Hospital-Acquired Venous Thromboembolism in Children with Sickle Cell Disease

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Abstract

Objectives: Sickle cell disease (SCD) is well recognized as a hypercoagulable state, however venous thromboembolism (VTE) risk factors in children remain largely unknown. In this study, we aim to describe the clinical characteristics, outcomes and recurrence of hospital acquired VTE in patients younger than 21 years of age. **Study Design/Methods**: Data were extracted from electronic medical records over a 10-year period (2011-2021). Data regarding sickle cell genotype, demographics, reason for admission, location of thrombus, presence of central venous catheter (CVC), intensive care unit (ICU) admission, presence of thrombophilia risk factors, resolution of VTE, mortality, and bleeding outcomes on anticoagulation were collected. Recurrence of VTE at 1 and 5 years was assessed. Descriptive statistics were used as indicated. **Results**: We identified a total of 21 VTE events over the ten-year study period. Six of these events occurred in those younger than 12 years of age. Fifteen (71%) VTE events occurred in the HbSS or HbSβThal ^{0} genotypes compared to 8 (29%) in HbSC. Eleven (52%) patients were admitted with acute chest syndrome (ACS). Most VTE events were associated with ICU admissions (n=13, 62%) and presence of central venous catheter (n=12, 57%). Major bleeding on anticoagulation occurred in 10%.All patients had resolution of index VTE at 12 weeks. Recurrence rate for VTE at 5 years was 13%. One patient died from the VTE event. **Conclusions**: Our study highlights that VTE can complicate SCD in children and young adults. Hospital acquired VTE were most associated with ICU admission, CVC, and ACS, but larger studies are indicated to validate our findings.

Introduction:

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy with an annual incidence of 300,000 to 400,000 live births worldwide.[1] SCD is considered a prothrombotic state due to enhanced platelet function,[2,3] impaired fibrinolysis[4] and chronic activation of coagulation cascade with decreased levels of natural anticoagulants and increased pro-coagulant factor activation.[5] All elements of Virchow's triad- endothelial injury, vascular stasis, and hypercoagulability- are present in SCD, creating a highly thrombogenic state.[6] Individuals with SCD are at increased risk for thromboembolism with estimates in adults ranging from 4-fold to 100-fold increase in risk.[7] Most of the data regarding the risk of thrombosis in SCD pertains to adults[8–10] and similar data regarding prevalence and risk factors for thrombosis in children with SCD is limited.

Over the past two decades, children's hospitals in the United States have seen an alarming 200% increase in the rate of hospital-acquired thrombosis.[11] In response, pediatric-specific venous thromboembolism (VTE) prophylaxis guidelines have been developed to prevent hospital-acquired venous thrombosis. However, these guidelines do not consider unique, disease-specific mechanisms that further increase the risks of VTE in

SCD. This has resulted in wide variability of thromboprophylaxis practices across different institutions for hospitalized children with SCD.[12]

At Texas Children's Hospital (TCH), our practice has been to prescribe thromboprophylaxis for patients with SCD who are 18 years of age and older admitted to the hospital or 16 years of age and older admitted to the intensive care unit (ICU). Over the past few years, we anecdotally observed an increase in the incidence of VTE events in younger children with SCD, prompting us to conduct this study. We hypothesized that the risk of VTE in SCD is higher in adolescents and in the setting of additional prothrombotic risk factors like intensive care unit (ICU) admission and presence of central venous catheter (CVC). Our objectives were to review our institutional cohort of subjects with SCD who had a hospital acquired VTE, describe their prothrombotic risk factors, and analyze treatment outcomes. Furthermore, we aimed to revise our institutional thromboprophylaxis guidelines, with the ultimate goals of reducing the rate of hospital-acquired thrombotic events and improving outcomes for this population.

Methods:

Study design:

This was a single institution (TCH) retrospective chart review study. Data were extracted for all hospitalized individuals with SCD and documented VTE during the hospitalization beginning January 2011, when our current electronic medical records went into effect, through January 2021. This study was approved by the Baylor College of Medicine Institutional Review Board.

