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Use of Thromboelastography to Predict Thrombotic Complications in Pediatric and Neonatal Extracorporeal Membranous Oxygenation

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Abstract: The objectives of this study were to investigate the correlation between thromboelastography (TEG) and conventional measures of anticoagulation, and to determine optimum values for citrated kaolin TEG R time (TEG RCK) and anti-Xa activity that would minimize both bleeding and thrombotic complications in pediatric and neonatal patients requiring extracorporeal membranous oxygenation (ECMO). A retrospective chart review of patients requiring veno-venous (VV) and venoarterial (VA) ECMO was performed. Combined medical and cardiac ICU within a single-center, tertiary care, freestanding, children's hospital. Non-pregnant patients <18 years and >2 kilograms requiring VV or VA ECMO from July 2013 through July 2015. Anti-Xa (OR = 0.62, 95% CI 0.53–0.72, $p < .001$) and TEG RCK (OR = 1.19, 95% CI 1.07–1.34, $p = .003$) were the only independent predictors for a significant thrombotic event. Receiver operating characteristic curves and traditional epidemiological data (sensitivity, specificity, PPV, NPV) were used to determine optimal target Anti-Xa and TEG RCK values. No independent predictors for significant bleeding events were identified in this cohort. A anti-Xa activity of .25 IU/mL (sensitivity = 81%, specificity = 67%, PPV = 81%, NPV = 58%) and TEG RCK time of 17.85 minutes (sensitivity = 84%, specificity = 68%, PPV = 82%, NPV = 59%) were established as the optimal thresholds for preventing thrombotic events. Anti-Xa and TEG RCK were independent predictors of thrombosis in this cohort of pediatric and neonatal ECMO patients. Targeting an anti-Xa activity greater than .25 IU/mL and a TEG RCK greater than 17.85 minutes may minimize the risk of thrombosis in pediatric and neonatal ECMO patients. Future investigation should evaluate targets for anti-Xa and TEG RCK, which additionally minimize the risk of significant bleeding in this patient population.
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Management of anticoagulation in patients requiring extracorporeal membranous oxygenation (ECMO) is arguably one of the most challenging aspects of caring for these patients (1–5). Historically, activated clotting time (ACT) has been the most widely used test of unfractionated heparin (UFH) efficacy in ECMO patients (6,7). Recently, anti-Xa and thromboelastography (TEG) have been increasingly used as measures of anticoagulation efficacy in patients requiring ECMO (8). Evidence is building that supports the use of these tests as an alternative to ACT (8–10).

Anti-Xa assay measures the functional activity of heparin in a given sample. TEG is a viscoelastic test of whole blood coagulation that evaluates the entirety of the coagulation cascade from initiation of clot formation to fibrinolysis. By contrast to the activated partial thromboplastin time (aPTT) and ACT which end at the time of initial clot detection, TEG provides a global assessment of hemostatic function from initiation of clot formation via platelet–fibrin interaction,

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platelet aggregation, clot strengthening, and eventual clot lysis (11). Therefore, TEG can detect perturbations in the coagulation profile throughout the coagulation cascade. TEG can also provide information regarding fibrinolysis which is not easily measured by traditional tests of coagulation. In ECMO patients, the use of paired TEG testing is especially appealing. One sample can be performed with heparinase (TEG_{CKH}) to degrade any heparin present in the blood. This will reflect the patient's in vitro coagulation in the absence of heparin. Another sample without heparinase (TEG_{CK}) will reflect the in vitro behavior of coagulation in the presence of heparin (12,13). Despite this, there is a paucity of data regarding optimal target values for TEG parameters in pediatric and neonatal ECMO patients. In addition, there are no data to support the use of thrombotic targets to predict bleeding or thrombotic complications.

The objectives of this study were to examine the performance of anticoagulation targets for predicting a significant bleed and/or a significant thrombotic event, to identify a target anti-Xa activity and TEG_{CK} R time which could minimize both bleeding and thrombotic complications, and to evaluate the correlation between TEG parameters and traditional measures of coagulation in pediatric and neonatal ECMO patients.

MATERIALS AND METHODS

A retrospective, single-center chart review of all pediatric and neonatal patients who received ECMO over a 2-year period in a large tertiary care center was conducted. The institution's internal review board approved this study.

