HHS Public Access

Author manuscript

Thromb Res. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Thromb Res. 2016 May ; 141: 35–38. doi:10.1016/j.thromres.2016.03.003.

Risk Factors for Venous Thromboembolism in Adults with Hemoglobin SC or Sβ+ thalassemia Genotypes

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Abstract

Introduction—Venous thromboembolism (VTE) is common in sickle cell disease (SCD); however, the risk factors associated with VTE in patients with sickle variant syndromes are not known. The primary aim of this study was to determine hematologic and clinical risk factors for VTE in adults with hemoglobin SC or $S\beta^+$ thalassemia genotypes.

Materials and Methods—We conducted a retrospective cross-sectional analysis of patients with hemoglobin SC and $S\beta^+$ thalassemia genotypes followed at the Sickle Cell Center for Adults from 2008 to 2012. Data on baseline hematologic parameters and SCD-specific comorbidities were collected from review of electronic records.

Results—A total of 116 patients, 85 (73%) with hemoglobin SC disease and 31 (27%) with $S\beta^+$-thalassemia, were included for analysis. Thirty-two (28%) patients had a verified history of non-catheter related VTE. Mean baseline hemoglobin levels were higher among individuals with a history of VTE compared to those without (11.7 g/dL vs. 11.0 g/dL, p=0.003). In addition, the prevalence of surgical splenectomy was higher among patients with VTE compared to those without (25.0% vs. 4.8%, p=0.001). On multivariate analysis, elevated baseline hemoglobin (odds ratio [OR] 2.45 (95% confidence interval [CI] 1.42–4.23) and history of surgical splenectomy (OR 5.76 [CI 1.43–23.22) were independently associated with VTE risk.

Conclusions—Higher baseline hemoglobin is a risk factor for non-catheter-related VTE in patients with hemoglobin SC or $S\beta^+$ thalassemia genotypes. Surgical splenectomy, which is a known risk factor for VTE in other hemoglobinopathies such as β-thalassemia intermedia, is also associated with VTE in sickle variant syndromes. Future studies are needed to validate these

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Addendum

R.P. Naik and S. Lanzkron designed the study and analyzed the results. T.T. Yu, J. Nelson, S. Lanzkron, and R.P. Naik collected the data. R.P. Naik, S. Lanzkron, and M.B. Streiff interpreted the findings. T.T. Yu, J. Nelson, M.B. Streiff, S. Lanzkron, and R.P. Naik wrote and critically revised the manuscript.

findings and to investigate the mechanisms of hypercoagulability observed in patients with hemoglobin SC and $S\beta^+$ thalassemia.

Introduction

Venous thromboembolism (VTE) is a common complication in adults with sickle cell disease (SCD),(1–3) occurring in over 10–15% of individuals with SCD by age 40.(1,2) As with other complications of SCD, genotype appears to modify the risk of VTE; however studies evaluating this genotypic variation in VTE have demonstrated conflicting results. Although patients with hemoglobin SC disease or $S\beta^+$ thalassemia were found to have a lower incidence of VTE compared to those with SS or $S\beta^0$ thalassemia in adolescence and early adulthood using data from the Cooperative Study of Sickle Cell Disease,(2) the prevalence of VTE was paradoxically higher among SC and $S\beta^+$ thalassemia patients using a more recent SCD cohort of older adult patients.(1) This age-related phenotypic variation is similar to that observed with osteonecrosis of the femoral head,(4) and, in the case of VTE, may reflect a complex interplay between risk factors such as catheter use, hemolysis, endothelial damage, hypercoagulability, and viscosity for venous thrombotic events in SCD. (5,6)

Few studies have evaluated risk factors for complications in adults with sickle cell variant genotypes. High baseline hemoglobin is associated with viscosity-related sequelae such as proliferative retinopathy and multi-organ failure in SC disease;(7–9) whereas hemoglobin levels do not appear to be associated with other common complications such as sensorineural hearing loss in SC patients.(8) To date, however, the risk factors for VTE in patients with sickle cell disease variants have not been investigated.

We hypothesized that VTE in patients with hemoglobin SC disease or $S\beta^+$ thalassemia is associated with characteristic baseline laboratory and clinical risk factors. In order to address this question, we performed a retrospective analysis of a large cohort of patients with sickle variant syndromes followed at the Sickle Cell Center for Adults at Johns Hopkins.

