Are Children with SARS-CoV-2 Infection at High Risk for Thrombosis? Viscoelastic Testing and Coagulation Profiles in a Case Series of Pediatric Patients

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July 20, 2020

Abstract

The coagulopathy of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is well documented in adults, with increases in D-dimer and prothrombin time strong predictors of mortality and anticoagulation shown to decrease this mortality. Viscoelastic parameters such as elevations in maximum clot firmness (MCF) on rotational thromboelastometry (ROTEM) have correlated with a hypercoagulable state in adults with SARS-CoV-2. We report our experience in children infected with SARS-CoV-2, with noted elevations in D-dimer and MCF on ROTEM (indicating hypercoagulability). Exploration of viscoelastic testing to provide additional laboratory-based evidence for pediatric-specific risk-assessment for thromboprophylaxis in SARS-CoV-2 is warranted.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found to induce an increased incidence of thrombosis[1, 2] and strokes[3] in adults. They developed a recognizable coagulopathy, characterized by increased thrombin generation, decreased fibrinolysis, elevated D-dimers and a prolonged prothrombin time (PT), which was found to be a strong predictor of mortality, with pulmonary microthrombi contributing significantly[4]. Anticoagulation has been shown to decrease this mortality[5].

Rannucci et al [6] reported baseline viscoelastic testing (using the Quantra Hemostasis analyzer system) obtained 2-5 days after admission to the ICU demonstrating increased clot strength, fibrinogen contribution to clot strength and elevated fibrinogen and D-dimer levels in 16 patients. After escalating thromboprophylaxis, there was a significant time-related decrease in fibrinogen, D-dimer levels and clot strength without significant thromboembolic events. Spieza et al [7] used another viscoelastic tool, Rotational Thromboelastometry (ROTEM), in acutely ill hospitalized SARS-CoV-2 patients and demonstrated elevated fibrinogen and D-dimers ($p < 0.0001$) and higher maximum clot firmness (MCF) in all ROTEM parameters in patients compared to controls ($p< 0.0001$).

Children develop thromboembolic complications in the face of catheter-related, genetic, anatomical and disease-related predisposing factors. Elevated fibrinogen and D-dimer levels are observed in various conditions in children such as infections and autoimmune diseases, including SARS-CoV-2. However, the prevalence of thromboembolic complications in children with SARS-CoV-2 infection has not been well documented, and there are no pediatric-specific thromboprophylaxis guidelines. Major hematology organizations, including the American Society of Hematology (ASH)[8] and the International Society of Thrombosis Haemostasis

(ISTH)[9] have published recommendations for anticoagulation of hospitalized symptomatic adults with SARS-CoV-2, which have been largely extrapolated to the pediatric population. A recent report by Loi et al[10] has made some diagnostic and therapeutic anticoagulation recommendations based on risk stratification of a single institutional experience. However, there remains a need in this population for laboratory-based risk-assessment tools to guide clinical decision making on the use of anticoagulant prophylaxis.

In an effort to explore the utility of viscoelastic testing in children with SARS-CoV-2, we added ROTEM (a viscoelasticity-based tool available for clinical use at our institution) to routine coagulation testing in children admitted with SARS-CoV-2. The objective of this analysis was to determine if standard coagulation tests and ROTEM testing could be obtained in children admitted with SARS-CoV-2 infection to assess its feasibility in determining thrombosis risk. And, if so, were changes in clot strength in children during an acute SARS-CoV-2 infection comparable to that seen in adults. We report our experience in this retrospective analysis of a case series of 8 children with SARS-CoV-2 infection.

Methods

Data were recorded on patients younger than 21 years of age admitted to Cohen Children's Medical Center between April 13th and April 29th, 2020, with varying illness severity associated with SARS-CoV-2 infection documented by a positive PCR-based test. Patients older than 21 years and those with known coagulopathy or undergoing anticoagulation for other conditions were excluded. In addition to clinical demographics, laboratory data including baseline coagulation and inflammatory markers along with results of ROTEM analysis (ROTEM delta, Instrumentation Laboratory – Werfen, Barcelona, Spain) were collected. Whole blood for ROTEM analyses was obtained within 1-4 days of admission and included EXTEM (for evaluation of the extrinsic pathway), INTEM (intrinsic pathway), FIBTEM (fibrinogen activity) and APTEM (fibrinolysis) as previously described[11]. The following ROTEM parameters were analyzed: (1) clotting time (CT) corresponding to the initiation phase of the clotting process; (2) clot formation time (CFT) reflects the measure of the propagation phase of whole blood clot formation; (3) maximum clot firmness (MCF) is the maximum amplitude in millimeters reached in the thromboelastogram.