Population

Patients less than the age of 18 years, more than 2 kg, and requiring ECMO from July 2013 through July 2015 were included in the study. Patients with known underlying coagulation disorders or heparin-induced thrombocytopenia, patients requiring the use of a direct thrombin inhibitor rather than UFH while on ECMO, and pregnant females were excluded from this study.

Study Procedure

Electronic medical records were reviewed and relevant data were abstracted using an Excel-based data collection form. Data points gathered included demographic data, underlying diagnosis, reason for ECMO cannulation, type of cannulation, heparin dosing, circuit changes, and thrombotic and bleeding complications as defined by the Extracorporeal Life Support Organization (ELSO) registry. ELSO defines thrombotic and bleeding complications as those that "require intervention." Therefore, clots that required a circuit or component change or resulted in limb or organ ischemia were recorded as complications. Hemorrhagic events that required intervention via surgical exploration, circuit change, transfusion, or intracranial hemorrhage were recorded as complications. Surgical exploration was at the discretion of the attending surgeon. Typically, patients demonstrating >5 mL/kg/h of blood loss for more than two consecutive hours are considered for exploration. Suggested red blood cell transfusion thresholds at our institution during VV ECMO are hemoglobin (Hgb) <12 g/dL and Hgb <10 g/dL during VA ECMO. However, the decision to transfuse is at the discretion of the attending physician. Occasionally, transfusions occur at a higher threshold because of hemodynamic instability, ongoing significant bleeding, or signs of inadequate oxygen delivery. Laboratory values collected included hematologic values and anticoagulation markers (platelet count, ACT, aPTT, fibrinogen, anti-Xa, and TEG values).

All laboratory values were drawn by pediatric intensive care nurses or ECMO specialists in our institution. In an effort to avoid heparin contamination, 4–5 mL of blood was drawn and disposed of before the sample was sent for laboratory analysis. During the first year of the study, 4–5 mL was disposed of, withdrawn, and discarded to allow for reliable anticoagulation labs. Because of concerns for infection, our institution does not allow blood drawn as "waste" to be returned to the patient. In the second year, heparin was removed from the arterial line fluids in ECMO patients, allowing for <1 mL of blood to be "wasted" for laboratory draws. Anti-Xa was analyzed using the BCS XP system via chromogenic assay (Siemens Healthcare Diagnostic Products, Malvern, PA). No exogenous antithrombin is added to the anti-Xa assay. TEG (citrated kaolin and heparinase samples) was analyzed using TEG® 5000 Thrombelastograph® hemostasis analyzer system (Haemonetics, Braintree, MA). ACT tests were performed as point-of-care tests using the Hemochron Junior (Accriva Diagnostics, San Diego, CA). ACTs are drawn from a separate pigtail, pre-heparin drip.

ECMO Circuit

All patients were managed on Medtronic ECMO circuits consisting of Carmeda-coated tubing with a Rotaflow centrifugal pump (Maquet, Germany). All circuits contained a Better Bladder™ (Circulatory Technology, Oyster Bay, NY).

Therapeutic Considerations

UFH dosing was directed as per institutional protocol (Figure 1) to maintain goal anti-Xa of .2–.7 IU/mL. ACT tests were performed hourly. Anti-Xa and aPTT were drawn every 6 hours and as needed to assess UFH dosing. TEG_{CK} and TEG_{CKH} were performed daily and as needed. Comparison of coagulation markers was only performed on samples collected within 30 minutes of one another. If traditional coagulation tests and TEGs were not collected within the 30-minute window, the data were excluded from our study.

