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Perioperative bleeding and thrombotic risks in patients with Von Willebrand disease

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Abstract

Von Willebrand disease (VWD) is an inherited bleeding disorder that often manifests clinically with hemorrhage after invasive procedures. We investigated the association between a diagnosis of VWD and bleeding and thrombotic outcomes following major non-cardiac surgery in a large national database from the United States. Patients age ≥ 45 years requiring major non-cardiac surgery were identified from Healthcare Cost and Utilization Project's National Inpatient Sample data from 2004 to 2013. Von Willebrand disease, perioperative major adverse cardiovascular events (MACE), thrombotic events, and hemorrhage were defined by ICD9 diagnosis codes. From 2004 to 2013, a total of 10,581,621 hospitalizations for major non-cardiac surgery met study inclusion criteria and VWD was identified in 3,765 (0.036%). In adjusted analyses, patients with VWD were significantly more likely to develop post-operative hemorrhage than patients without VWD (5.5% vs. 1.9%, $p < 0.001$; adjusted OR 3.49, 95% CI 3.03–4.03), but had similar frequencies of perioperative MACE and thrombotic events. A diagnosis of VWD was associated with increased risks of bleeding with non-cardiac surgery, without a corresponding reduction in perioperative thrombosis in comparison to patients without VWD. Perioperative management of patients with hereditary bleeding disorders and mitigation of thrombotic risks requires further study.

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Introduction

Von Willebrand disease (VWD) is an inherited bleeding disorder characterized by qualitative and/or quantitative defects of von Willebrand factor (VWF), a circulating glycoprotein required for hemostasis. Von Willebrand disease has an estimated prevalence of approximately 0.01% and manifests clinically with hemorrhage after invasive procedures.[1] Although bleeding risks in VWD are established, perioperative thrombotic complications in patients with VWD are not well characterized.[2,3] Prior studies in non-surgical cohorts have reported lower rates of cardiovascular disease in patients with VWD.[4,5] We investigated the association between a diagnosis of VWD and bleeding and thrombotic outcomes following major non-cardiac surgery in a large national database from the United States.

Methods

Patients age ≥45 years requiring major non-cardiac surgery were identified from Healthcare Cost and Utilization Project's National Inpatient Sample data from 2004 to 2013, as previously described.[6] Patients were included if they had a principal *International Classification of Diseases, Ninth Revision* (ICD-9) procedure code for a major therapeutic operating room procedure (HCUP Procedure Class 4). Principal CCS procedure codes, which represent an aggregate of relevant primary ICD-9 procedure codes by surgical subtype, were used to exclude patients who underwent cardiac procedures (n=1,655,567), cardiac surgery and cardiac transplantation (n=582,726), bone marrow transplantation (n=18,151), ophthalmologic surgery (n=13,342), radiation therapy (n=9,817), dental surgery (n=1,779), and non-operating room procedures (n=386) as a principal in-hospital procedure. Von Willebrand disease was identified using ICD-9 diagnosis code 286.4. Perioperative major adverse cardiovascular events (MACE), thrombotic events, and perioperative hemorrhage during the index surgical hospital admission were defined by ICD9 diagnosis codes (Table 2 footnote). Multivariable logistic regression models were generated to estimate odds of perioperative events, adjusted for patient demographics, cardiovascular risk factors, and surgery type. Statistical analyses were performed using SPSS 20 (IBM SPSS Statistics, Armonk, NY). P-values < 0.05 were considered to be statistically significant.

Results

From 2004 to 2013, a total of 10,581,621 hospitalizations for major non-cardiac surgery met study inclusion criteria and VWD was identified in 3,765 (0.036%). Patients with a diagnosis of VWD were younger (61.3 vs. 65.7, $p<0.001$), more likely to be female (75.2% vs. 56.6%, $p<0.001$), and less likely to have cardiovascular risk factors (Table 1). In unadjusted analyses, patients with VWD had similar frequencies of perioperative MACE, perioperative stroke, and death in comparison to patients without VWD, but were less likely to develop perioperative AMI (0.5% vs. 0.9%, $p=0.013$), VTE (1.5% vs. 2.1%, $p=0.014$), or

any perioperative thrombotic event (2.4% vs. 3.5%, $p<0.001$) as shown in Table 2. However, differences in the frequency of thrombotic outcomes were fully attenuated after adjustment for age, sex, and other clinical variables. In adjusted analyses, patients with VWD were significantly more likely to develop post-operative hemorrhage than patients without VWD (5.5% vs. 1.9%, $p<0.001$; adjusted OR 3.49, 95% CI 3.03–4.03). Similar findings were observed in sensitivity analyses of patients with elective surgical hospital admission (data not shown).

Discussion

Bleeding associated with non-cardiac surgery in patients with VWD remains a major concern. Perioperative management to mitigate the risk of bleeding requires consideration of patients' VWD subtype (qualitative versus quantitative; partial versus total VWF deficiency) as well as the specific risks associated with the intended surgical approach. Although preoperative desmopressin is often sufficient prior to minor procedures, the mainstay of therapy is the prophylactic administration of plasma-derived concentrates of VWF, with or without factor VIII, prior to major surgery. Adjunctive therapies, such as intravenous immunoglobulins and tranexamic acid, have also been reported.[7,8] Although current measures to mitigate surgical bleeding in VWD appear to be safe and well tolerated in small series, effects of pharmacology on perioperative thrombotic risks remain uncertain.[7–9]

In this analysis of patients undergoing non-cardiac surgery, patients with VWD were more likely to have perioperative bleeding than patients without VWD, but had similar risks of perioperative thrombotic events after adjustment for covariates. These results are surprising in light of prior data with lower cardiovascular disease rates in VWD.[4,5] However, this finding may reflect the unintended, prothrombotic effects of perioperative management of VWD, with administration of red blood cells or VWF- containing concentrates to prevent bleeding or mitigate hemorrhage. Thus, the present analysis demonstrates the complexity of relationships between perioperative bleeding and thrombosis, and highlights the need for further investigation to determine the optimal management of surgical patients with VWD.

