states [9–12]. Despite the above-mentioned thrombotic risk, a significant bleeding risk of 2–9% has been

documented in VWD patients undergoing surgery [13]. To further understand how to balance these risks in VWD patients, characterizing the physiological response of VWF and FVIII to surgery in normal individuals would be useful and was the objective of this study.

Methods

Patients

Patients were recruited through the preanaesthetic clinic at the Hotel Dieu Hospital in Kingston, Ontario from March 2009 to April 2009. Inclusion criteria were age >18 years, undergoing total hip arthroplasty (THA) / total knee arthroplasty (TKA). Exclusion criteria were a known bleeding disorder, positive bleeding score as determined by the Condensed MCMDM1-VWD Bleeding Questionnaire [2], hormone replacement therapy and use of oral contraceptive therapy or pregnancy. Consecutive patients were invited to participate in the study. Patients who met the inclusion/exclusion criteria were enrolled in the study. Background information regarding gender, age, comorbid conditions, medications and smoking status were collected from patients or through chart reviews. Informed consent for participation in the study was obtained in accordance with an investigational protocol approved by the Institutional Review Board of the Kingston General Hospital, Kingston, ON, Canada.

Study design

Five blood samples were to be drawn from each patient. These included a sample drawn 1–2 weeks prior to surgery, collected at their preoperative assessment to serve as a baseline (time point 1), a 30 min preoperative sample collected at the same day admitting unit (time point 2), an intraoperative sample drawn 30 min after surgical incision (time point 3), a recovery room (time point 4) and postoperative day 1 sample (time point 5). Nursing staff collected all samples, except the intraoperative sample. The anaesthesiologist collected the intraoperative sample.

Laboratory tests

Blood samples collected were analysed for a complete blood count (CBC), prothrombin time (PT)/ International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), ABO blood group, VWF: Ag, VWF:RCo, FVIII:C and VWF multimers. CBCs were performed on the Sysmex XE-2100 analyzer (Sysmex Corporation, Kobe, Japan) and ABO group by forward and reverse typing. Platelet poor plasma was separated by centrifugation of the citrated blood sample at 3220 g for 10 min. VWF:Ag was measured by the IMUBIND VWF enzyme-linked immunosorbent assay (ELISA) kit according to the procedure supplied by the manufacturer (American Diagnostica, Greenwich, CT, USA). The VWF:RCo was measured by platelet aggregometry using freshly prepared, washed normal platelets. FVIII:C was measured using a one-stage assay. All measurements of VWF:Ag, VWF:RCo, and FVIII:C were made against a non-ABO-matched commercial reference plasma that has been calibrated against the 91–666 or 97–586 World Health Organization (WHO) Plasma Standard [14,15].

VWF multimer profiles were analysed by electrophoresis using a 0.8% stacking and 1.4% separating sodium dodecyl sulphate agarose gel followed by electrotransfer to a PVDF nylon membrane and visualization using antihuman VWF HRP-conjugated antibody (DAKO) and Western Lightening Chemiluminescence Reagent Plus (PerkinElmer LAS, Boston, MA, USA). Multimer films were scanned and saved without image enhancement. Lanes were analysed for migration distance using AlphaEaseFC version 3.1.2 (Alpha Innotech, San Leandro, CA, USA). Low molecular weight (bands 1–5), intermediate molecular weight (bands 6–10) and high molecular weight (>10 bands) multimers were quantified by densitometry [16,17] ADAMTS-13 activity assays were performed by ELISA according to the procedure supplied by the manufacturer (Kainos Laboratories Inc, Tokyo, Japan).

Power and statistical analysis

Power calculations were completed based on previously published data by Zezos *et al.* 10. The study aimed to recruit 50 patients, giving 100% power to detect a difference between the presurgical and intraoperative results, with a precision of 17.2 points, and to allow for subgroup analysis. We aimed to recruit 25 orthopaedic patients, undergoing THA or TKA.

