

# Preoperative Detection of Low Von Willebrand Factor Activity and Operative Blood Loss in Pediatric Scoliosis Patients Undergoing Posterior Spinal Fusion

## Abstract

**Purpose:** Patients with von Willebrand disease (VWD), typically have von Willebrand Ristocetin cofactor activity (VWF: RCo) levels  $\leq 30\%$ . Patients with marginal levels 30-70 % don't receive replacement therapy unless there is a bleeding history. Our program screens for VWF: RCo activity in advance of posterior spinal fusion (PSF) surgery. We hypothesized all patients with levels  $< 70\%$  are at higher bleeding risk when undergoing scoliosis repair.

**Design:** this is a retrospective review of prospectively gathered data from a dedicated patient blood management program database.

**Methods:** 169 scoliosis patients with preoperative VWF: RCo  $> 70\%$  were initially matched to 59 patients with activity  $\leq 70\%$ . Stratification was done at VWF: RCo levels  $> 70\%$ , 61-70%, 51-60% and  $\leq 50\%$ , to examine blood loss. Matching was done by scoliosis type (idiopathic, neuromuscular, others), and operative difficulty. Both logistic regression and multivariate regression were used to examine the various levels.

**Results:** Patients with VWF: RCo  $> 70\%$  compared to those with  $\leq 70\%$  had similar demographics, blood loss, and transfusion rates. On stratification, blood loss/segment fused with VWF: RCo levels  $\leq 50\%$  was significant compared to other levels; 51-60%, 61-70% or  $> 70\%$ ,  $p = 0.044$ . Multivariate regression revealed compared to other levels, those patients with VWF: RCo levels  $\leq 60\%$  were most likely to have higher blood loss even on controlling for potential confounders ( $p < 0.005$ ). Sixteen patients with levels  $< 50\%$  had significant bleeding despite factor replacement in 15.

**Conclusion:** Layered multivariate analysis showed that patients with VWF: RCo levels  $\leq 60\%$  carried higher risk of operative bleeding/ level fused. Prospective therapeutic studies are much needed.

**Keywords:** Von Willebrand factor; Ristocetin cofactor; pediatric scoliosis; Spinal fusion; Operative blood loss

## Research Article

Volume 6 Issue 1 - 2017

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**Received:** October 27, 2016 | **Published:** January 16, 2017

**Abbreviations:** VWF: Von Willebrand Factor; VWD: Von Willebrand Disease; PSF: Posterior Spinal Fusion; PRBCs: Packed Red Blood Cells; ANOVA: Analysis of Variance

## Introduction

Von Willebrand Factor (VWF) plays a critical dual role in primary hemostasis (platelet adhesion and plug formation), by binding to receptors on both platelets and endothelial cells, forming a vascular plug which serves as an adhesive bridge between the platelets and damaged sub endothelium at the site of vascular injury [1,2]. Von Willebrand disease (VWD), the most common inherited bleeding disorder, exhibits a heterogeneous inheritance pattern and phenotypic manifestations that starts in childhood with a subtle bleeding history [3-5].

## Measurement of VWF

RColevel is essential to diagnosing and treating VWD [2,6]. Patients with VWF: RCo  $< 30\%$  are generally considered to have VWD. It is recommended that in such patients VWF: RCo levels should be raised to  $100\%$  prior to any major surgery [6]. Yet, there are pediatric patients with marginally low levels that have the same bleeding tendencies without an established history of bleeding and don't meet the criteria for perioperative therapy. However, the perioperative management of patients with VWF: RCo of  $> 30\%$ , and mild bleeding history is not well defined.

Posterior spinal fusion (PSF), a procedure performed to correct spinal deformities such as scoliosis and kyphosis can be associated with profound blood loss. Surgical correction is

dependent on factors such as neuromuscular scoliosis, number of levels fused, degree of curvature, and duration of surgery and hypothermia which can be predictive of increased operative blood loss [7-9]. One previous study indicated that patients with patients with levels <70 were prone to higher blood losses while undergoing PSF [10]. Scoliosis is managed by a team that often includes a blood management protocol (see Appendix 1) [10,11]. This includes preoperative measurement of VW antigen, VWF: RCo and hematology referral for those with borderline low activity levels *circa* 30 % or if the preoperative data was suggestive of a bleeding tendency. This is important because therapy exists for patients with VWD as a human VWF concentrate (Humate-P®) is available for patients with increased risk of bleeding.

