Knowledge of Blood Group Decreases von Willebrand Factor Panel Testing in Children

Natasha M. Archer¹, Peter W. Forbes², Carlo Brugnara³

Correspondence: Natasha M. Archer, Pediatric Hematology/Oncology, Dana-Farber/Children's Hospital Blood Disorders and Cancer Center, 300 Longwood Ave, Boston, MA 02115
(e-mail: natasha.archer@childrens.harvard.edu).

Von Willebrand factor (VWF) and Factor VIII:C testing are often initiated in the evaluation of pediatric patients with a concern for a bleeding disorder. Subjects with O blood group are known to have significantly lower baseline von Willebrand factor (VWF) values than subjects with non-O blood groups and thus are more likely to fall within a low VWF category (low VWF or disease) than any other blood group.¹ Repeat VWF panel (VWF antigen [VWF:Ag], VWF ristocetin cofactor [VWF:RCo], and Factor VIII:C drawn on same date and at same time) testing has been advocated to help improve clinician diagnostic ability,² but there is little evidence to suggest that it does. In subjects with low VWF, knowledge of blood group might not only be useful in decreasing overall VWF panel testing but also help in the diagnosis of patients with true bleeding disorders. We aimed to determine if the timing of blood group testing influenced the number of VWF panels performed.

We conducted a retrospective cohort study of all pediatric subjects age 0 to 18 years at the time of their first VWF panel and who also had a blood group in our electronic medical record system between June 1990 and October 2015. Subjects with hemophilia were excluded. Subjects with greater than 7 panels (n=10) were excluded because of the assumption that greater than 7 panels was less likely related to bleeding than

inflammation. Subjects with more than 1 blood group in our system (secondary to bone marrow transplant) were also excluded. The second of 2 panels done on the same day was excluded as it was part of a DDAVP (desmopressin) challenge and often above baseline values.

Subjects were placed into 3 final diagnosis categories (normal, low VWF, and disease) based on the results of panel testing extracted from the electronic medical record. To be classified as normal, all VWF:Ag and VWF:RCo values had to fall within the normal range (≥ 50 IU/dL), while low VWF (≥ 30 IU/dL and < 50 IU/dL) or disease (< 30 IU/dL) needed at least 1 or more panels within their respective ranges to fall within the category. If a subject had panels that fell within the low VWF and disease value ranges, they were categorized as disease.

Factor VIII:C, VWF functional (VWF:RCo) and antigenic (VWF:Ag) were measured on Siemens BCX and BCS-XP analyzers using Innovance VWF Ac Kit and VWF Ag Kit (Siemens Healthcare Diagnostics, Marburg, Germany).

The primary study outcome was number of VWF panels tested. Additional variables collected included age, sex, blood group, test date of blood group, VWF:Ag, VWF:RCo and FVIII:C values, and test date of VWF panel. Statistical analysis used SAS version 9.3 (SAS Institute Inc., North Carolina, USA). The Kruskal-Wallis test was used when comparing the 3 disease groups. The Wilcoxon 2-sample test was used to compare number of panels between groups defined in terms of the timing of their initial VWF panel. Fisher's exact test was used to compare groups on categorical variables.

During the study period, 2497 VWF panels were tested in 1610 pediatric subjects (median age at first panel 9.3 years, range 0–18 years) (Table 1). Participants were most often tested for personal and/or family history of bleeding or bleeding disorder or abnormal coagulation study, usually prolonged partial thromboplastin. Most children (1074, 67%) had only 1 panel sent. A total of 85 children were diagnosed with VWD and 344 were diagnosed with low VWF (Table 1). Of those characterized by low VWF or VWD, 77% and 74%, respectively, have O blood group, while only 51% of subjects in the normal group have O blood group. In subjects with VWD, those who had their blood group identified before or on the same day as their initial VWF panel had on average a total of 2.48 (SD 1.05) panels performed compared with an average of 3.54 (SD 1.65) panels for those with a blood group tested after the initial VWF panel ($P=0.003$) (Table 2). Subjects with normal or low VWF values also had 25% to 30% fewer VWF panels tested if their blood group was known

Funding/support: NMA was supported by the Harvard Catalyst Program for Faculty Development and Diversity Inclusion Faculty Fellowship, and the American Society of Hematology/Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Award. PWF was supported by the Harvard Catalyst, the Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers.

Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

¹Pediatric Hematology/Oncology, Dana-Farber/Children's Hospital Blood Disorders and Cancer Center, Boston, MA

²Clinical Research Center, Boston Children's Hospital, Boston, MA

³Laboratory Medicine, Boston Children's Hospital, Boston, MA

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HemaSphere (2017) 1:1(e3)

Received: 8 August 2017 / Accepted: 20 October 2017

<http://dx.doi.org/10.1097/HS9.0000000000000003>

Table 1**Baseline Characteristics of Study Population**

Baseline Characteristics	Disease (n=85)	Low VWF (n=344)	Normal (n=1181)	P
Sex, number of male (%)	42 (49%)	151 (44%)	504 (43%)	0.46
Age (years) at first panel, mean (SD)	7.4 (5.7)	8.9 (5.6)	9.6 (5.6)	<0.001
Blood group O, number of (%)	63 (74%)	266 (77%)	606 (51%)	<0.0001
Blood group before or same day as initial VWF panel, number of (%)	50 (59%)	199 (58%)	1055 (89%)	<0.0001
VWF:Ag (IU/dL), mean SD	47 (25)	67 (26)	119 (64)	<0.0001
VWF:RCO (IU/dL), mean SD	33 (23)	52 (24)	110 (68)	<0.0001
FVIII:C (IU/dL), mean SD	69 (33)	81 (27)	119 (52)	<0.0001
Mean panels, mean (SD)	2.92 (1.42)	2.26 (1.22)	1.24 (0.61)	<0.0001

VWF = von Willebrand factor.

at the time of initial VWF panel. The difference between VWF values in subjects with a blood group before or same day versus after the initial panel was not statistically significant ($P > 0.38$).

Subjects with O blood group have approximately 75% of values of the other blood groups. The proposed mechanism for this is decreased clearance of VWF secondary to AB antigens.^{3,4} Klarmann et al further specified that the difference between O blood group and non-O blood group only begins to manifest itself in childhood as the ABO system develops.⁵ The difference between O blood group and non-O blood group VWF:Ag and VWF:RCO values is also present in healthy children with no personal or family history of bleeding.⁶

While the above studies have shown a relationship between ABO blood group and VWF values, it is not standard practice to check ABO blood group with an initial VWF panel.⁷ Based on our study results, knowing the blood group prior to the initial VWF panel results in fewer VWF panels performed. Thus, pediatric subjects age 0 to 18 years undergo less intensive VWF panel testing if their blood group is determined before or on the same day as the initial VWF testing irrespective of blood group

(1.36 vs 2.35, $P < 0.0001$). Table 2 shows the number of panels by final diagnosis category, blood group, and timing of blood group. As hypothesized, these data show that subjects have fewer panels performed when they are identified as having O blood group before or on the same day as their initial VWF panel compared with after for all final diagnosis categories.

Using the average number of panels when blood group is known at initial VWF panel testing (1.36 [SD .78]), approximately 12% or 302 panels (drawn from 536 children), could have potentially been avoided if the blood group had been determined with the initial VWF panel. This not only would lead to cost savings but decreased phlebotomy visits and missed days from work and school.

While this study shows that knowledge of blood group results in less diagnostic VWF panel testing, it is still unclear whether blood group, especially in low VWF, predicts outcome. Future prospective studies should address whether O blood group subjects with low VWF or VWD are less or more likely to bleed than non-O blood group with low VWF or VWD. This would further support reduced testing in patients identified as having

Table 2**Mean Number of Panels by Final Diagnosis Category, Blood Group and Timing of Blood Group**

Final Diagnosis Category	Blood Group	Timing of Blood Group in Relation to Initial VWF Panel	Number of Patients, Mean (SD) Number of Panels	P
Normal	All blood groups	Before/same day	1055, 1.2 (0.55)	<0.0001
		After	126, 1.61 (0.89)	
	O	Before/same day	539, 1.22 (0.56)	<0.0001
		After	67, 1.64 (0.83)	
	Non-O	Before/same day	516, 1.18 (0.55)	<0.0001
		After	59, 1.58 (0.97)	
Low	All blood groups	Before/same day	199, 1.94 (1.13)	<0.0001
		After	145, 2.7 (1.2)	
	O	Before/same day	157, 1.86 (1.13)	<0.0001
		After	109, 2.72 (1.18)	
	Non-O	Before/same day	42, 2.26 (1.08)	0.17
		After	36, 2.67 (1.26)	
Disease	All blood groups	Before/same day	50, 2.48 (1.05)	<0.003
		After	35, 3.54 (1.65)	
	O	Before/same day	39, 2.41 (1.04)	0.005
		After	24, 3.54 (1.61)	
	Non-O	Before/same day	11, 2.73 (1.10)	0.34
		After	11, 3.55 (1.81)	
All subjects	All blood groups	Before/same day	1304, 1.36 (0.78)	<0.0001
		After	306, 2.35 (1.33)	
	O	Before/same day	735, 1.42 (0.82)	<0.0001
		After	200, 2.46 (1.30)	
	Non-O	Before/same day	569, 1.29 (0.71)	<0.0001
		After	106, 2.15 (1.36)	

VWF = von Willebrand factor.

blood group O before or on the same day as initial VWF panel testing. In addition, understanding the bleeding phenotype associated with ABO blood group, especially in patients with low VWF, will help clinicians manage patients after they have been diagnosed.

This study suggests that subjects being tested for VWD should have their blood group determined at their initial assessment, an intervention that might mitigate unnecessary testing. This study is retrospective. While we do not know the exact rationale behind each repeat VWF panel or whether the repeat testing influenced the subject's clinical outcome, these data support the addition of a blood group to the initial laboratory evaluation of VWD. We recommend blood group testing be added to the initial diagnosis and management of VWD guidelines.

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