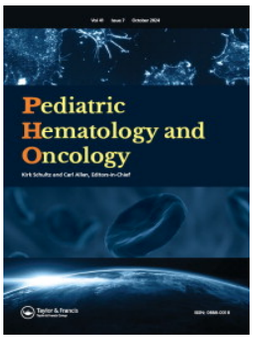

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Hospital acquired venous thromboembolism in children with sickle cell disease

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ABSTRACT

Sickle cell disease (SCD) is well recognized as a hypercoagulablestate, however, it remains unclear whether a subgroup of children with SCD at higher risk of venous thromboembolic event (VTE) during hospitalization may benefit from thromboprophylaxis. Our objectives were to describe the clinical characteristics, outcomes and recurrence of hospital acquired VTE in patients with SCD younger than 21 years. This was a single center retrospective study. Data regarding demographics, reason for admission, location of VTE, risk factors like central venous catheter (CVC), intensive care unit (ICU) admission among others were extracted from electronic medical records over a 10-year study period (2011–2021). Recurrence of VTE at 1 and 5 years was assessed. Descriptive statistics were used as indicated. We identified a total of 20 VTE events over the 10-year study period. Six of these events occurred in those younger than 12 years of age. Fourteen (70%) VTE events occurred in the HbSS or HbSβThal0 genotypes compared to 6 (30%) in HbSC. Most common VTE was isolated pulmonary embolism (PE) ($n=10$, 50%). VTE were most often associated with acute chest syndrome (ACS) ($n=14$, 70%), ICU admissions ($n=10$, 50%) and CVC ($n=5/9$, 55%). One patient died from the VTE event. One patient with additional underlying risk factors had a recurrent VTE at 13 months. Our study suggests that ICU admission, ACS and presence of CVC increases the risk of VTE in children and young adults with SCD, but larger studies are indicated to validate our findings.

Abbreviations: ACS: Acute chest syndrome; APLAS: Antiphospholipid antibodies; CSVT: Cerebral vein sinus venous thrombosis; CVC: Central venous catheter; DRVVT: Diluted Russell viper venom time; DVT: Deep vein thrombosis; ICU: Intensive care unit; ISTH: International Society on Thrombosis and Haemostasis; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; SCD: Sickle cell disease; SLE: Systemic lupus erythematosus; TCH: Texas Children's Hospital; VTE: Venous thromboembolic event

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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 the coagulation cascade with decreased levels of natural anticoagulants and increased pro-coagulant factor activation.[5] All elements of Virchow's triad, namely, 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 are limited.

Over the past two decades, children's hospitals in the United States have seen an alarming 130% 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, there are no standardized guidelines for thromboprophylaxis in children with SCD, and most of the guidelines are extrapolated from adult literature. This has resulted in wide variability of thromboprophylaxis practices across different institutions for hospitalized children with SCD.[12]

Our institutional practice has been to prescribe thromboprophylaxis for patients with SCD who are18 years of age and older admitted to the hospital or 16 years of age and older admitted to the intensive care unit (ICU). We follow around 1200 patients with SCD at our institution. 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. Our objectives were to review our institutional cohort of subjects with SCD who had a hospital acquired VTE, assess the prothrombotic risk factors, and describe outcomes with anticoagulation with the ultimate goal of identifying the subgroup of patients who may benefit from thromboprophylaxis during hospitalization.

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 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, 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.

Variables collected

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 and length of hospitalization were collected from the electronic medical record.

The index VTE date was defined as the date of the diagnostic imaging study. Data were collected on the type (DVT, CSVT, and PE) and location of the thrombotic event (eg cerebral veins, upper or lower extremity), any thromboembolic complication, choice of anticoagulant, mechanical thrombectomy or thrombolysis. Additionally, charts were reviewed for presence of 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, surgery within the past 30 days,[13–15] factor V Leiden gene mutation, prothrombin gene mutation, deficiency of protein C, S 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 the International Society on Thrombosis and Haemostasis (ISTH) criteria.[16] Secondary outcomes included recurrent VTE and mortality. Recurrent VTE was defined as an acute VTE that occurred at least 90 days or beyond after the index VTE with prior radiologic evidence of resolution of the index VTE.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics.

Results

Clinical characteristics of the cohort

During the 10-year period, a total of 20unique individuals with hospital acquired VTE events were identified. None of these patients had documentation of a prior VTE. Table 1 summarizes the clinical characteristics of the cohort. Most common VTE location was isolated PE (10/20, 50%), followed by isolated DVT(6/20, 30%) and combined DVT + PE (3/20, 15%). There were 6 total lower extremity DVTs and 6 total upper extremity DVTs, with some patients having DVTs in both locations. Majority of the subjects belonged to HbSS or HbSβThal0 genotype ($n = 14$, 70%). Age ranged from 1.5 years to 19.5 years, with a median age of 14 years. Fifty percent of the cohort

Table 1. Baseline demographic characteristics of the study cohort.