Currently in patients with a diagnosis of VMD, it's recommended that VWF: RCo levels <30 be elevated to 100% prior to surgery. Thus it becomes important to understand the bleeding risk for patients with levels 30-100% [6]. We hypothesized that patient with VWF: RCo levels <70 will have significant bleeding when undergoing posterior spinal fusion. To accomplish this we first compared perioperative blood loss in those with levels ≤70% to matched controls of those with >70%. Then we examined perioperative blood loss relative to stratified VWF: RCo levels in order to tentatively establish a threshold that could potentially predict bleeding risk while controlling for the complexity of the procedures.

## Materials and Methods

IRB approval was obtained prior to conducting this study. This is a retrospective case controlled examination of prospectively collected data on pediatric scoliosis patients who had undergone PSF surgery at our institution from September 2007 to February 2012.

### Inclusion criteria

Included in the study were patients with a diagnosis of scoliosis (idiopathic, neuromuscular and other types) with or without kyphosis, who had undergone only posterior spinal fusion, received full preoperative evaluation inclusive of VWF: RCo measurement, and had surgeries performed by the same two fellowship trained pediatric spine surgeons operating simultaneously.

### Exclusion criteria

Patients with a diagnosis of isolated kyphosis, single surgeon procedures, combined anterior/posterior spinal fusion, or growing rods (VEPTR) placement were excluded. Also excluded were patients without pre-operative VWF: RCo testing, those with a history of thrombophilia or underlying abnormality in other coagulation studies.

### Study design and matching

Previous reports from Hassan et al. [10] and our institutional reference range of 58-150 % for VWF: RCo. All patients in the database with VWF: RCo ≤70% were identified. Those who fulfilled the inclusion criteria, were matched to patients with activity levels >70%. These patients were matched by type of scoliosis (idiopathic, neuromuscular, and other types), and maximum Cobb

angles range (≤50, 51-≤80, and >80 degrees groups), while blood loss was corrected for the number of spinal segments repaired. We first examined if there was a difference in bleeding between <70 % and > 70 %. Then further stratification of VWF: RCo levels was done to determine if a relationship existed between lower levels of VWF: RCo and the primary endpoints (VWF: RCo levels ≤50%, 51-60%, 61-70, and >70 %). Among the 59 patients with reduced VWF: RCo, 16 received VWF concentrate (comparisons done to 71 matched controls), and 43 did not (comparisons done to 98 matched controls).

The primary end point was blood loss per segment fused, while the secondary end point was the need for packed red blood cells (PRBCs) transfusions. Blood loss estimate was carefully estimated from what is in the cell saver dishes, canisters and soaked sponges count. This is done by the anesthesiologist and the theatre staff. We have a dedicated team of anesthesiologist that only work with the orthopedic surgical team. This arrangement makes it so that any bias is equally distributed between the study and control groups.

### Data collected

Patient demographics, pre-operative laboratory values, number of segments fused, intra and postoperative blood loss, transfusion requirements, VWF administration, ICU and hospital stay. Family and personal history suggestive of bleeding or clotting tendencies were gathered with a screening questionnaire on the blood management protocol administered by physicians or the blood management coordinator during the preoperative evaluation (Appendix 1). A family or patient history of bleeding was considered positive if there was a "yes" marked in the questionnaire. A surgical history of bleeding was considered positive if bleeding during any previous surgical procedure was more than anticipated.

### Dosing and mode of administration of the human VWF concentrate (Humate-P®)

Patients suspected of having VWD or have marginally low serum VWF: RCo were evaluated by a pediatric hematologist. The Ristocetin cofactor is generally the most sensitive screen for decreased von Willebrand activity. Once these were determined to be abnormal then further testing was done for serum VWF antigen, Factor VIII activity level and VW multimer analysis. Humate P® is a virally inactivated FVIII/VWF concentrate that has a multimeric pattern similar to that of VWF antigen in normal plasma, and a standardized ratio of nearly 1:2.5 IU of FVIII: VWF activity respectively. This has been approved for hemophilia A, and more recently for VWD by the Food and Drug Administration as therapy [6]. Recommendation for VWF replacement, either pre-, peri- or post-operatively were at the discretion of the treating hematologist taking into consideration family history, personal bleeding history and laboratory evaluations for VWD where applicable. If recommended, VWF 50 IU/kg was administered intravenously 30 minutes prior to surgery. Postoperatively, VWF: RCo determination and/or additional doses of VWF administered at the discretion of the hematology service. The cost of Humate P® administration was acquired from the pharmacy and presented in the result section.

