Thrombosis Research 179 (2019) 132–139

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Routine laboratory measures of heparin anticoagulation for children on extracorporeal membrane oxygenation: Systematic review and meta-analysis

D.P. Padhya[a], G.J. Prutsky[b,c,*], M.E. Nemergut[d], G.S. Schears[d], R.P. Flick[d], W. Farah[e], Z. Wang[f], L.J. Prokop[g], M.H. Murad[f], M. Alsawas[f]

[a] Department of Pediatrics, Reading Hospital, Reading, PA, USA
[b] Department of Pediatrics, Mayo Clinic Health System, Mankato, MN, USA
[c] Unidad de Conocimiento y Evidencia (CONEVID), Universidad Peruana Cayetano Heredia, Lima, Peru
[d] Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA
[e] Internal Medicine, St Joseph Mercy Hospital, Ann Arbor, MA, USA
[f] Mayo Clinic, Evidence-based Practice Center, Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Rochester, MN, USA.
[g] Mayo Clinic Libraries, Rochester, MN, USA

ARTICLE INFO

Keywords:
Extracorporeal membrane oxygenation
Pediatrics
Anticoagulation
Laboratory measures
Complications

ABSTRACT

Objective: Specific protocols for anticoagulation for children on ECMO vary across institutions, with most using a continuous infusion of unfractionated heparin. The goal of this study is to aid clinician's decision on the best measure of heparin anticoagulation test; which would be the one that correlates well with heparin activity and helps in predicting hemorrhagic and thrombotic complications.
Data sources: A comprehensive search of MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Scopus was conducted from each database's inception to 07/13/2018.
Study selection: Studies evaluating children (< 18 years) treated with ECMO and evaluating ACT, aPTT, TEG and Anti-Xa in any language were included.
Data extraction: Two reviewers selected and appraised studies independently, and abstracted data.
Results: We included 19 studies (759 patients, mean age 19.8 months). Meta-analysis showed strong correlation between heparin dosing and anti-Xa. Additionally, there was not a strong correlation between laboratory tests and complications (hemorrhagic and thrombosis), or mortality.
Conclusion: Based on current evidence, Anti-Xa is the only laboratory test that shows strong correlation with heparin infusion dose and seems like the most suitable test for monitoring of anticoagulation with heparin in children on ECMO.

1. Introduction

Extracorporeal Membrane Oxygenation (ECMO) was initially limited to short periods. Once the first membrane oxygenator was developed, patients could be supported for a prolonged time. ECMO is currently an invaluable tool in the armamentarium of life sustaining measures in children [1].

Even when ECMO has shown clear benefits, it is still associated with significant complications [1]. Due to the interaction between blood and an artificial circuit, anticoagulation is needed to prevent thrombotic complications [2]. Specific anticoagulation practices for children on ECMO are widely variable, with most institutions using a continuous infusion of unfractionated heparin [3]. Unfortunately, this regimen, when convenient (rapid onset and easy reversal with protamine), presents marked limitations such as the disparities among methods for measuring its effect, individual variability across patients and the hypercoagulation syndromes associated with deficiency of antithrombin [4]. Despite significant efforts, all anticoagulation regimens continue to be associated with major thrombotic and hemorrhagic complications leading to significant morbidity and mortality [5–7]. Due to this, maintaining the balance between hemostasis and anticoagulation is crucial for a favorable outcome [8]. This balance is particularly challenging in children since clotting factors are maturing and levels of procoagulants or anticoagulants are variable [9].

* Corresponding author at: Department of Pediatrics, Mayo Clinic Health System, 1025 Marsh St., Mankato, MN 56001, USA.
E-mail address: Prutskylopez.gabriela@mayo.edu (G.J. Prutsky).

https://doi.org/10.1016/j.thromres.2019.05.006
Received 4 February 2019; Received in revised form 3 May 2019; Accepted 6 May 2019
Available online 07 May 2019