There are some notable limitations of this study. Analyses were based on administrative coding data, which may be subject to reporting bias or coding errors. Type and severity of VWD could not be determined. Medical therapy, including administration of VWF- containing concentrates, was not available from this dataset. The analysis was limited to adults ≥ 45 , the population at greatest risk for cardiovascular complications of surgery. Finally, the timing of cardiovascular complications following non-cardiac surgery cannot be firmly established from this administrative dataset.

In conclusion, a diagnosis of VWD was associated with increased risks of bleeding with non-cardiac surgery, without a corresponding reduction in perioperative thrombosis in comparison to patients without VWD. Perioperative management of patients with hereditary bleeding disorders and mitigation of thrombotic risks requires further study.

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Table 1

Baseline characteristics of patients with and without a diagnosis of Von Willebrand Disease.

	Diagnosis of Von Willebrand Disease		P Value
	Present (n=3,765)	Absent (n=10,577,856)	
Age	61.32 ± 11.48	65.74 ± 12.32	<0.001
Female Sex	2,827 (75.2%)	5,972,971 (56.6%)	<0.001
Race / Ethnicity			<0.001
White NH	2788 (74.1%)	6,876,278 (65.0%)	
Black NH	122 (3.2%)	833,198 (7.9%)	
Hispanic	121 (3.2%)	598,436 (5.7%)	
Other / Unknown	734 (19.5%)	2,269,944 (21.5%)	
Tobacco Use	292 (7.8%)	1,044,555 (9.9%)	<0.001
Hypertension	1923 (51.1%)	6,126,549 (57.9%)	<0.001
Hyperlipidemia	835 (22.2%)	2,998,224 (28.3%)	<0.001
Diabetes	591 (15.7%)	2,569,369 (24.3%)	<0.001
CKD	164 (4.4%)	80,0751 (7.6%)	<0.001
CAD	416 (11.0%)	1,878,594 (17.8%)	<0.001
Elective Surgery	2525 (67.2%)	6389243 (60.6%)	<0.001
Surgery Type			<0.001
Endocrine	63 (1.7%)	122751 (1.2%)	
General / Transplant	815 (21.6%)	2293524 (21.7%)	
Genitourinary	246 (6.5%)	770050 (7.3%)	
Neurosurgery	266 (7.1%)	601863 (5.7%)	
Obstetric / Gynecologic	316 (8.4%)	628229 (5.9%)	
Orthopedic	1537 (40.8%)	4251684 (40.2%)	
Otolaryngology	67 (1.8%)	78260 (0.7%)	
Skin / Breast	190 (5%)	465404 (4.4%)	
Thoracic	56 (1.5%)	232872 (2.2%)	
Vascular	209 (5.6%)	1133219 (10.7%)	

Table 2

Perioperative outcomes with and without a diagnosis of Von Willebrand Disease.

	Diagnosis of Von Willebrand Disease				P Value	Unadjusted OR (95%CI)	Adjusted OR ^a (95%CI)
	Present (n=3,765)	Absent (n=10,577,856)					
Major Adverse Cardiovascular Events ^b	93 (2.5%)	310,619 (2.9%)	.090	0.837 (0.681 – 1.028)	1.154 (0.932 – 1.427)		
Death	61 (1.6%)	176,898 (1.7%)	.803	0.968 (0.752 – 1.247)	1.283 (0.987 – 1.668)		
Myocardial Infarction ^c	19 (0.5%)	93,563 (1.0%)	.013	0.568 (0.362 – 0.892)	0.832 (0.528 – 1.310)		
Ischemic Stroke ^d	19 (0.5%)	70,694 (0.7%)	.218	0.754 (0.480 – 1.183)	0.998 (0.625 – 1.593)		
Venous Thromboembolism ^e	58 (1.5%)	224,125 (2.1%)	.014	0.723 (0.558 – 0.937)	0.989 (0.752 – 1.301)		
Any Thrombotic Outcome ^f	92 (2.4%)	371,788 (3.5%)	<0.001	0.688 (0.559 – 0.846)	0.959 (0.770 – 1.193)		
Post-Operative Hemorrhage ^g	207 (5.5%)	201,999 (1.9%)	<0.001	2.988 (2.597 – 3.438)	3.494 (3.033 – 4.024)		

^a Adjusted for age, sex, race, tobacco use, hypertension, hyperlipidemia, diabetes, chronic kidney disease, coronary artery disease, elective surgery, and surgery type

^b Composite of death, myocardial infarction, and ischemic stroke

^c Defined by ICD9 diagnosis codes 410.x1

^d Defined by ICD9 diagnosis codes 33.x1, 434.x1, 436, and 437.1

^e Defined by ICD9 diagnosis codes 415.1, 415.11, 415.12, 415.13, 415.19, 451.1x, 451.81, 453.2, 453.4x

^f Composite of myocardial infarction, ischemic stroke, and venous thromboembolism

^g Defined by ICD9 diagnosis codes 998.11 and 998.12