Demographics	n (%)
Sex	
• Male	12 (60)
• Female	8 (40)
Age (median and range)	14 years (1.5–19.5 years)
Genotype	
• HbSS/HbSβThal^0	14 (70)
• HbSC	6 (30)
• Other genotypes	0 (0)
On hydroxyurea	10 (50)
Admission diagnosis	
• Vasoocclusive pain crisis	12 (60)
• Acute chest syndrome	15 (75)
• Fever	7 (35)
• COVID-19	2 (10)
• Other	2 (10)
Location of VTE	
• DVT	6 (30)
• PE	10 (50)
• Both DVT and PE	3 (15)
• IVC thrombus	1 (5)

VTE venous thromboembolic event, DVT deep vein thrombosis, PE pulmonary embolism, IVC inferior vena cava.

were on hydroxyurea at the time of VTE ($n = 10$). More than 70% of the VTE occurred in children with SCD who were12 years and older.

Table 2 gives a detailed summary of the clinical risk factors for each patient. Overall, 75% of the patients with VTE had ACS on admission or during hospitalization ($n = 15$). Majority of the patients with PE had ACS during their hospitalization ($n = 12/15$, 75%). Around half of the patients were admitted to the ICU at the time of VTE ($n = 10$, 50%). Although 9 patients had a CVC at the time of VTE (4 were acutely inserted for illness, while 5 had CVC prior to admission), CVC-associated VTE was noted only in5 of these patients ($n = 5/9$, 55%). CVC type was either tunneled catheters ($n = 4$, 80%) or peripherally inserted central catheter ($n = 1$, 20%).

Decision regarding thrombophilia testing was per provider preference. Not all patients were tested for inherited thrombophilia, but among those who were tested, 2(10%) patients had protein C deficiency, 1 (5%) patient had protein S deficiency, and 2 (10%) patients had antiphospholipid antibodies. One patient with protein C deficiency was diagnosed after her sibling was found to have genetically proven heterozygous protein C deficiency; baseline antigen/activity levels were never obtained once genetic diagnosis of protein C deficiency was made. The second patient with protein C deficiency had baseline protein C antigen and activity levels of 66% and 56% respectively; genetic testing was not performed. Patient with protein S deficiency had baseline protein S activity of 26% and did not undergo genetic testing. Regarding antiphospholipid antibodies, one 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 six months later, patient continued to have intermittent positive Staclot likely due to the underlying SLE. Anti-beta-2 glycoproteins IgG and IgM were normal. The other patient with positive antiphospholipid antibodies had positive lupus

Table 2. Detailed summary of all patients with a hospital acquired VTE.

Patient	Age (years)	Gender	Genotype	Reason for admission	VTE Type	Risk factor(s)	Reason for CVC	On ppx anticoagulation	Recurrence	Additional Comments
1	6	F	HbSC	ACS	PE alone	ICU	N/A	No		
2	14	F	HbSC	VOC	DVT and PE	-Protein C def	N/A	No		PC genetics: *PROC* gene sequencing; c.151C > T, p.Arg51Cys; heterozygous (sister of patient with known PC deficiency)
3	19	F	HbSS	VOC, then ACS	PE alone	N/A	N/A	No		
4	14	M	HgSC	VOC, ACS	DVT and PE	-ICU	N/A	No		
5	17	M	HbSC	VOC Hypertensive urgency	DVT	-ICU	N/A	Yes		
6	18	M	HbSS	Fever and ACS	PE alone	N/A	N/A	No		
7	17	F	HbSS	Fever and ACS	PE alone	N/A	N/A	No		
8	14	F	HbSS	Fever and VOC	DVT	-ICU	Hemodynamic monitoring, access for medications and frequent blood draws	No		Catheter related
9	1.42	M	HbSS	Fever and ACS	DVT	N/A	Long term Abx	No		Bacteremia and Osteomyelitis during hospitalization DVT catheter related
10	18	M	HbSS	Fever and ACS	PE alone		Exchange transfusion for ACS	Yes		Patient was admitted with ACS, went home and readmitted within the week for PE; line was not the cause of the PE as it was removed before going home during the first admission
11	17	M	HbSS	VOC, then ACS	DVT x 2	-ICU	Exchange transfusion for ACS	Yes		DVTs catheter related Patient died suddenly after pulling of line, suspected cause of death was PE, no autopsy done
12	14	M	HbSS	Liver failure	IVC thrombus	-ICU	Access for medications and frequent blood draws	No		Not catheter related
13	7	F	HbSS	VOC and ACS	PE alone	-Presence of APLA -ICU	N/A	No	Yes	Lupus, intermittently positive staclot APLAS Anticoagulation—now warfarin

(*Continued*)

Table 2. Continued.