Anticoagulation Test Response Table

anti-Xa (0.3-0.7 units/mL)	ACT (Determined range)	Response
Therapeutic	↑	Check fibrinogen, replace if < 150 mg/dL then repeat Anti-Xa and ACT If unchanged, check heparinase TEG and correct underlying coagulopathy if present –repeat TEG, ACT, and Anti Xa If ACT still elevated and Anti Xa therapeutic after completing above, adjust goal ACT range 10 seconds on either side of current ACT. (Example: Anti-Xa = 0.4 IU/mL, ACT = 260 seconds, new goal ACT range is 250-270 seconds) Continue current heparin rate. (consider kaolin TEG to confirm goal R value 20-30 minutes to reflect adequate heparinization)
Therapeutic	In desired range	Maintain current heparin rate
Therapeutic	↓	Consider checking kaolin TEG – goal R value 20-30 minutes to reflect adequate heparinization Maintain current heparin rate, adjust goal ACT range 10 seconds on either side of current ACT (Example: Anti Xa = 0.4 IU/mL ACT = 205 – new goal ACT range is 195-215 seconds)
↓	↑	Check Antithrombin level, replace if< 80% (see below). Repeat Anti-XA and ACT after antithrombin replacement, if Anti-Xa still low and ACT high, Titrate the heparin drip to achieve an ACT range 20 seconds higher than current ACT range, and then recheck anti-Xa. (example Anti Xa = <0.1 IU/mL, ACT = 250, titrate heparin to achieve ACT 250-270) Draw Anti-Xa four hours after achieving new goal ACT range. Consider checking kaolin TEG (goal R 20-30 minutes indicates likely adequate heparinization), consider checking heparinase TEG and plasma free Hgb to evaluate for underlying DIC
↓	In desired range	Titrate the heparin drip to achieve an ACT range 20 seconds higher than current ACT range, and then recheck anti-Xa. (Example: Anti Xa = 0.1 IU/mL, ACT = 230 seconds, new goal ACT range 230-250) Draw Anti-Xa four hours after achieving
		new goal ACT range. (consider checking kaolin TEG goal R 20-30 minutes could indicate adequate heparinization);
↓	↓	**If the ACT is ≤ 20 seconds below the goal range, increase the heparin drip by 5-10% to achieve ordered ACT range.** **If ACT is >20 seconds below the goal, bolus with 0.5-1 x the amount of heparin infused in the previous hour and increase the gtt by 5-10%** Continue to repeat this process until ACT is therapeutic. ACT can be checked q 15 minutes with changes. Check AT level and replace if <80% Repeat anti Xa 4 hours after ACT in goal range
↑	↑	Decrease heparin infusion rate by 5-10% , repeat Anti-Xa in 4 hours
↑	In desired range	Consider confirming desired heparinization by checking kaolin TEG (goal R 20-30 minutes; if R is at goal, maintain current heparin infusion rate – repeat TEG in 4-6 hours; if R is too long, adjust goal ACT range 20 seconds lower). (Example: Anti-Xa = 0.9 IU/mL, ACT 235, R = 40 minutes, decrease goal ACT to 215-235 by decreasing heparin gtt by 5-10%) Draw anti-Xa four hours after achieving new goal ACT range.
↑	↓	Consider checking kaolin TEG – goal R value 20-30 minutes could reflect adequate heparinization. If R value at goal, maintain current heparin infusion rate and adjust goal ACT range by 10 seconds on either side of current value; if R value is too long, decrease ACT range by 20 seconds and repeat kaolin TEG and Anti Xa in 4 hours

Notes: Adjust maintenance IVF rate when adjusting heparin drip rate to maintain same total mL/hr.

*When titrating heparin gtt for new goal ACT range, follow instructions in bold print above repeat labs until you have attained the goal. Repeat Anti Xa should be drawn 4 hours after goal range is reached.

ATIII dosing: (80%-(actual patient%)) * wt in kg = units to administer
To accurately dose the ECMO patient, the circuit volume must be considered. For every 75 mL of volume within the ECMO circuit, add an additional one kg. For a 500 mL circuit, add 6 kg. For a 1000 mL circuit, add 12 kgExample: ATIII result 55%, patient weighs 5 Kg, circuit volume 500 mL (80-55) * (5 + 6) = 275 units. Repeat ATIII 1 hour after infusion complete.

Figure 1. Anticoagulation test response table.

Statistical Analysis

Demographic characteristics of patients were analyzed using descriptive statistics. Mean receiver operator characteristic area under the curves was used to evaluate data for the previously described aims. Correlation and linear regression evaluations were used to compare the different assays. Separate stepwise random effects logistic regression models were used to assess which predictors significantly and independently predicted a significant thrombotic event and a significant bleeding event. Chi-square tests were used to determine which cutoff was optimal and minimized the error rate of prediction (false positives and false negatives).

RESULTS

Forty-nine subjects received ECMO at our hospital during the study period. Thirty subjects met the inclusion criteria and were included in the study. Subjects were stratified into n = 26 patients received VA ECMO and n = 4 patients for comparions. A total of n = 238 individual, paired laboratory values were collected. Overall, most of the subjects were females (n = 18, 64.3%). The most common admission diagnosis was congenital heart disease (n = 14, 50.0%).