Data collected were entered into an Excel spreadsheet designed for this study and imported into SPSS (IBM SPSS version 19.0 for Windows, 2011; IBM Corporation, Armonk, NY, USA) for statistical analysis. Descriptive statistics included frequencies and percentages for categorical data, and means and standard deviations for continuous data. Data were also plotted to assess the underlying distribution. If the data were not normally distributed, the non-parametric equivalents were used in the place of the parametric tests identified below.

Change in coagulation and VWF parameters over three time points, preoperative, intraoperative, and postoperative was evaluated. Repeated measures analysis of variance (ANOVA) was used to evaluate trends over time for complete data sets. Paired *t*-tests were used to maximize the sample size for patients without complete data sets. Change scores were calculated and used as the basis of independent samples *t*-tests to compare the change in VWF parameters between gender, surgical and age groups. Differences by blood type were assessed using the one-way ANOVA, with post hoc testing to identify the specific between group differences if applicable. Those variables that were close to significant on bivariate testing were evaluated as a group using multivariable linear regression to identify the variable(s) with the strongest association with the changed scores.

Results

Patients

Thirty-eight patients were recruited to participate in the study and 30 patients were included in the final analysis (Fig. 1). Twenty underwent TKA, three underwent bilateral TKA, and seven underwent unilateral THA. The mean age was 65 years (range 33–82) and 21 were women. Additional detail about patient characteristics can be found in Table 1.

Laboratory tests

Of the 30 patients enrolled, 15 had complete data sets (and were analysed by repeated measures ANOVA). All available patient data were analysed using the paired *t*-test to maximize the use of available data. There were no major differences in the trends seen on those with complete data sets and those analysed by paired *t*-test. In terms of the CBCs, an expected upward trend in WBC was observed, concurrent with a downward trend in haemoglobin and platelet count (Fig. 2). Screening tests of coagulation showed an upward trend in INR, which although statistically significant was not clinically significant. No change in aPTT was observed (Fig. 3).

The mean values of VWF:Ag, VWF:RCo and FVIII were 1.35 IU mL⁻¹, 1.33 IU mL⁻¹ and 1.44 IU mL⁻¹, respectively, at time point 1. VWF:Ag, VWF:RCo and FVIII levels were all observed to decrease intraoperatively to 1.15 IU mL⁻¹, 1.03 IU mL⁻¹ and 1.06 IU mL⁻¹, respectively, and then to increase postoperatively to 1.79 IU mL⁻¹, 1.63 IU mL⁻¹ and 1.82 IU mL⁻¹ respectively (Fig. 4). Multimer analysis showed a decrease in high molecular weight multimers intraoperatively (from a mean of 28–21%) with an increase postoperatively (to 35%). Normal patient plasma run on the same gel showed a mean % HMWM level of 22%. Humate P (plasma-derived concentrate of VWF and FVIII used to treat patients with VWD) had a mean %HMWM of 15% loaded at 1.0 IU mL⁻¹ (Fig. 5). ADAMTS-13 levels decreased over the study period from 1.68 U mL⁻¹ at time point 1 to 0.96 U mL⁻¹ at time point 5 (Fig. 4).

Complications

No patients had significant bleeding events and none required intraoperative or postoperative transfusion. All patients in this study received thromboprophylaxis with fondaparinux or low molecular weight heparin (LMWH) and no thrombotic events were documented.

Subgroup analysis

Subgroup analysis was carried out on 23 patients with data available for the preoperative, intraoperative and POD 1 time points. Variables examined were age, gender, blood group O and anaesthesia type. Male gender was associated with a significantly greater rise in VWF:Ag and FVIII ($P = 0.005$ and $P = 0.01$ respectively) postoperatively and trend towards a significantly greater rise in VWF:RCo ($P = 0.12$) postoperatively. Spinal anaesthesia was associated with a greater intraoperative drop in VWF:Ag ($P = 0.02$) whereas older age was associated with a smaller intraoperative drop in VWF:Ag ($P = 0.001$). Blood group was not significantly associated with changes in VWF parameters.

Discussion

The changes noted in the CBC parameters were as expected. The WBC count was noted to increase postoperatively, likely secondary to an inflammatory response. Similar results have been reported by Hughes *et al.*, where leucocytosis was observed post TKA and THA along with leucocyte activation [18]. The intraoperative and postoperative decrease in

haemoglobin and platelet count was likely secondary to blood loss and consumption respectively.