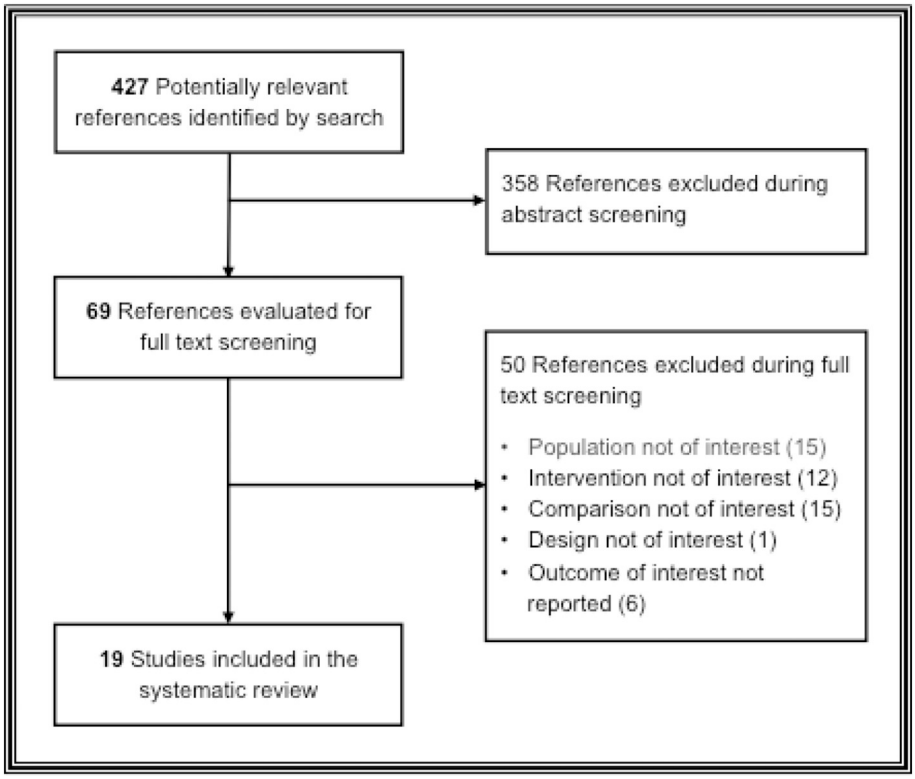

Fig. 1. Flow chart of references.

Methods used for monitoring the heparin effect include activated clotting test (ACT), activated partial thromboplastin time (aPTT), anti-factor Xa activity (anti-Xa) and the recently introduced thromboelastogram (TEG). The best method of monitoring anticoagulation during ECMO is not known and all of them present specific limitations and benefits that should be considered. Presently, there is no consensus on the most appropriate and feasible anticoagulation test to be used in children supported with ECMO.

The primary objective of this systematic review was to compare global (ACT, aPTT, TEG R) and specific (anti-factor Xa activity) measures of anticoagulation used in clinical practice and determine their congruence (i.e., correlation). We also sought to evaluate if the choice of laboratory tests of anticoagulation affected the risk of complications such as mortality, bleeding and thrombosis. Hemorrhagic complications common in these patients on ECMO are intracranial hemorrhage, hemothorax, adrenal hemorrhage, retroperitoneal hemorrhage and hematoma at access site. Thrombosis complications are mainly related to oxygenator or circuit clotting requiring replacement. The overarching goal of this study is to aid clinician's decision on the best measure of heparin anticoagulation test; which would be the one that correlates well with heparin activity and helps in predicting hemorrhagic and thrombotic complications in children on ECMO.

2. Materials and methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [10].

2.1. Eligibility criteria

Following a predesigned protocol we included studies evaluating children (< 18 years) treated with ECMO and evaluating ACT, aPTT, TEG and Anti-Xa. We did not employ any language restrictions. Case reports were excluded.

2.2. Data sources and search strategies

A medical reference librarian (LJP) designed and conducted comprehensive electronic search strategies with input from the study investigators. Databases included, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus were search from inception to July 13th, 2018. Controlled vocabularies supplemented with keywords were used without language restrictions. Additionally, we reviewed the reference lists of the eligible primary studies, narrative reviews and queried experts.

The detailed strategy is available as Supplemental Material 1.