The majority of patients in our study also received an antifibrinolytic agent infusion intraoperatively with similar frequency of receiving either epsilon aminocaproic acid (Amicar®, Hospira, Lake Forest, IL) or tranexamic acid (Cyklokapron®, Pfizer, Kalamazoo, MI).

### Statistical analysis

Data are presented as means and standard deviations, and quantitative data were compared using the student t-test and the Fisher's exact test or chi-square test for comparison of incidences. Analysis of variance (ANOVA) test was used to compare the multiple patients' subgroups

First a simple model of logistic regression analysis was performed to examine correlation of VWF: RCo with total blood loss, and blood loss per fused segment. A multivariate logistic regression analysis was used to see if there were differences in key variables when comparing those with Ristocetin levels >70 vs ≤ 70 (the dependent variable). The independent variables were: maximum Cobb angle, number of vertebral segments fused, intra operative blood loss per segment, height, sex, weight, and number of levels of osteotomy. In all three separate multivariate logistic regression models were run changing the dependent variable to be VWF: RCo ≤ 50 or >50 for the first, next VWF: RCo ≤ 60 or >60 and finally VWF: RCo ≤ 70 or >70.

### Results

#### Patient characteristics

Two hundred fifty-one patients underwent PSF during the study period from Sept. 2007 to Feb. 2012. 11 patients did not have the required preoperative testing data, and five patients had clotting tendencies and were excluded from the study. The remaining patients (235) had all preoperative tests performed and blood loss data available. Fifty-nine of them (16.9%) had a VWF: RCo less than 70% and represented the study group while the matching 169 controls were selected from the remainder of the 235 patients. Patients with VWF: RCo ≤70 % (n=59) were compared to matched controls with VWF: RCo>70% (n=169). Both groups had similar distribution of the type of scoliosis. Cobb angles were categorized according to (≤50, 51-≤80, and >80 degrees groups). Distribution within these categories in the study group was 10 (16.9%), 42 (71.2%), and 7 (11.9%) respectively, while in the control group it was 22 (13.1%), 126 (74.5%), and 21(12.4%) respectively, p= 0.730. Both groups also were comparable with regards to age, sex, weight, and height. There was no statistical difference noted in number of osteotomies, PICU stay, hospital stay total stay, nor blood loss per segment fused (102 ± 114 ml in patients with VWF: RCo ≤ 70% compared to 88 ± 54 ml in those with VWF: RCo > 70%, p-value <0.218) (Table 1).

#### Further stratification by VWF: RCo levels

In order to delineate if lower levels of VWF: RCo conferred a higher bleeding risk, patients with activity ≤70% were further subdivided and compared to those with VWF: RCo>70%. Types of scoliosis were similarly distributed. Blood types O and A was more prevalent in lower VWF: RCo groups however several

missing data points weaken such conclusion. Compared to other subgroups, the group with VWF: RCo ≤50% had significantly higher incidence of personal (medical or surgical), or family history of bleeding such as frequent bruising, epistaxis, or heavy menses (9 of 16, 56 %, p=0.0001), while surgical bleeding was more frequent in all subgroups with VWF: RCo ≤70%. Fifteen of the sixteen (94%) patients with VWF: RCo ≤50% received VWF replacement intraoperatively and postoperatively (Table 2).

**Table 1:** Characteristics of Study (VWF: RCo ≤70%) and Control (VWF: RCo >70%) groups.

Characteristics	VWF: RCo Groups		p value (t-test)
	≤70% N = 59	>70% N = 169	
Average Age (years, mean)	14.5 ± 4	14.0 ± 4.3	0.145
Average Weight (kg, mean)	51.8 ± 17.6	51.23 ± 18.6	0.836
Average Height (cm, mean)	146.1 ± 31.5	150.2 ± 22.7	0.272
Gender (females)	42	114	0.629*
Type of Scoliosis			0.885**
Idiopathic	38 (64.4%)	99 (58.6%)	
Neuromuscular	15 (25.4%)	50 (29.5%)	
Others	6 (10.2%)	20 (11.9%)	
VWF: RCo % (mean)	56 ± 0.6	104 ± 29.9	0.000*
Max Cobb Angle (mean)	62 ± 16.7	63.25 ± 15.06	0.462
Number of Segments Fused	10.03 ± 4.02	10.40 ± 3.74	0.687
Number of Osteotomies	4.27 ± 4.71	4.97 ± 4.38	0.303
PICU Stay (days)	1.8 ± 1.4	1.7 ± 1.2	0.515
Hospital Stay (days)	5.2 ± 1.8	5.5 ± 2.1	0.855
Blood Loss ml/Segment Fused	102.85 ± 114.4	88.83 ± 54.4	0.218