Similarly, changes in the INR and aPTT were also as expected and reflect the presence of a consumptive process. Although the INR did show a statistically significant change over time, it was not clinically significant as the INR remained within the normal range at all five time points. The PTT did not show a statistically significant change and this may be attributed to the smaller sample sizes.

All VWF parameters were noted to decrease intraoperatively and rise postoperatively with a corresponding intraoperative decrease and postoperative increase in %HMWM. The intraoperative decrease in VWF parameters is postulated to have been primarily secondary to a consumptive process with the postoperative rise consistent with an acute phase response well described in previous literature [9–12]. Although recent studies have demonstrated the induction of a dilutional hypercoagulable state with the rapid infusion of intraoperative fluids, it is unlikely that enough intravenous fluids would have been administered at the time of the intraoperative VWF parameter measurements (30 min from the time of the initial surgical incision) to account for the changes seen [19]. Given the timing, the postoperative rise in VWF may well be the result of both a release of the protein from endothelial cell stores and, at time point 5, enhanced de novo synthesis. Significantly, the mean VWF parameters were all seen to remain greater than 1.0 IU mL^{-1} at all times in the perioperative and intraoperative period, including at baseline 1–2 weeks preoperatively. The elevation in baseline values (time point 1) may be a reflection of the age of the cohort and/or patient anxiety in the clinic. Data presented here establish a physiological baseline for VWF parameters in the normal population and demonstrate mean VWF/FVIII levels greater than 1.0 IU mL^{-1} intraoperatively. The goal of current guidelines for surgical prophylaxis is to achieve a therapeutic level of 1.0 IU mL^{-1} VWF:RCo [1] in an attempt to mimic the physiological response of normal individuals and to provide equivalent haemostasis. As such, the current management strategy in VWD patients does not appear to mimic the physiological response to surgery seen in normal individuals.

The perioperative management of VWD poses unique challenges in the management of a significant bleeding risk as well as an increased risk of significant postoperative thromboembolic disease. Previous studies have shown a significant bleeding risk in the VWD population undergoing surgery at mucocutaneous sites and major surgery of 2–9% [13]. In addition, dosing guidelines in these studies varied greatly and in many circumstances exceeded current maximum dosing guidelines, suggesting that a bleeding risk of 2–9% may in fact be an underestimate of the true bleeding risk in the VWD population [20,21]. None of the participants in this study had significant bleeding events and none required perioperative or intraoperative blood transfusions. In addition to the decrease in VWF parameters, the HMWM levels were also noted to decrease intraoperatively to a level of 21%. Although Humate P is noted to have the highest HMWM content of the commercially available replacement therapies, the published content is still noted to be lower than normal patient plasma at 84% of normal plasma [22], and well below the baseline of the patients in this study. As such, one can hypothesize that the intraoperative percentage of HMWM in VWD patients treated prophylactically with replacement therapy

will be lower than that in the current population. In addition, Mannucci *et al.* have shown an increased rate of joint arthroplasty in haemophilia A patients as compared to haemophilia B, suggesting different dynamics of thrombin generation in the two disorders [23]. Hoffman *et al.* have also postulated the important role of thrombin in facilitating wound healing [24]. The ratio of VWF:RCo to FVIII in Humate P is known to be approximately 2.4:1 [25]. Gill *et al.* have studied the use of Humate P for the management of elective surgery in adults and children with von Willebrand disease. This study demonstrated median FVIII levels of 100 IU dL⁻¹ (51–176 IU dL⁻¹), levels remained >90 IU dL⁻¹ until 4 h after infusion, and median FVIII level achieved for the first 3 days post surgery were 102–171 IU dL⁻¹ [25]. Our study demonstrated mean FVIII levels >100 IU dL⁻¹ throughout the perioperative period. The lowest mean FVIII level, 106 IU dL⁻¹, was noted at time point 3 (30 min post surgical incision), suggesting significant intraoperative consumption of FVIII. FVIII was also noted to increase to a mean level of 182 IU dL⁻¹ at time point 5 (POD 1), which is higher than the median levels achieved with Humate P supplementation in the study conducted by Gill *et al.* Monroe *et al.* have demonstrated the role of ongoing haemostasis, with thrombin production, in proper wound healing up to 12 days post injury [26]. The results of this study suggest that current dosing guidelines for Humate P do not achieve the physiological levels of VWF:RCo and HMWM and FVIII seen in normal individuals, which may in part explain the significant perioperative and intraoperative bleeding risk documented in the VWD population.