Mean and ranges were calculated as appropriate for normalcy of data. Comparisons were performed with Spearman's correlation and Mann Whitney testing using SPSS Statistics (Version 1.0.0.1347, Armonk, NY). The Northwell Health Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

Results

The demographics and laboratory values of eight hospitalized children diagnosed with SARS-CoV-2 infection are shown in Table 1. Average age was 12.9 years, with equal gender distribution and 38% were overweight or obese (BMI >25 kg/m^2 or >30 kg/m^2 respectively). Seventy-five percent required oxygen supplementation and 63% required ICU admission. Central lines in 25% remained in place for an average of 6 days; half of the patients were treated with hydroxychloroquine and 25% received Remdesivir (compassionate use, Gilead Sciences). Prophylactic enoxaparin (0.5 mg/kg/dose subcutaneously every 12 hours) was initiated in patients based on institutional adult guidelines of oxygen requirement, and elevated D-dimer levels. It was escalated to therapeutic enoxaparin (1 mg/kg/dose subcutaneously every 12 hours) in 63 % of patients for clinical deterioration with increasing hypoxia requiring admission to intensive care and/ or ventilator support. Anti-Xa levels were monitored only in the presence of deteriorating renal function or thrombocytopenia to reduce clinical staff exposure. There were no observed bleeding complications, thromboembolic complications or deaths.

Abnormal laboratory data expressed as means included lymphopenia (37.5%), mild thrombocytopenia (13 %), prolonged PT (50 %), elevated ferritin (37%) and C-reactive protein (88%). Elevations in D-dimer levels (75%), and fibrinogen (88 %) were observed on the day ROTEM was drawn for analyses.

ROTEM analysis (Table 2) showed a predominance of hypercoagulable profiles with elevated EXTEM MCF (50%), elevated INTEM MCF (38%), and both elevated FIBTEM A10/20 and elevated FIBTEM MCF (in

75% of patients), which is comparable to that seen in adults. Averages and ranges cannot be reported due to variability of age-based reference ranges in pediatrics[10]. There was no statistically significant correlation between fibrinogen and EXTEM MCF (p=0.116), INTEM MCF (p=0.232) or FIBTEM MCF (p=0.130) on the day ROTEM was obtained, nor was there correlation of d-dimer levels with these parameters [d-dimer and EXTEM MCF (p=0.949), INTEM MCF (p=0.731) or FIBTEM MCF (p=0.748)]. However, we observed that all patients admitted to the ICU had a 3 to 10-fold elevation in D-dimer levels, and a 2- fold elevation in fibrinogen levels and 80 % of the patients had elevated FIBTEM parameters.

Discussion

Most revealing from this study, we observed increased evidence of clot strength in ROTEM parameters of EXTEM MCF and FIBTEM MCF (suggestive of increased clot firmness by contribution from fibrinogen), similar to that reported by Rannucci et al[6]. We also noted that in the early stages of SARS-CoV-2 infection, children under age 21 had elevated fibrinogen, D-dimer levels, and CRP (all suggestive of a highly inflammatory state), in addition to lymphopenia and prolonged PT (similar to those observed in adults). However, our pediatric cohort did not develop symptomatic thromboembolic events or increased mortality, despite demonstration of a comparable hypercoagulable state.

Although our patient population was heterogeneous with respect to clinical course and level of coagulopathy, our small sample size precludes a demonstrable correlation between fibrinogen, D-dimers or viscoelastic testing or its predictive value in assigning risk for thrombosis on prophylactic anticoagulation in children. However, we demonstrated that ROTEM testing is feasible and recommend that it's utility in determining the hypercoagulable state merits further study in children, who we and others, have shown can exhibit clinical severity and laboratory evidence of a coagulopathy identical to that seen in adults with SARS-CoV-2.

Acknowledgements:

Charlotte Kvasnovsky and Danielle Soberman for statistical analyses; Marium Malik, Pooja Desai, Sibgha Zaheer for coordinating studies; Donna DiMichele for helpful suggestions on the manuscript; residents and nursing staff caring for children with SARS-CoV-2 infection; the Northwell Covid-19 Research Consortium; and the Robert Chasanoff family for funding the ROTEM tool.

M. Al-Ghafry: performed research, analyzed data and wrote the paper; B. Aygun, A. Appiah-Kubi, A. Vlachos: Analyzed and interpreted data; G. Ostovar, C. Capone, T. Sweberg, N. Palumbo, P. Goenka: took care of patients; L.C. Wolfe, and J.M. Lipton: interpreted data and revised the paper; S.S. Acharya: designed research, interpreted data and wrote the paper.

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