2.3. Selection of studies and data abstraction

Search output was uploaded into a web-based system (DistillerSR, Ottawa, Canada). Two independent reviewers (PDP, PGJ, AM, FW) screened titles and abstract. Disagreements were considered eligible for the full text review. During this phase we achieved 90% of agreement. During the full text screening conflicts between reviewers were solved by consensus (PDP, PGJ, AM).

Data were extracted by independent pairs of reviewers using a predesigned, piloted web-based extraction form.

2.4. Methodological quality assessment

To assess the methodological quality of included studies (i.e., risk of bias), we used relevant items from the Newcastle Ottawa scale [11].

2.5. Outcomes

The outcomes of this study were the correlation measure (estimated as the Pearson correlation coefficient) between the different laboratory tests (Anti-Xa, ACT, Heparin, aPTT, and TEG R), and clinical outcomes

Table 1
Study characteristics.

Study	Country	Design	Population/setting	N	Weight (kg) Age	Outcomes assessed	ECMO indications (N)	ECMO mode (N)	ECMO duration (d)
Alexander (2010)	Australia	Retrospective cohort	Children in whom TEG was performed at least once	27	NR 32.4 m (0 m-16y)	Correlation ACT, APTT, TEG	Respiratory [4], Cardiac [19], Sepsis [3], Liver failure (1)	VA [20], VV (1), VAD [3], ECMO and VAD [3]	11.2
Ambrose (2001)	USA	Case series	PICU	13	NR 1d −10.5y	Correlation Act, Anti-Xa	Respiratory [6], Cardiac [5], Sepsis [2]	NR	NR
Bembea (2013)	USA	Prospective cohort	Patients < 18 years in ECMO for any indication	35	NR 10d (2d–10y)	Correlation of ACT, aPTT, Anti-Xa with heparin, Complications	Respiratory [18], Cardiac [9] ERCP [7], Sepsis (1)	VA (29), VV [3], VV to VA (30)	7 (3–14)
Bingham (2018)	USA	Retrospective cohort	Infant and Pediatric patients on ECMO for > 3d	35	3.9 +/− 4.28 39d (IQR 7.5–392.5)	Correlation of aPTT, ACT, INR, blood loss, TEG, HDR, AT, anti-Xa. Complications	Respiratory [5], Cardiac (29), ECRP (1)	NR	Study evaluated the first 5 d on ECMO
Henderson (2015)	USA	Retrospective cohort	Neonatal and pediatric patients	30	NR NR	Correlation ACT, APTT, TEG, Anti-Xa.	NR	NR	NR
Irby (2014)	USA	Retrospective cohort	Pediatric patients who had daily measurement of anti-Xa levels	62	NR 2.4y ± 4.9	Complete circuit/oxygenator change, Bleeding while monitored by Anti –Xa	Respiratory failure [22], Cardiac post-op [15], ECPR [16], Septic shock [2], Bridge to transplant [2]	NR	NR
Kessel (2017)	USA	Case- Control	PICU (comparing 2 different anticoagulation protocols)	18	NR 1d - 17y	Correlation between ACT and aPTT with heparin infusion dose in 2 anticoagulation protocols	Respiratory [12], Cardiac [6]	VA [9], VV [5], VV to VA [4]	5–33
Khaja (2010)	USA	Retrospective cohort	NICU	21	NR 2d (0–4)	Correlation of ACT, PTT and Anti-Xa.	Respiratory [19], Sepsis (1), PHTN (1)	NR	10.8