Methods

We conducted a retrospective cross-sectional analysis of patients with either hemoglobin SC or $S\beta^+$ thalassemia cared for at the Sickle Cell Center for Adults at Johns Hopkins between August 2008 and January 2012. Inclusion criteria were age ≥ 18 years and known genotype. The study was approved by the Institutional Review Board and was deemed to be exempt from informed consent.

Relevant comorbidities for each patient were collected via review of electronic records. Demographic information including age, sex, and genotype were recorded for all patients, as were sickle-cell specific comorbidities including VTE, avascular necrosis, retinopathy, stroke, leg ulcer, and history of surgical splenectomy. Baseline hematologic parameters, including white blood cell count (WBC), hemoglobin, platelet count, and absolute reticulocyte count (ARC), were also collected and were defined as a steady-state, non-pregnancy-related outpatient value taken at least one month after hospitalization and at least three months after a transfusion.

VTE events were verified by duplex ultrasound, ventilation-perfusion scan or computed tomography angiography when available. In situations where radiology reports were not available, only patients who had been prescribed treatment doses of anticoagulation were included as cases. Catheter-related VTE events were excluded from this study. Only patients who had complete information on all steady-state hematologic parameters and comorbidities were included. The present report represents a secondary analysis of a previously published study of VTE using all SCD genotypes from this cohort.(1)

Bivariate analyses were performed using t-test and chi-squared statistics. Logistic regression was used to identify independent risk factors for VTE among patients with sickle cell variants. All statistics were performed using STATA Data Analysis and Statistical Software (Version 12; College Station, TX). Statistical significance was defined as a p-value <0.05.

Results

Of the 158 patients with electrophoresis-verified SC or Sβ^+-thalassemia in our cohort, 39 were missing steady-state or transfusion-free hematologic values and 3 experienced a catheter related VTE. We therefore included 116 patients with sickle cell variant genotypes in the present study. Demographic, hematologic, and clinical characteristics according to history of VTE are summarized in Table 1. In the cohort, 85 (73%) patients had SC disease, and 31 (27%) had Sβ^+-thalassemia disease. A history of non-catheter-related VTE was recorded in 32 (28%) patients. Of the 32 VTE events, 15 were pulmonary emboli (PE), 7 were isolated deep venous thromboses (DVT), 8 were both PE and DVT, 1 was a cerebral vein thrombosis and 1 was an abdominal vein thrombosis. Additionally, 1 patient with DVT/PE also experienced a cerebral vein thrombosis, and 1 patient with PE had catheterization-proven chronic thromboembolic pulmonary hypertension. Females comprised 57% of the cohort, and the median age of the cohort was 43 years (range 21–72 years). There were no significant differences for age, sex, or sickle variant genotype between patients with and without VTE.

For the hematologic parameters, the VTE group demonstrated a higher mean baseline hemoglobin level compared to the non-VTE group (11.7 g/dL vs. 11.0 g/dL, p=0.003) (Figure 1). Of the VTE events, 26/32 (81%) occurred in patients with baseline hemoglobin ≥ 11 g/dL (p=0.002) and 20/32 (63%) occurred with baseline hemoglobin ≥ 11.5 g/dL (p=0.006). On subgroup analysis by genotype, the mean baseline hemoglobin levels for the VTE group compared to the non-VTE group for patients with hemoglobin SC disease was 11.7 g/dL vs. 11.2 g/dL (p=0.038) and for Sβ^+-thalassemia patients was 11.6 g/dL vs. 10.5 g/dL (p=0.012). Mean WBC, platelet counts, and reticulocyte counts did not differ between the groups. In addition, the prevalence of prior splenectomy was significantly higher on bivariate analysis comparing patients with VTE to those without (25.0% vs. 4.8%, p=0.001). No differences between groups were found for the other recorded comorbidities.