\*Fisher; \*\*Chi Square test; VWF: RCo: von Willebrand: Ristocetin cofactor activity

#### Blood loss during and after surgery in subgroups according to VWF RCo

Patients with VWF: RCo ≤50% (6.8% of the population) had the most intraoperative bleeding (1265 ± 925 ml), compared to 717 ± 678ml in patients with VWF: RCo 51- 60%, 787 ± 718 ml in patients with VWF: RCo 61-70%, and 777 ± 487ml in those with VWF: RCo> 70% (p = 0.012). This was significant even when the blood loss was standardized according to the number of vertebral segments fused (p = 0.044). Total hospital stay blood loss showed statistical significance (p = 0.021), but the significance was lost when standardized by segments fused (p = 0.057) (Table 3).

**Table 2:** Characteristics of Patients' Subgroups.

Characteristics	VWF: RCo Subgroups				
	≤ 50% (n = 16)	51-60% (n = 18)	61-70% (n = 25)	Controls >70% (n = 169)	Pearson's Chi <sup>2</sup> (p value)
Type 1 von Willebrand Profile * (%)	15 (94%)	17 (94%)	22 (85%)	0	0.765
Type of Scoliosis					
Idiopathic	7	14	17	99	0.405
Neuromuscular	8	2	5	50	
Others	1	2	3	20	
Blood Type					
A	4	3	5	32	0.001
AB	0	0	0	2	
B	0	2	1	8	
O	12	17	13**	47***	
Family History of Bleeding	4 (25%)	2 (11%)	3 (12%)	1 (0.6%)	0.000
Medical History of Bleeding	5 (31%)	2 (8%)	0	0	0.000
Surgical History of Bleeding	2(12.5%)	2 (11.1%)	2 (8%)	0 (0%)	0.000
Received Antifibrinolytic Therapy****	15 (94%)	16 (88%)	21 (84%)	148 (87%)	0.335
Received VWF	15 (94%)	1 (5.5%)	0 (0%)	0(0%)	0.000

\*VW activity: antigen ratio > 0.7; \*\* Missing 6 data points; \*\*\*Missing 75 data points; \*\*\*\*Antifibrinolytic therapy is either tranexamic acid or aminocaproic acid

**Table 3:** Comparing patients in VWF: RCo activity subgroups.

VWF: Rco Activity % Subgroup (N)	Number Received VWF	Max Cobb Angle (Degrees)	Intra-Op Blood Loss/Segment	Total Stay Blood Loss	Total Stay Blood Loss/ Segment	Patients Transfused N (%)	PICU LOS (Days)	Hospital LOS (Days)
≤50% (16)	15	65 ± 12	119 ± 133	1452 ± 1179	137 ± 171	6 (37.5%)	2.1 ± 1.5	5.4 ± 2.03
51-60% (18)	1	56 ± 11	81 ± 60	850 ± 805	89 ± 66	5 (28%)	2.1 ± 1.9	5.5 ± 2.18
61-70% (25)	0	61 ± 16	72 ± 44	935 ± 860	86 ± 58	2 (9%)	1.5 ± 1.1	5.1 ± 1.2
>70%(169)	0	63 ± 15	78 ± 47	881 ± 598	88 ± 53	37 (22%)	1.72 ± 1.2	5.1 ± 1.9
p value (ANOVA)		0.313	0.044	0.021	0.057	0.141*	0.436	0.768

\*Pearson's Chi-square; LOS: length of stay  
Values presented as means and standard deviations or percentages.

### Patients with VWF:

RCo ≤50% subgroup: The distribution of scoliosis types in this subgroup was comparable to other VWF: RCo subgroups. Six of the sixteen patients required transfusions (37.5%). Three patients had a family history of bleeding; four had personal (medical or surgical) history of bleeding, two had both familial and personal histories (total 9/16, 56%), and four of those (44%) were transfused (Table 4). Fifteen of sixteen patients (94%) received VWF replacement intraoperatively and postoperatively (every 12 hours) at 50 units/kg body weight. The average number of administrations was two per patient at a cost of \$0.77/unit, with a total cost range of \$1,232- \$17,248 (median \$5,873) per patient (depending on patient's weight and number of doses).