Liveris (2014)	USA	Retrospective cohort	Patients who had at least three sets of simultaneous measurements for all tests	17	NR 0.83y	Correlation of ACT, PTT, and Anti-Xa	Respiratory [4], Cardiac [8], Cardiac post-opn(1), Sepsis [3], PHTN (1)	VA [15], VV [2]	6 (4–8)
Maul (2012)	USA	Retrospective controlled cohort	Pediatric patients with respiratory and/or cardiac distress leading to ECMO	47	8.8 1.9y ± 4.7	Correlation of ACT and aPTT, Complications	Respiratory (30), Cardiac [17]	NR	NR
Moynihan (2017)	Australia	Retrospective cohort	Children with anticoagulation monitoring undertaken including TEG	32	3.9 (IQR 3.2–11.6) 17 d (IQR 2–764)	Correlation between ACT, anti-Xa, aPTT, TEG and heparin infusion dose. Bleeding, thrombotic events and death	Respiratory [13], Cardiac [5], Postoperative cardiac [10], ECPR [2], sepsis [2]	VA (29), VV [5], VAD (1)	6.01 (IQR 3.6–9.22)
Nankervis (2007)	USA	Retrospective cohort	Patients placed on VA ECMO in the NICU	12	3.7 NR	Correlation ACT, Anti-Xa and heparin dose.	Respiratory [8], Sepsis [2], PHTN [2]	VA [12]	11.4 ± 4.3
Niebler (2018)	USA	Prospective controlled Cohort	Patients at a Children's Hospital receiving ECMO support	230 (274 runs)	4.8 0.39y	Correlation between ACT and Anti-Xa with HDR. Hemorrhagic and thrombotic complications	Recent cardiac surgery (86), no recent cardiac surgery (144)	NR	109.75 (IQR 60.5–172.4)
O'Meara (2015)	USA	Retrospective cohort	Consecutive ECMO cases in the pediatric CICU managed with anti-Xa and consecutive, cases managed with ACT	22	4 12.5d (1d-17y)	Anti-Xa compared with ACT protocol, Complications	Cardiorespiratory failure in perioperative period [13], ECPR [8], PHTN (1)	VA [20], VV [2]	3.6 (2.4–7.6)
Reed (2010)	USA	Retrospective cohort	All patients who were on ECMO prior to death and underwent autopsy	29	NR 1.92 m	PT, PTT and thrombotic and bleeding complication	Respiratory [3], Cardiac [20], Abdominal surgery [2]	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Design	Population/setting	N	Weight (kg) Age	Outcomes assessed	ECMO indications (N)	ECMO mode (N)	ECMO duration (d)
Saini (2015)	USA	Retrospective cohort	Children < 18 years who received ECMO support in the PICU	24	NR 0.75y (0.08–5.8)	Complication	Respiratory [6],Cardiac [14], Pulmonary hypertension [4]	VA [18], VV [6]	8 (6, 10)
Sulkowski (2014)	USA	Retrospective cohort	Neonates placed on ECMO	26	3.4 < 30 d	Anti-Xa compared to ACT and aPTT. Survival	Respiratory failure [16], Cardiomyopathy (1) PHTN [7], Sepsis [2]	NR	3.9 (2.5,7.4)
Teruya (2014)	USA	Retrospective cohort	Pediatrics patients on ECMO from tertiary care children's hospital	47	NR NR	Correlation aPTT, Anti-Xa	NR	NR	7 (4,12)
Yu (2017)	USA, Canada	Prospective controlled Cohort	Neonatal and pediatric patients. Patients were excluded if they had a coagulopathy or thrombotic disorder	32 (95 runs)	5.55 NR	ACT, Anti-Xa, aPTT, AT, Fibrinogen, INR Hemorrhagic, thrombotic complications and mortality	Respiratory (27), Cardiac (41), ECPR (27)	VA (85), VV [10]	7 (IQR 4.5–8.5