Patient	Age (years)	Gender	Genotype	Reason for admission	VTE Type	Risk factor(s)	Reason for CVC	On ppx anticoagulation	Recurrence	Additional Comments
14	1.8	M	HbSS	Moya Moya needing surgery	DVT	-ICU -Sx	Exchange transfusion	No		Developed right lower extremity DVT on POD #3 Clot was not catheter related
15	11	F	HbSC	VOC, then ACS	PE alone	-ICU	Exchange transfusion	No		PE not catheter related
16	18	M	HbSS	Fever, VOC, and ACS	PE alone	-Protein C def -APLA	N/A	No		Protein C deficiency by labs only, no genetic testing done APLA—cleared by 3 months, not APLAS.
17	14	M	HbS-BThal0	VOC and ACS	PE and DVT PE- hosp acquired	-Protein S def	N/A	No		PE was hospital acquired, but DVT was not
18	16	M	HbSC	Chest wall trauma and rib contusion, then developed ACS	PE alone	-N/A	N/A	No		
19	7	M	HbSS	Fever and VOC, then developed ACS	DVT	-N/A	Red cell exchange	No		Catheter in place before admission, DVT was catheter related
20	16	F	HbSS	VOC, then ACS	PE and DVT	-ICU	Difficult venous access, prolonged IV therapy, frequent blood draws, medication requiring CVC, need for multiple lines, hemodynamic monitoring	Yes		Hospitalization complicated by Bacteremia Catheter related Bleeding: Epistaxis

PPX prophylaxis, ACS acute chest syndrome, VOC vasoocclusive crisis, PE pulmonary embolism, DVT deep vein thrombosis, IVC inferior vena cava, ICU intensive care unit, CVC central venous catheter, APLAS antiphospholipid antibody syndrome, APLA antiphospholipid antibody.

anticoagulant assays (DRVVT and staclot) with normal anticardiolipin IgG/IgM and anti-beta-2 glycoproteins IgG/IgM at the time of thrombotic event. Repeat testing three months later showed normal levels of all three antibodies.

VTE outcomes

All patients with documented thrombosis received therapeutic anticoagulation with unfractionated heparin ($n = 7$, 33%), low molecular weight heparin ([LMWH], $n = 20$, 100%), warfarin ($n = 2$, 9%), rivaroxaban ($n = 2$, 9%), and/or apixaban ($n = 1$, 5%). Only 1 patient (with PE and lower extremity DVT) additionally underwent catheter directed thrombolysis and mechanical thrombectomy given the extensive nature of the lower extremity thrombosis. All patients ($n = 20$, 100%) had resolution of the primary VTE on imaging after12 weeks of therapeutic anticoagulation. There were 2(10%)major and clinically relevant non major bleeding episodes. There was 1 (5%) death, and it is thought that this patient likely died from dislodged DVT causing a PE and cardiorespiratory arrest that occurred shortly after CVC removal.

Recurrent VTE

The patient with SLE had recurrent PE by 5-year follow-up after the index PE, despite being on prophylactic LMWH 40 mg daily at home. This patient had a previous history of pulmonary hemorrhage secondary to capillaries in the setting of SLE, hence weighing in risks vs benefits of anticoagulation for the antiphospholipid antibodies, she was kept on prophylactic dose of LMWH rather than the recommended therapeutic dosage for APLAS to prevent recurrent pulmonary hemorrhage. There were no other recurrent VTEs in the cohort.

Discussion

In this study, we describe an institutional experience with hospital acquired VTE in children and young adults with SCD. Most common VTE was PE, and majority of the patients who developed PE were admitted for ACS. Adolescents more often experienced VTE compared to younger patients. VTE recurrence was noted in only one patient who also had additional underlying thrombophilic risk factors namely, SLE and APLAS. Our data support the growing recognition of the risk of VTE in SCD, even at a younger age, and need for SCD-specific standardized pediatric thromboprophylaxis guidelines to prevent such outcomes.