### Logistic regression model

Treating VWF: RCo as a continuous variable, logistic regression analysis of those with levels ≤70% demonstrated a modest but statistically significant correlation between higher blood loss/segment fused, and lower VWF: RCo, in spite of VWF administration in 16 of these patients (R-.268, p 0.044) (Figure 1).

### Multi-variate logistic regression

Three separate multivariate logistic regression models were run results summarized in Table 5: the dependent variable was different for each. First, VWF: RCo levels ≤ 50 or >50, next for levels ≤ 60 or >60 and finally levels ≤ 70 or >70%. The independent variables were the same for all 3 analyses: Cobb

angle, levels instrumented and fused, intraoperative blood loss per segment, height, gender, weight and number of osteotomies. Higher operative blood loss/segment was associated with lower VWF: RCo levels (p 0.005), and ≤50 % (p 0.001) (Table 5).

**Table 4:** Individual patients with pre-operative Ristocetin cofactor activity ≤ 50%.

Patient No.	Type Of Scoliosis	VWF: Rco Level (%)	Family History of Bleeding	Personal History of Bleeding	VWF Given Intra-Op	VWF Given Post-Op	Post-Surg. # Doses	Blood Loss/Segment	PRBC (Mls)
1	I	26	menorrhagia		Yes	Yes	1	80	
2	NM	31			Yes	No	0	53	
3	NM	31		epistaxis trauma associated	Yes	Yes	1	244	500
4	NM	35			Yes	Yes	3	71	952
5	NM	40		epistaxis	No	No	0	109	620
6	NM	42	epistaxis	bruising dental bleeding	Yes	Yes	6	175	1140
7	NM	42			Yes	Yes	7	41	
8	I	43			Yes	Yes	2	71	
9	I	43	surgical bleeding		Yes	Yes	3	100	
10	I	43	menorrhagia		Yes	Yes	0	66	
11	NM	44			Yes	No	0	88	250
12	I	45		epistaxis	Yes	Yes	1	136	
13	O	47		bruising tonsillectomy	Yes	Yes	3	128	900
14	NM	47		epistaxis	Yes	Yes	4	100	
15	I	49			Yes	Yes	1	150	
16	I	49			Yes	No	0	111	

**Table 5:** Multivariate Logistic regression examining Blood Loss/Segment Fused at different levels of VWF: RCo.

VWF: RCo* subgroup(n, % )	OR (95% CI)	p-value
≤ 50% (16, 4.6%)	0.984 (0.974 – 0.994)	0.001
≤ 60% (34, 9.7%)	0.990 (0.984 – 0.997)	0.005
≤70% (59, 16.8%)	0.995 (0.989 – 1.001)	0.128

The VWF: RCo levels were the dependent variable. (n=number of patients within the subgroup and % of the entire population). The independent variables were the same for all 3 analyses: Cobb angle, levels instrumented and fused, intraoperative blood loss per segment, height, gender, weight, and number of osteotomy levels. The only independent variable reaching significance is blood loss as above.

## Discussion

The prevalence of VWD could lead to it being surreptitiously associated with bleeding in surgical procedures whereas posterior spinal fusion can lead to surgical blood loss that can be considerable even in routine cases [12-16]. Thus, we felt it important to understand if any predictive relationship existed between pre-surgical VWF: RCo levels and surgical blood loss in patients undergoing PSF. We found the linear regression analysis suggesting a VWF: RCo level <70% could be associated

with increased blood loss, while the more robust multivariate regression analysis defined that threshold to be < 60%. Proving our hypothesis is somewhat confounded by the therapeutic approach to patients with very low levels of VWF: RCo as they received factor replacement prior to surgery. In spite of that, the group with <50% activity had the highest operative blood loss though most received therapy with VWF replacement.