The increase in VWF parameters postoperatively has been described in literature and corresponds to a postoperative decrease in ADAMTS-13 activity. Interestingly, the postoperative increase in FVIII was noted to be as high as 4.50 IU L⁻¹ on POD 1. Wells *et al.* have shown that a FVIII level >2.30 IU L⁻¹ is independently correlated with an increased risk of thrombosis in the Canadian population [27]. Studies have also documented cases of venous thromboembolism (VTE) in the VWD population and have described the development of VTE in patients supplemented with replacement therapy with FVIII levels in the normal as well as the supra-therapeutic range [8]. A recent study by Coppola *et al.*, described the increased risk of VTE in VWD patients as compared to haemophilia patients undergoing supplementation with replacement therapy for surgery and bleeding events. All major VTE were noted to occur in the VWD patients with thrombophlebitis representing all episodes of thrombosis in haemophilia patients. The authors speculated that elevated FVIII levels, due to increased endogenous production combined with external supplementation and increased half-life of FVIII in VWD patients compared with haemophilia patients, accounted for the increased risk seen in VWD patients and argued for the accurate monitoring of FVIII levels and the consideration for thromboprophylaxis [28]. As this study was conducted in a normal population, all patients received VTE prophylaxis starting POD 1 with LMWH or fondaparinux. None of the study participants developed a VTE confirmed by imaging. In addition, HMWM, known to be thrombogenic in the arterial circulation, were noted to increase to 35% on POD 1. It is not clear whether continued replacement in the postoperative period in the VWD patient population, in addition to an endogenous response in the type 1 and type 2 VWD population, results in a relative increase in HMWM postoperatively, placing these patients at further increased risk of thromboembolism. Subgroup analysis revealed a great deal of interindividual variability with male gender and younger patients demonstrating a greater postoperative rise in FVIII and VWF:RCo levels

and baseline values being the most important predictor of post-operative levels. This suggests the possibility of defining subpopulations at increased risk of thromboembolism and developing risk stratified thromboprophylaxis strategies.

This study serves largely as a hypothesis generating study and strongly suggests the need to further study the change in haemostatic variables in response to surgery in the VWD population supplemented according to current guidelines in a design similar to this study. Such a study would clarify the bleeding risk in VWD patients treated according to current guidelines as well as provide important information regarding the perioperative changes in HMWM and FVIII levels to further characterize the thromboembolic risk in this population. This data will likely provide a rational basis for the generation of guidelines for thromboprophylaxis in this patient population.

In conclusion, data presented in this current study establish a physiological baseline for VWF parameters in the normal population and demonstrate mean VWF/FVIII levels greater than 1.0 IU mL⁻¹ intraoperatively. As such, current management in VWD patients does not appear to mimic the normal physiological response to surgery. This study provides a strong rationale to better define the baseline response of coagulation parameters in VWD patients undergoing orthopaedic surgery as well as defining the bleeding and thrombotic risk in this population.

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Fig. 1.
Flow of patients through study.

For all $P < 0.001$, $n = 20$

Fig. 2.
CBC parameters.

$P < 0.001, n = 18$

$P = 0.44, n = 12$

Fig. 3.
INR and PTT.

Fig. 4.
VWF parameters, HMWM and ADAMTS-13 Levels, $n = 30$.

Fig. 5.
VWF multimers.

Table 1

Patient characteristics.

Patient characteristics
Age (years)
Mean – 65 (33–82)
30–50 – 4
51–70 – 14
71–90 – 12
Race
Caucasian – 28
Native American – 1
East Indian – 1
Gender
Male – 9
Female – 21
Blood group
Other – 18
O – 12
Anaesthesia type
General – 8
Spinal – 22