For the VA ECMO patients, the most common reasons for ECMO cannulation were cardiogenic shock (n = 11, 42.3%) and cardiac arrest (n = 5, 19.2%). Ten patients died (38.5%). Thirteen patients (50.0%) experienced a significant bleed. Fourteen patients (53.8%) experienced a significant thrombotic event. Five patients (19.2%) experienced both significant bleeding and thrombotic events. The median age was 2.3 ± 2.0 years, weight was 6.1 ± 17.6 kg, and the median time on ECMO was 146.8 ± 38.5 hours. Additional demographic details are provided in Table 1.

Correlation of TEG with Traditional Anticoagulation Measures

There was a moderate correlation between TEG R_{CK} and anti-Xa ($r = .571$, $p < .01$). There was a weak correlation between TEG R_{CK} and ACT ($r = .338$, $p = .011$) and aPTT ($r = .302$, $p = .019$). ACT demonstrated moderate correlation with aPTT ($r = .532$, $p < .01$). Anti-Xa was weakly correlated with aPTT ($r = .205$, $p = .022$) and moderately correlated with TEG R_{CK} ($r = .571$, $p < .01$). There was also a moderate correlation between ACT and aPTT ($r = .532$, $p < .01$). There was no significant correlation between Xa and ACT ($r = .169$, $p = .529$), TEG maximum amplitude (MA) and platelet count ($r = .212$, $p = .384$), and TEG K and fibrinogen ($r = .83$, $p = .813$).

All four measures showed good discrimination for predicting a thrombotic event (TEG R_{CK} [area under the curve (AUC) = .81, $p < .01$], anti-Xa [AUC = .79, $p < .01$], aPTT [AUC = .68, $p = .02$] and ACT [AUC = .64, $p = .03$]) (Figure 2). None of the four measures had good

Table 1. Demographics.

Total Number of Patients	VA ECMO, n = 26 (%)	VV ECMO, n = 4 (%)	*p* Value
Female	16 (61.5%)	2 (50.0%)	.531
Mean age of patients	27.0 months	67.5 months	.112
Hours on ECMO	146.8	189.36	.397
Deaths	10 (38.5%)	3 (75.0%)	.203
No. with bleeding complications	13 (50.0%)	3 (75.0%)	.352
No. with thrombotic complications	14 (53.8%)	3 (75.0%)	.409
No. of circuit or oxygenator changes	9 (34.6%)	1 (25.0%)	.593
Reasons for ECMO	Cardiogenic shock (11), cardiac arrest (5), hypoxemia (7), refractory shock (2), and severe hypercarbia (1)	Hypoxemia (3) and respiratory failure (1)	–

discrimination for predicting a significant bleed (AUCs were as follows: for TEG R_{CK} .58, for anti-Xa .54, for aPTT .54, and for ACT .52, all p values >.05). That is, the four measures were not significantly better than simply flipping a coin in identifying/discriminating who would have a significant bleed. Anti-Xa (odds ratio [OR] = .62, 95% confidence interval [CI]: .53–.72, $p < .001$) and TEG R_{CK} (OR = 1.19, 95% CI: 1.07–1.34, $p = .003$) were the only independent predictors of a significant thrombotic event. However, none of the measures showed good discrimination for independently predicting a significant bleeding event (AUCs were as follows: for TEG R_{CK} .55, for anti-Xa .53, for aPTT .51, and for ACT .50, all p values >.05.).

Optimal TEG Target Parameters

17.85 minutes was established as the optimal target for TEG R_{CK} (sensitivity = 84%, specificity = 68%, positive predictive value [PPV] = 82%, and negative predictive value [NPV] = 59%) for predicting a significant thrombotic event (Table 2). After controlling for age and mode of ECMO in a multivariate analysis, TEG R_{CK} was the remaining significant predictor for a thrombotic event (OR = 1.28, 95% CI: 1.03–1.53, $p < .001$) (Table 3).

Optimal Anti-Xa Cutoff Values

A value of .25 IU/mL was established as the optimal cutoff (sensitivity = 81%, specificity = 67%, PPV = 81%, and NPV = 58%) and performed significantly better than a cutoff of .2 IU/mL for predicting thrombotic complications (sensitivity = 54%, specificity = 47%, PPV = 47%, and NPV = 54%). However, anti-Xa did not perform well at predicting a significant bleed (AUC = .567, 95% CI: .35–.79, $p = .549$) (Table 2).