The logistic regression model for VTE is shown in Table 2. Individuals with sickle variant syndromes were found to have a 2.5 fold (95% confidence interval (CI) 1.4–4.2) increased risk of VTE for every 1 mg/dL increase in hemoglobin level. On subset analysis by genotype, patients with hemoglobin SC disease had a 2.1 fold (CI 1.1–3.8) increased risk of

VTE per 1 mg/dL of hemoglobin, and those with $S\beta^+$-thalassemia had a 6.3 fold (CI 1.19–33.25) increased risk of VTE per unit of hemoglobin. History of surgical splenectomy was also associated with VTE, with an OR of 5.8 (CI 1.4–23.2). Subgroup analysis by VTE type revealed that prior splenectomy was primarily associated with an increased risk of PE or unusual vein thrombosis (OR 5.6 [CI 1.4–21.5]) rather than isolated DVT (OR 1.2 [CI 0.1–13.2]), although these analyses were based on a small number of events. A similar differential risk between PE and DVT was not observed with hemoglobin level.

Discussion

VTE is now recognized as a common complication of SCD; however, a comprehensive evaluation of risk factors for VTE in sickle variant genotypes has not yet been performed. In this cohort of over 100 patients with SC or $S\beta^+$ thalassemia, we found that elevated baseline hemoglobin and history of surgical splenectomy were significantly associated with VTE. This relationship was independent of age and sex, which have been shown to influence hemoglobin levels in SCD.(7,10) These findings suggest that high hemoglobin levels may influence VTE risk in SCD and that surgical splenectomy may contribute to hypercoagulability in SCD patients.

Increased whole blood viscosity has long been hypothesized to underlie certain sequelae of SCD, including proliferative retinopathy and avascular necrosis (AVN). Proliferative retinopathy is more prevalent in individuals with SC compared to SS genotype,(11) and baseline hemoglobin levels have been shown to be higher among both SS and SC patients with retinopathy compared to those without. (7,12) A similar association with higher hemoglobin levels has also been demonstrated for femoral head AVN, and individuals with coinheritance of hemoglobin SS and α-thalassemia genotypes have a higher incidence of osteonecrosis of the femoral head compared to those with SS alone.(4) In light of these observations, several clinical groups routinely perform therapeutic phlebotomy for patients with sickle cell variant syndromes who experience clinical complications.(8,13,14) The role of viscosity in the pathophysiology of VTE and role of phlebotomy for treatment or prophylaxis for VTE in patients with SC or $S\beta^+$ thalassemia, however, requires more formal investigation.

Our finding of surgical splenectomy as a risk factor for VTE in SC or $S\beta^+$ thalassemia is consistent with the phenomenon observed in other hemolytic disorders, such as β-thalassemia intermedia and hereditary spherocytosis.(15,16) We were unable to verify the time from splenectomy to VTE in our cohort; however, previous reports have suggested that the increased risk of VTE after splenectomy persists for years to decades and is not solely attributable to the surgical procedure itself.(15–17) Although the pathophysiology of VTE risk with splenectomy remains unclear, potential theories include decreased clearance of abnormal erythrocytes, chronic intravascular hemolysis, and increased coagulability.(18–20)

In SCD, functional asplenia occurs in nearly 90% of infants with SS disease by age 1,(21) whereas splenic dysfunction in sickle variants syndromes can be delayed until adolescence and early adulthood.(10,22) Therefore, we would expect that a majority of patients in our cohort would have some degree of functional asplenia. However, in one study of individuals

with SC disease, erythrocyte pit counts were highest among patients who had undergone surgical splenectomy, suggesting that surgical splenectomy results in a more profound degree of splenic dysfunction compared to functional asplenia alone.(22) This finding may relate to the increased risk of VTE that we specifically observed among splenectomized patients in our study. Further studies are needed to determine the role of splenic dysfunction in VTE risk in SCD.

The major strength of our study is our large cohort of adult patients with sickle variant genotypes and available sickle-cell specific phenotypic data. Limitations include the retrospective nature of our study, inability to document the date of splenectomy, and reliance on a single hemoglobin value to define baseline counts. We also did not have measures of viscosity and splenic function in the present study. In addition, a history of comorbidities may not have been recorded in electronic records of some patients.

Conclusions

In summary, elevated hemoglobin level and surgical splenectomy are significantly associated with VTE risk in patients with SC or $S\beta^+$ thalassemia genotypes. Further studies are needed to validate these findings and to investigate the pathophysiology of increased coagulability in SCD.

Acknowledgments

R.P. Naik was supported by National, Heart, Lung, and Blood Institute (NHLBI) award K08HL125100.