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.[17,18] A relatively high prevalence of PE in SCD has also been observed in previous adult studies and is presumed to be from in situ pulmonary artery thrombosis.[19–21] Notably, majority of the patients at our center with PE were initially admitted for ACS. Another single center pediatric study found that seven out of the eight patients with PE (88%) had ACS in the preceding 30 days.[22] Similarly, another large multicenter study of ACS with predominantly pediatric patients reported that PE was the most common cause of death in ACS.[23] Based on this data, it can be postulated that in situ pulmonary

artery thrombi might be more frequent in patients with ACS than is recognized. Some supporting evidence comes from a study conducted by Dessap et al.[21] In 144 cases of patients with ACS, they found that 17% had pulmonary artery thrombi on chest computed tomography, but none of these patients had a DVT on lower extremity ultrasonography suggesting that the pulmonary artery thrombi were an in situ phenomenon, rather than an embolic event. Given the high proportion of PE in patients with ACS in our cohort, we have revised our institutional anticoagulation guidelines to recommend prophylactic anticoagulation for patients 12 years of age and older admitted with ACS (implemented in 2022). However, given our relatively small sample size, the incidence of PE may not be reflective of population estimates. There is a need to conduct large, multicenter pediatric studies to validate our findings and evaluate the efficacy and safety of anticoagulation in children and young adults with SCD admitted for ACS to prevent life threatening PE.

Our findings regarding the risk factors for VTE are consistent with previous studies investigating the epidemiology of VTE in SCD.[24,25] Similar to previous studies, majority of the patients in our cohort with VTE were either in the ICU and/or had a CVC. The usual reasons for a CVC in children with SCD are venous access, chronic transfusion therapy, need for long term antibiotics, and emergent erythrocytapheresis.[26] CVCs are well recognized as a risk factor for thrombosis in children with SCD. Hence, many institutional guidelines recommend pharmacologic thromboprophylaxis for individuals with SCD with a CVC, but this is not a standardized practice nationwide. This is again highlighted in our cohort – although few patients met the criteria for prophylactic anticoagulation, they did not receive prophylaxis. The ultimate decision regarding prophylaxis is made by the attending on service and shows the variability in practice amongst individual providers and need for education. This variability across institutions is further highlighted by a recent study by Davila et al. They utilized Pediatric Health Information System Database to assess trends in the use of pharmacologic and mechanical thromboprophylaxis in adolescent patients with SCD admitted to the hospitals and found that the range varied from 0 to 62%.[27] Lastly, low circulating amounts of natural anticoagulants like protein C and S can be observed in individuals with SCD[28] as seen in a few of our patients, which further increases the risk of thrombosis.

Rates of recurrent VTE are 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 on 43% patients.[8] Furthermore, a large population-based study of adult SCD patients 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.[29] Based on these findings, the American Society of Hematology now recommends indefinite anticoagulation for adults with SCD after their first unprovoked VTE.[30] However, there is dearth of data to guide anticoagulation recommendations in pediatrics. We were unable to close this knowledge gap given the retrospective nature of this study and loss to follow up or transition of certain individuals to adult providers before the 5-year follow up. There was only one individual in our study with a recurrent VTE, and this patient had additional thrombophilic risk factors. Larger prospective studies are indicated to assess the recurrence rate to help physicians make more informed decisions regarding the duration of anticoagulation.

This study has certain limitations. VTE in SCD is a rare event. Hence, as a single institution study the generalizability of the findings may be limited. Additionally, given the retrospective nature, it is not possible to determine causation, and we can only report observed trends. Prolonged immobility during hospitalizations is a known risk factor for VTE.[4,10] Braden Q score is an objective way of assessing immobility. But this score was not consistently measured for all the patients, hence we are unable to comment on the role of immobility in this cohort. Although most 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. Lastly, there were a few patients who developed a VTE while on prophylactic anticoagulation. Since we collected data only for the individuals with SCD who developed a VTE, we were unable to calculate the proportion of patients who developed a VTE while on prophylaxis, and future studies are warranted to assess the temporal relationship. Strengths of our study include manual validation of the cohort which limits misclassification; and description of risk factors for recurrence of VTE in children with SCD.

In conclusion, this study identifies a subgroup of children and young adults with SCD who are at a higher risk of hospital acquired VTE and who may benefit from pharmacologic thromboprophylaxis on admission to the hospital. Larger, multicenter collaborative studies are indicated to better understand safety and efficacy of pharmacologic thromboprophylaxis and ultimately, create a consensus anticoagulation guideline for children and young adults with SCD to optimize care and improve outcomes.

Disclosure statement

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Clinical trial registration

Not applicable.

Contributors statement

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