Desmopressin (DDVAP) has been previously used to stimulate endothelial release of VWF in patients with VWD undergoing

surgical procedures [17], but concerns over the ensuing fluid retention, risk of hyponatremia, and inconsistent efficacy have limited its use in PSF [18-20]. Human derived von Willebrand Factor/Factor VIII concentrate (Humate-P®) have been in clinical use to treat VWD, and been shown to be safe, and well tolerated despite being a pooled product [21]. The indications and optimal dosing for the use of Humate-P® in patients with VWD remain in need of further study. VWF: RCo **levels are used to determine initial dosing as well as need for further therapy** [22]. In an effort to identify patients at higher risk for bleeding with PSF, we screened patients using VWF: RCo **levels**. The current recommendations are that in patients with levels <30 have their levels increased to 100%. The question that arises is if a level of 100% is the pre-operative therapeutic target in these patients; then should we be treating patients whose levels are between 30-100%? Our report shows that patients with levels > 70 % have standard risk but the 17 % of the patients with levels below 70% could have increased risk for peri-operative blood loss.

Trying to understand what expected intraoperative blood loss would be for these procedures, we found blood loss in the study above to be 93ml/segment in the idiopathic and 101 ml/segment in the neuromuscular subgroups [10]. In another report by Jain et al. [22] on a similar population of PSF, patients' EBL was 89.5 ml/segment [22]. The reported blood losses in these two reports are comparable to our study patients with VWF: RCo>70%. Our patients with VWF: RCo ≤ 50% had significantly higher intraoperative and total hospital blood loss (123 and 145 ml/segment respectively), despite the administration of VWF.

Patients with VWF: RCo levels of <30, up to even ≤50% with bleeding symptoms are considered as possible type VWD by some experts [23]; Woods, et al reported that in patients with type 1 or possible type 1, ora history of bleeding following dental extraction could be used predict the potential for major operative hemorrhage. However, a family history of bleeding by itself or isolated low VWF: RCo levels [24] were not predictive. In our study, seven of the 16 patients with VWF: RCo levels ≤50% (44%) had no family, medical or surgical history of bleeding. Transfusion rate was 22% in those with levels >70%, 37% in those with levels <50% and 44% if there was any history of bleeding.

Our data suggest that, isolated low preoperative VWF: RCo levels may serve to identify patients at risk for excessive operative blood loss during PSF, however, the best therapeutic approach for these patients is far from clear. The actual efficacy of the rather expensive HumateP® remains questionable as the correlation between low VWF: RCo levels and higher intraoperative blood loss remained significant despite administration of VWF concentrate and an antifibrinolytic drug. It may be reasonable to speculate the blood losses could have been much higher if the patients were not pretreated with VWF, however a prospective randomized study design will be necessary to truly clarify that. Lastly the recent introduction of recombinant VWF into clinical use [25] needs research to examine if it confers an advantage over the currently used human derived VWF.

Conducting any study on VWD is fraught with challenges as there is still ongoing debate on the relative contribution of

bleeding history and the exact VWF: RCo threshold to make the diagnosis [26]. In the next decade, our understanding of inherited bleeding disorders and the appropriate use of pro-coagulant therapy will evolve as high throughput gene sequencing tests are being developed to assess bleeding disorders in a highly specific manner [27]. Indeed there are new genomic loci for VWD being determined and our understanding of the downstream disruption of the coagulation pathway from having a low VWF: RCo levels will become better characterized and even potentially personalized [28].

### Limitations

This Variability in patient's complexity and surgical approach can be strong confounders; however, we conducted this review at a time period during which our surgical team, and the delivery of perioperative care remained consistent. Another potential confounder is the use of either Tranexamic acid or Aminocaproic acid, the latter confers a slightly weaker hemostatic effect [29]. However, the distribution of antifibrinolytic treatments was statistically similar among the study groups. Patients with thrombotic history were excluded, however those without a suggestive history could not be practically identified. It is theoretically possible that a patient may have undiagnosed low VWF activity as well as a thrombotic tendency. This could only be detected in a careful prospective design. Our study is also limited by the relatively small numbers of patients with VWF: RCo levels ≤50%.

### Conclusion

Preoperative screening may identify patients at risk for excessive bleeding. Von Willebrand activity ≤ 60% may be of value in predicting blood losses and planning an operative course. Patients with marginally low VWF activity may not have a preceding history suggesting a bleeding tendency. Increased operative blood loss was seen despite of provision of antifibrinolytic therapy and VWF replacement. The role of VWF replacement in treating this group awaits validation in a prospectively controlled design.

### Compliance with Ethical Standards

The authors throughout the process of conducting this study and writing the manuscript remained in compliance with all the listed ethical standards in the instructions to the authors.

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