Study population

We included patients less than 21 years of age with any sickle cell genotype (HbSS, HbSC, and HbSβThal$^{0/+}$) and a VTE event during hospitalization (deep vein thrombosis [DVT], cerebral sinus venous thrombosis [CSVT], and pulmonary embolism [PE]). We excluded patients with sickle cell trait, arterial thrombosis, and/or acute stroke. These patients were identified using ICD9 and ICD10 codes for SCD, DVT, CSVT, and PE. Patient charts were then manually reviewed for confirmation of SCD diagnosis and presence of hospital-acquired VTE on imaging. We defined hospital-acquired VTE as any VTE occurring at least 48 hours after admission, or within 1 week after discharge, consistent with the guidelines from the Solutions for Patient Safety.[13]

Variables collected:

Data were collected regarding demographics (age, sex, and sickle cell genotype), reason for hospitalization (vaso-occlusive pain crisis, acute chest syndrome [ACS], fever, COVID-19, and others), ICU admission andlength of hospitalization..

With respect to VTE, the index VTE date was defined as the date when the imaging study identified the VTE. Data were collected on the type (DVT, CSVT, and PE) and location of the thrombotic event (e.g., cerebral veins, upper or lower extremity), any thromboembolic complication, choice of anticoagulant, mechanical thrombectomy or thrombolysis. Additionally, charts were reviewed for presence of traditional risk factors for thrombosis including central venous catheter (CVC), family or personal history of thrombosis, cardiac comorbidity, obesity, use of estrogen-containing oral contraceptive pills, recent surgery within the past 30 days[14–16], Factor V Leiden gene mutation, prothrombin gene mutation, deficiency of protein C, S and/or antithrombin, and presence of antiphospholipid antibodies.

Outcomes assessed:

Primary outcomes of interest were VTE resolution on imaging and bleeding complications with anticoagulation. Major bleeding was defined as per International Society on Thrombosis and Hemostasis criteria.[17] Secondary outcomes included recurrent VTE and mortality. Recurrent VTE was defined as an acute VTE that occurred 90 days or more after the index VTE (with radiologic evidence of resolution of the index VTE).

Statistical analysis:

Descriptive statistics were used to compare demographic and clinical characteristics between individuals with SCD younger than 12 years and those 12 to 21 years of age with VTE. The age at the time of index VTE was used as a binary variable to compare the clinical characteristics between the two groups based on the known change in VTE rate after puberty.[8] Fisher's exact test was used to compare categorical variables because of the small sample size in any given cell of the contingency table. A two-sided p-value of 0.05 was used for statistical significance.

Results:

Clinical characteristics of the cohort:

During the 10-year period, a total of 21 hospital acquired VTE events were identified. No patient had documentation of a prior VTE. Table 1 summarizes the clinical characteristics of the cohort. Most common VTE location was isolated PE (n=9, 43%), closely followed by isolated DVT (n=8, 38%). There were 6 total lower extremity DVTs and 6 total upper extremity DVTs, with some patients having DVTs in both locations. Majority of subjects had HbSS or HbSβThal^0 genotype (n=15, 71%). Age ranged from 1.5 years to 19.5 years, with a median age of 14 years. Fifty-two percent of the cohort were on hydroxyurea at the time of VTE (n=11). More than seventy percent of the VTE occurred in children with SCD who were 12 years and older (n=15).

Overall, more than half of the patients with VTE had ACS on admission or during hospitalization (n=11, 52%). Thirteen thrombotic events (62%) were associated with ICU admission. CVC-associated thrombosis was seen in 43% (n=9) of the cohort. CVC type was either tunneled catheters (n=8, 89%) or peripherally inserted central catheter line (n=1, 11%). Table 2 summarizes the risk factors sub-stratified into the two age groups for VTE. None of these clinical variables reached statistical significance, likely owing to small sample size. No patients reported the use of oral contraceptive pills or personal or family history of thrombosis.

Not all patients were tested for inherited thrombophilia, but among the ones who were tested, 3 (14%) patients had protein C deficiency, 1 (5%) patient had protein S deficiency, and 2 (9%) patients had antiphospholipid antibodies. Two patients with protein C deficiency were siblings with genetically proven diagnosis of heterozygous protein C deficiency. Sibling one had baseline protein C antigen and activity levels of 63% and 34% respectively, while sibling two's baseline levels were never obtained once genetic diagnosis of protein C deficiency was made. The third patient with protein C deficiency had baseline protein C antigen and activity levels of 66% and 56% respectively; genetic testing was not performed. The patient with protein S deficiency had baseline protein S activity of 26% and did not undergo genetic testing. In the two latter patients, while the protein C and protein S levels were obtained in the acute thrombosis setting, repeat values months later were still below normal, which could be due to the baseline lower levels of protein C and protein S observed in patients with SCD.[18] Regarding the 2 patients with antiphospholipid antibodies, 1 patient had systemic lupus erythematosus (SLE) along with positive anticardiolipin IgM and IgG antibodies and a lupus anticoagulant (positive by DRVVT and staclot) at the time of thrombotic event. While the anticardiolipin antibodies normalized 6 months later, this patient continued to have intermittent positive staclot, likely due to the underlying systemic lupus erythematosus (SLE). Anti beta2 glycoproteins IgG and IgM were normal. The other patient with antiphospholipid antibodies had positive lupus anticoagulant assays (DRVVT and staclot) with normal anticardiolipin IgG/IgM and anti beta2 glycoproteins IgG/IgM at the time of the thrombotic event. Repeat testing 3 months later showed normal levels of all 3 antibodies.