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Highlights

- Venous thromboembolism is common in adults with hemoglobin SC disease and $S\beta^+$ thalassemia genotypes.
- Higher baseline hemoglobin is significantly associated with VTE risk in patients with hemoglobin SC disease and $S\beta^+$ thalassemia.
- History of prior splenectomy is also significantly associated with VTE risk in these patients.

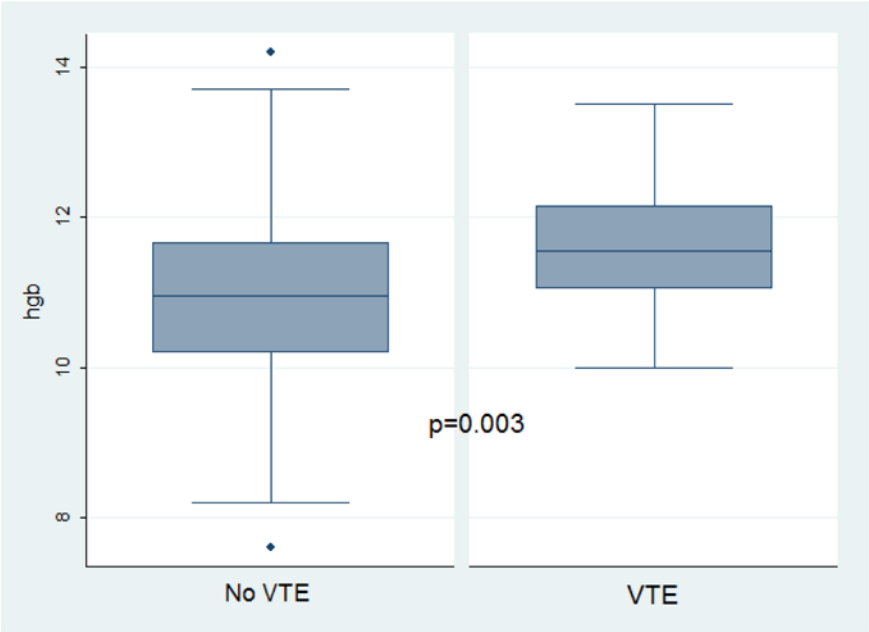

Figure 1.

Hemoglobin values by venous thromboembolism (VTE) status for patients with SC or $S\beta^{+}$ thalassemia genotypes

Table 1

Baseline characteristics by VTE status for patients with SC and Sβ$^+$-thalassemia genotypes

	No VTE (n=84)	VTE (n=32)	p-value
Demographics:			
Age (years)	41.4 (21–72)	47.3 (23–70)	0.032
Female	49 (58.3%)	17 (53.1%)	0.613
Hemoglobin SC disease	63 (75.0%)	22 (68.8%)	0.497
Hemoglobin Sβ$^+$-thalassemia	21 (25%)	10 (31.2%)	0.497
Laboratory Values:			
Hemoglobin (g/dL)	11.0 (7.6–14.2)	11.7 (10.0–13.5)	0.003
Platelets (K/cu mm)	276 (72–648)	316 (123–521)	0.157
Reticulocyte count (%)	3.7 (1.1–15.3)	3.2 (1.5–6.4)	0.236
Absolute reticulocyte count	148 (45–534)	138 (60–255)	0.452
White blood cell count (K/cu mm)	8.2 (4.0–14.9)	8.3 (4.0–13.9)	0.742
Comorbidities:			
Avascular necrosis	28 (33.3%)	13 (40.6%)	0.463
Retinopathy	52 (61.9%)	16 (50.0%)	0.245
Stroke	7 (8.3%)	4 (12.5%)	0.494
Surgical splenectomy	4 (4.8%)	8 (25.0%)	0.001
Leg ulcer	3 (3.6%)	2 (6.2%)	0.525

VTE = venous thromboembolism. Results reported as mean (range) or number (%).

Table 2

Logistic regression risk factor model for VTE

Variable	OR	95% CI
Age	1.05†	1.01–1.09
Female	1.97	0.66–5.85
Hemoglobin SC genotype	0.62	0.21–1.80
Hemoglobin	2.45†	1.42–4.23
Surgical splenectomy	5.76*	1.43–23.22

VTE = venous thromboembolism.

*p < 0.05,

†p < 0.01