Resident Scholarly Project
Name Hannah Major-Monfried, MD PGY2
Faculty Mentor Cindy Neunert, MD
Title of Project Effects of Antithrombin III Replacement on Pediatric ECMO Circuit Anticoagulation
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1. Study Purpose and Rationale

Extracorporeal membranous oxygenation (ECMO) is a temporary life-support technique applied in cases of cardiac and/or pulmonary failure. While its use for neonatal and pediatric patients continues to expand around the world, mortality is high, with an overall survival rate to hospital discharge of 61%, and complications are common, including thrombotic and bleeding events, which afflict approximately a third of patients and are associated with decreased survival of 40%.[1,2] These hematologic complications arise from the use of an external circuit, which engenders a pro-thrombotic state by continuously exposing blood to a foreign membrane, leading to consumption of platelets as well as pro- and anti-coagulant components of the clotting cascade. Dysregulation of the coagulation cascade is further exacerbated by patient specific risk factors, including systemic inflammation, indwelling catheters, and underlying disease state.

Intravenous unfractionated heparin (UFH) is the anticoagulation agent of choice for most pediatric ECMO centers.[3] UFH primarily achieves its anticoagulation effect by binding with antithrombin (AT), a serine protease inhibitor which inactivates factor II (thrombin) and factor Xa, among others. When bound together, heparin potentiates the inhibitory action of antithrombin by a factor of 1000 compared to antithrombin alone.[4] However, UFH itself exerts variable effects, and requires constant monitoring to prevent over anticoagulation and bleeding complications.[5] Additionally, antithrombin levels can be exhausted by a range of factors in pediatric populations while on ECMO: neonates have an immature coagulation system, with known low levels of antithrombin,[6] while older children can acquire AT deficiency through consumption from disease processes, like disseminated intravascular coagulation, or low production.

As UFH is dependent on antithrombin for full effect, AT deficiency has been looked to as a reversible cause of poor hemostatis and UFH resistance. Accordingly, the empiric administration of AT during ECMO has increased steadily in pediatric and neonatal patients, with nearly 90% of international Extracorporeal Life Support Organization centers providing AT during ECMO, including Columbia Presbyterian's Morgan Stanley Children's Hospital (CHONY).[3] However, there is currently no established consensus regarding best practices for anticoagulation,[7] and studies of AT administration during ECMO have not yielded consistent results, especially regarding heparin dose requirements. These studies overall suggest that AT administration does not have a significant effect on important clinical outcomes, including clots or hemorrhages, transfusions, length of stay, or in-hospital mortality.[8-11] Additionally, a recent meta-analysis of 30 RCTs with a total of 3933 participants, including pediatric patients, found that AT replacement had no effect on mortality in critically ill patients, but does increase the risk of bleeding events.[12] There is a clearly defined need for more rigorous examination of the benefits or harms of AT replacement in ECMO, and the Pediatric Cardiac Intensive Care Society recently put out a call for standardized studies exploring AT replacement in ECMO, including comparison of bleeding, thrombosis, heparin dosing, and blood product use in patients treated and not treated with AT.[7]

Like many other critical care centers, the CHONY ECMO team has recently instituted a protocol in which AT is now only administered in the setting of documented heparin resistance. We now plan to investigate the impact of AT administration on hemostasis in the ECMO circuit by comparing time to therapeutic UFH, stability of anticoagulation and UFH dose adjustments, AT levels, transfusion requirements, and bleeding and thrombotic complications in patients who did not receive AT infusions under CHONY's new protocol as compared to patients treated previously. We will also compare rates of circuit failure, duration of ECMO, and mortality. We hypothesize that patients who have been treated under this new protocol will not experience significant differences in the outcomes despite lack of AT repletion.

2. Study Design and Statistical Procedures

This is a retrospective cohort study of all pediatric patients 0-21 years of age who underwent ECMO for any indication in the pediatric and neonatal ICUs of the Morgan Stanley Children's Hospital of New York, comparing clinical outcomes in patients who did not receive AT replacement under CHONY's new ECMO anticoagulation protocol compared to matched historical controls who were exposed to the intervention. Data on patient characteristics, ECMO indication, circuit duration, circuit failure, heparin dosing, including maximal dose and time to achieve therapeutic dose, AT dosing and activity, thrombotic and bleeding complications, length of stay, and mortality will be extracted from the medical record for all patients. The effects of AT administration on the above measures will be evaluated using general linear mixed model regression. Patient characteristics from each treatment group will be compared with χ tests (categorical variables) and Wilcoxon rank sum tests (continuous variables).

3. Study Procedures

No procedures are being performed as part of this study

4. Study Drugs or Devices

NA

5. Study Instruments

NA

6. Study Subjects

All neonatal and pediatric patients who underwent extracorporeal membrane oxygenation since the new AT anticoagulation protocol was put in place will be included, and matched with historical controls from the same patient population from before the new protocol was put into place.

7. Recruitment

There is no planned recruitment for this study, as the data will be gathered from a retrospective chart review.

8. Informed Consent Process

We believe that this study qualifies as exempt from the informed consent process, as it consists of a review of existing medical documentation for patients already followed by this institution.

9. Confidentiality of Study Data

We plan to use unique, coded identifiers for each subject in this study. All collected data will be stored electronically, on an encrypted and password protected computer accessible only to study investigators. The linking code will be stored in another location to which only the study investigators and the administrator will have access.

10. Privacy Protections

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner as described above.

11. Potential Risks

The risks associated with the proposed project are minimal, and include loss of confidentiality. All study personnel will be trained in accordance with HIPAA guidelines and any identifying information collected during chart review will be secured as described above.

12. Data and Safety Monitoring

We do not expect any safety events to occur as this study is non-interventional and requires data extraction from chart review.

13. Potential Benefits

Study participants are not guaranteed benefit from participation in this research study as it is a retrospective chart review. However, the information gained from this study may have an impact on the future management of anticoagulation in patients who require the lifesaving support of ECMO.

14. Alternatives

NA

15. Compensation to Subjects

NA

16. Costs to Subjects

There will be no compensation or cost to subjects.

17. Minors as Research Subjects

This study does not involve greater than minimal risk to the pediatric subjects involved.

18. Radiation or Radioactive Substances

NA

References

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