VTE outcomes:

All patients with documented thrombosis received therapeutic anticoagulation with at least 1 of the following: unfractionated heparin (n=7, 33%), low molecular weight heparin ([LMWH], n=21, 100%), warfarin (n=2, 9%), rivaroxaban (n=2, 9%), or apixaban (n=1, 5%). Only 1 patient (with PE and lower extremity DVT) additionally underwent catheter-directed thrombolysis and mechanical thrombectomy. All patients (n=21, 100%) had resolution of the primary VTE on imaging after 12 weeks of therapeutic anticoagulation. The rate of major bleeding was 10%. There was 1 death (5%), and it is thought that this patient likely died from showered emboli causing a PE and cardiorespiratory arrest that occurred shortly after the central line was

pulled.

Recurrent VTE

Of the 21 patients, 16 (76%) were followed for 5 years or more since the time of index VTE. Of the 5 patients who were not followed for at least 5 years, 3 were transitioned to adult care and 2 were lost to follow-up. Among the 16 patients with long-term follow-up data, there were no documented recurrences at 1-year follow-up after the index VTE, but 2 patients (13%) had recurrent thrombosis by 5-year follow-up after the index VTE, neither CVC-related. One of these 2 patients with recurrent VTE had PE on initial presentation and recurrent PE 13 months later while on prophylactic LMWH. Additional thrombotic risk factors in this patient were systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APLAS). This patient had a previous history of pulmonary hemorrhage secondary to capillaritis in the setting of SLE, and she was kept on prophylactic dose of LMWH rather than the recommended therapeutic dosage for APLAS to prevent recurrent pulmonary hemorrhage. The other patient with recurrent VTE had CSVT on initial presentation and presented with PE in the setting of brachial vein thrombosis 4 years and 3 months after the index VTE. Additional thrombotic risk factor in this patient was protein C deficiency confirmed by genetic testing and managed on warfarin (goal INR of 2.0-3.0) prior to the recurrent VTE. At the time of recurrent VTE, he was admitted to the hospital for a hip surgery. Prior to the procedure, he was bridged from warfarin to LMWH, which was held for 24 hours before and after the surgery. He was on a therapeutic dose, confirmed by anti-Xa levels, at the time of PE.

Discussion:

In this study, we describe a cohort of 21 patients with SCD at a quaternary care pediatric hospital who developed a hospital-acquired VTE over a 10-year period. Majority of the events occurred in adolescents. Recurrence rate at 5-year follow-up was 13% (n=2), and both subjects had additional underlying thrombophilic risk factors (protein C deficiency and APLAS, respectively). Our data support the growing recognition of the risk of VTE in SCD, even at a younger age, and the risk of recurrent VTE in a subgroup of patients with SCD.

Although no clinical characteristic reached statistical significance, likely owing to small sample size, the overall trend showed that hospital-acquired VTE in our cohort was most frequently associated with CVC, ICU admission, and ACS. Based on these data, we have revised our own institutional practice for thromboprophylaxis in SCD to reduce the incidence of hospital-acquired thrombosis and improve patient outcomes (Table 3). While the majority of questions regarding thromboprophylaxis in children with SCD can be answered by prospective clinical trials, in the absence of data, we have attempted to risk-stratify in our institutional practice based on findings from this study. For instance, patients aged 12 years and older are considered to be at higher risk for VTE if they are admitted to the ICU or diagnosed ACS or COVID-19; while patients younger than 12 years are considered to be at higher risk for VTE if they are admitted to the ICU and have an additional risk factor (e.g., presence of CVC). Anticoagulation comes with a risk of bleeding, as seen in our study with 10% incidence of major bleeding; hence the assessment of risks and benefits of prophylactic anticoagulation is necessary in each patient with SCD.