Optimal aPTT Cutoff Values

A value of 42 was established as the optimal cutoff (sensitivity = 76%, specificity = 64%, PPV = 78%, and NPV = 55%). However, after adjustment for demographics (age and gender) and other measures of anticoagulation,

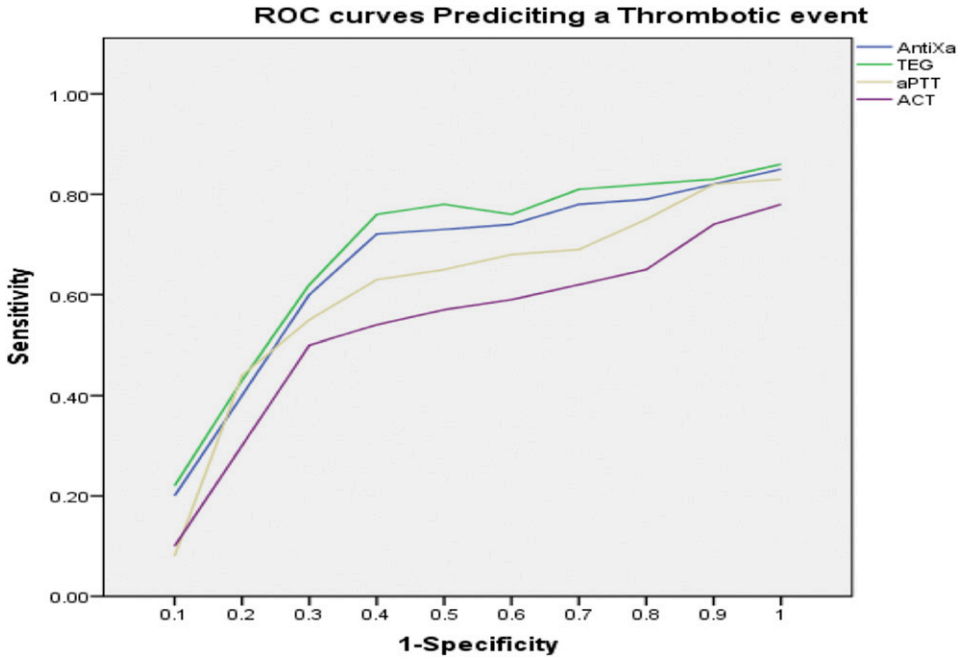

Figure 2. ROC curves predicting a thrombotic event.

Table 2. AUC values for predicting a thrombotic event and a significant bleed for all measures of anticoagulation.

Outcome	AUC (95% CI)	*p* Value
Thrombotic event	.72 (.53–.92)	.038
Bleeding event	.57 (.35–.79)	.59

aPTT did not perform well at predicting a significant bleed or thrombotic event.

Optimal ACT Cutoff Values

A value of 253 was established as the optimal cutoff (sensitivity = 73%, specificity = 68%, PPV = 75%, and NPV = 59%). However, after the same adjustments, ACT did not perform well at predicting a significant bleed or thrombotic event.

DISCUSSION

To our knowledge, this is the first study to examine the performance of anticoagulation targets to predict thrombotic and bleeding complications and to attempt to define target values for anticoagulation measures which would minimize bleeding and thrombotic complications in pediatric and neonatal ECMO patients. In addition, this study sought to investigate correlations between the multiple anticoagulation parameters currently available for assessing anticoagulation during pediatric and neonatal ECMO. Although a previous study has described the correlation of TEG parameters with traditional anticoagulation laboratory values, that study allowed labs to be drawn within a 4-hour time frame (10). As coagulation status can change rapidly during ECMO, tests drawn within a narrow time window, 30 minutes in this study, allow for more accurate assessment of true correlations between the various measures of anticoagulation. However, coagulation status can change rapidly during ECMO. Clinical picture must be monitored diligently and if there is any question of changes in coagulation, tests must be run more frequently.

This study, similar to previous studies, demonstrated a weak-to-moderate correlation between measures of anticoagulation efficacy in pediatric and neonatal ECMO patients (9,14,15). This finding is not particularly surprising, given that each test measures a different end target of anticoagulation therapy and is subject to its limitations.

Table 3. Predicting a thrombotic event.