The proportion of patients with PE observed in our cohort is significantly higher than the previous estimates in pediatric patients with SCD and overall in pediatrics.[19,20] A relatively high prevalence of PE in patients with SCD has also been observed in previous adult studies and is presumed to be from in situ pulmonary artery thrombosis.[21–23] ACS was identified as a risk factor for VTE in our cohort. There is some evidence that these pulmonary arterial thrombi are found more frequently in patients with ACS.[24] In a large study of ACS in both adult and pediatric patients, PE was the most common cause of death in ACS, although VTE and fat embolism could not be differentiated.[25] The uncertainty regarding the etiology of pulmonary arterial thrombi also results in wide variation in anticoagulation practices. In pediatrics, anticoagulation is not recommended as an adjunct to ACS treatment, while in adults with SCD, therapeutic anticoagulation for patients with a positive radiograph is sometimes considered.[23] At our institution, we have revised our anticoagulation guidelines to recommend prophylactic anticoagulation for patients 12 years of age and older admitted with

ACS. However, given our relatively small sample size, the incidence of PE may not be reflective of population estimates. For this reason, there is an urgent need to conduct large, multicenter pediatric studies to validate our findings and evaluate the utility of anticoagulation in children and young adults with SCD admitted for ACS to prevent life-threatening PE.

Other risk factors identified in our cohort are recognized risk factors for thrombosis in general population, such as presence of CVC and ICU admission.[26] The usual reasons for a CVC in children with SCD are venous access, chronic transfusion therapy, need for long-term antibiotics, and emergent erythrocytapheresis.[27] While COVID-19 is a highly thrombogenic condition as well,[28] less than 10% of our patients with SCD and VTE were diagnosed with COVID-19 at the time of VTE. The likely reasons could be this acute illness was prevalent only in the last 2 years of the 10-year study period. Additionally, patients with SCD were recognized as high-risk for thrombosis based on our institutional guidelines for thromboprophylaxis in COVID-19 and were placed on thromboprophylaxis when admitted to the hospital. This may have resulted in the overall lower incidence of VTE in this subgroup.

Recurrence of VTE is largely unknown in children and young adults with SCD. A single center retrospective study in adults with SCD showed a recurrence rate 33% while on anticoagulation, however, there was missing data in 43% patients.[8] Furthermore, a large population-based study of adult patients with SCD treated at various institutions in California showed a 5-year recurrence rate of 28% for those with severe disease (defined as [?]3 hospitalizations in one year) and 12% for those with less severe disease.[24] Based on these findings, the American Society of Hematology now recommends indefinite anticoagulation for adults with SCD after their first unprovoked VTE.[29] However, there is dearth of data to guide anticoagulation recommendations in pediatrics. One of the objectives of our study was to close this knowledge gap. We found a 13% recurrence rate at 5 years, however, there were missing long-term follow-up data on 5 patients (24%) of our cohort, thereby limiting our conclusions. Larger prospective studies are indicated to assess the recurrence rate to help physicians make more informed decisions regarding the duration of anticoagulation.

We do want to acknowledge some limitations of our study. This is a single institution study which may limit the generalizability of the findings. Additionally, given the retrospective nature, it is not possible to determine causation, and we can only report association with several high-risk factors. Although the majority of patients were followed long-term at our center, there were some that were lost to follow-up or transitioned to adult care, and this fragmentation of care may have resulted in incomplete data collection. Future studies should also compare the risk factors for VTE in a SCD cohort to a cohort without SCD.

In conclusion, this study identifies a subgroup of children and young adults with SCD who are at a higher risk of VTE and may benefit from thromboprophylaxis on admission to the hospital. Given the wide variability in anticoagulation practices across different pediatric institutions, our proposed guidelines may serve as a framework for other institutions to adopt. Moreover, our data highlight the need for large, multicenter collaboration to create a consensus anticoagulation guideline for children and young adults with SCD to optimize care and improve outcomes.

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Contributors statement page:

Drs Shreya Agarwal, Kayla L Foster, Shaniqua J Anum, HyoJeong Han, Mary C. Shapiro and Sarah E. Sartain conceptualized and designed the study, collected data, drafted the initial manuscript and critically reviewed and revised the manuscript.

Dr Gladstone Airewele conceptualized the study, critically reviewed and revised the manuscript.

Dr Michael Scheurer performed data analysis, critically reviewed and revised the manuscript.

All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

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