Predictor	OR	95% CI	*p* Value
TEG	1.19	1.07–1.34	.003
Anti-Xa	.62	.53–.72	<.001
aPTT	.98	.91–1.13	.384
ACT	1.02	.90–1.12	.496

The ACT is attractive to clinicians managing ECMO patients as it is a whole blood point of care test which provides a global assessment of hemostasis. However, many factors may influence the ACT including hypothermia, hemodilution of clotting factors, platelet activation, and activation of the hemostatic system, which is a known consequence of extracorporeal therapy (15,16). The aPTT has traditionally been used to monitor UFH activity in most clinical scenarios. The aPTT reflects the function of the intrinsic and common pathways of the coagulation cascade. Limitations to the aPTT include the effects of consumptive coagulopathy, diurnal variation, and reliability of results due to fluctuations secondary to underfill of blood sample tubes (17). Once the UFH concentration is greater than 1 U/mL, the aPTT becomes infinitely prolonged (18). For these reasons, aPTT monitoring to assess heparin effect in ECMO patients is less commonly used (7).

Because of these limitations, anti-Xa analysis and TEG use in ECMO patients are growing in practice. Anti-Xa allows for an assessment of the functional activity of heparin. Specific TEG parameters give indications as to where perturbations in the coagulation cascade may be occurring and may provide a targeted approach to correction of coagulopathy. TEG R time reflects factor IIa generation and fibrin formation. The TEG_{CK} R time reflects the effect of heparin on coagulation, if present. The TEG angle and κ reflect fibrin mesh formation. TEG MA reflects platelet function and platelet fibrin interaction. TEG LY30 represents the percent of clot lysis 30 minutes after the MA (19). Taken together and separately, these parameters can provide significant insight into the ECMO patient's underlying coagulation cascade and the effect on heparin in this patient.

This is the first study to describe targets for TEG R_{CK} (>17 minutes) and anti-Xa activity (>.25 IU/mL) that may minimize the risk of thrombosis in the pediatric and neonatal ECMO population. Unfortunately, we were unable to identify a statistically significant TEG R_{CK} that predicted bleeding events in our ECMO population. In our study population, the incidence of bleeding and thrombosis was 52 and 61.5%, respectively. A recent multicenter prospective study by Dalton et al. (20) of seven pediatric ECMO centers found an incidence of 70% for bleeding and 37% for thrombosis. Notably, in the Dalton study, the incidence of bleeding and thrombotic events varied from center to center, which is likely a reflection of the lack of standardization in anticoagulation practices across centers (20). As such, it is not surprising that the incidence of bleeding and thrombosis in our single-center study differs from that presented in published reports. Further prospective validation of the values shown in this study to minimize thrombotic complications could prove an important milestone for the future of anticoagulation therapy in ECMO patients. As demonstrated by Bembea et al. (7), no universal protocol for the management of ECMO anticoagulation exists across centers. The most common

complications in these patients are due to bleeding or thrombotic events (21). Validated anticoagulation targets could allow for the development of anticoagulation protocols which could be studied in multicenter trials.

Further study should be performed to evaluate target values for both anti-Xa activity and TEG R time, which minimize the risk of a significant bleeding complication as well.

Limitations

The limitations of this study include the small sample size and retrospective nature. As noted previously, despite having greater than 200 data points, only 30 patients were included in the study.

A second issue is the relative absence of statistically significant laboratory findings that predicted bleeding. TEG R_{CK} was the primary TEG parameter evaluated, but other TEG values, including but not limited to MA, angle, and *K* value, could also be useful in predicting bleeding complications while on ECMO and should be the target of future investigations. Anti-Xa levels between .15 and .35 IU/mL were studied. Arguably, higher values should be evaluated, which may correlate more with clinically significant bleeding while on ECMO. Last, differences in coagulation cascade function between neonates and older children represent a significant confounder, given the heterogeneity of our population (22). This could be addressed in the future by an age-stratified design. Unfortunately, our sample size was too small to make this possible and such a design would likely require a multisite approach.

Conclusion

Target anti-Xa activity of .25 units and a TEG R_{CK} of greater than 17 minutes minimize the risk of thrombosis in pediatric and neonatal ECMO patients. The "holy grail" of ECMO management remains the optimization of anticoagulation therapy which would minimize thrombosis and bleeding complications. This study provides evidence for target values of anticoagulation performance which could be used in the development of future anticoagulation protocols to optimize this difficult but necessary therapy in pediatric and neonatal ECMO patients. Future studies should focus on establishing empiric-based ranges for anti-Xa and TEG R_{CK}, which minimize the risk of both bleeding and thrombosis in this population.

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