Abbreviations.- ACT: Activated clotting time, aPTT: Activated partial thromboplastin time, AT: Anti-thrombin time, CICU: Cardiac intensive care unit, d: days, ECLS: Extracorporeal life support ECMO: extracorporeal membrane oxygenation, ECRP: Extracorporeal cardiopulmonary resuscitation, HDR: heparin dose rate, ICU: Intensive care unit, INR: International normalized ratio, m: moths, PICU: Pediatric intensive care unit, TEG: thromboelastography, VA: venous- arterial, VAD: Ventricular assist device VV: venous-venous, y: years.

such as hemorrhagic complications, thrombotic complications and death.

2.6. Data analysis

We used Fisher's z transformation to normalize Person correlation coefficient [12] and pooled the transformed z values using D-L random effect models [13]. The pooled results were then transformed back to Person correlation coefficient. Correlation was considered very weak, weak, moderate, strong or very strong based on correlation coefficient values of 0.00–0.19,0.20–0.39, 0.40–0.59, 0.60–0.79 and 0.80–1.00; respectively.

To evaluate the association between tests and adverse effects, we planned to log transform the rates of adverse affects and conduct single random-effect meta-regression by adjusting mean lab values [14]. To measure heterogeneity across studies, we used the I^2 index; in which I2 > 50% suggests substantial heterogeneity. All statistical analyses were conducted using Stata version 14.1 (StataCorp LP, College Station, TX).

2.7. Assessment of publication bias

The small number and heterogeneity of the trials made the assessment of publication bias unfeasible [15].

3. Results

3.1. Search results and study description

The initial database search identified 427 potentially eligible studies, of which 69 were evaluated in full text screening. Finally, 19 studies published in English fulfilled the eligibility criteria and were included (Two were abstracts not published as full manuscripts). None of the studies published in other languages met our inclusion criteria. The mean age of the population was 19.8 months (1 day–17 years). The study selection process is depicted in Fig. 1.

The included studies evaluated 759 patients, two studies included only neonates [16,17], and the remaining studies included both neonates and children younger than 18 years (Table 1).

3.2. Methodological quality assessment

Most of the included studies were single arm retrospective cohorts, one was a case- control and two were a prospective controlled cohort. The pertinent details of the Newcastle Ottawa scale are presented on Table 2. Overall this body of evidence was considered at high risk of bias.

3.3. Outcomes of interest

3.3.1. Correlation between tests

Meta-analysis showed very weak correlation between ACT and Heparin dose; and ACT and platelet count. There was weak correlation between Anti-Xa and ACT; Anti-Xa and aPTT; ACT and TEG-R, aPTT and Heparin dose; and aPTT and TEG-R. The correlation between Anti-Xa and TEG-R; and ACT and aPTT was moderate. The strongest correlation was found between heparin dosing and anti-Xa. Table 3 summarizes correlation measures between tests as a pooled estimate (across studies) with 95% confidence interval.

3.3.2. Correlation between tests and outcomes

The correlations between laboratory tests and complications (hemorrhagic and thrombosis), as well as mortality were evaluated in 9 studies. The following laboratory tests were evaluated: ACT, aPTT, AT, Anti-Xa, INR, Fibrinogen, PT, Heparin infusion dose, TEG-R. None of them showed a strong correlation with clinical outcomes. These results

Table 2
Methodological quality of included studies.

Study	Design	Selection			Comparability	Exposure			Outcomes		
		Is the spectrum of patients' representative?	Is the control definition adequate?	Is non-exposed cohort from the same community?	Comparability of cases and controls on the basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate	Were both groups assessed in the same manner?	Was follow-up long enough?	Adequacy of follow up
Alexander (2010)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Bembea (2013)	Prospective cohort	Somewhat representative of the average	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Bingham (2018)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Henderson (2015)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Irby (2014)	Retrospective cohort	Somewhat representative of the average. Study evaluated all pediatric patients on ECLS with daily measures of anti-Xa	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Kessel (2017)	Case- Control	Somewhat representative of the average	Yes	Yes, patients admitted to same PICU requiring ECMO	Yes, patients were matched based on age and diagnosis	Yes, secure record were used	Yes	NA	Yes	Yes	Yes
Khaja (2010)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Liveris, 2014	Retrospective cohort	Somewhat representative of the average	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Maul (2012)	Retrospective controlled cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Moynihan (2017)	Retrospective cohort	Somewhat representative of the average	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Niebler (2018)	Prospective controlled Cohort	Somewhat representative of the average	Yes	Yes, patients admitted to same PICU requiring ECMO	Yes, same characteristics	Yes	Yes	Yes	Yes	Yes	Yes
O'Meara (2015)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Reed (2010)	Retrospective cohort	Somewhat representative of the average. It evaluates patients that did not survive after requiring ECLS	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Saini (2015)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Sulkowski (2014)	Retrospective cohort		NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes

(*continued on next page*)

Table 2 (*continued*)

Study	Design	Selection			Comparability	Exposure			Outcomes		
		Is the spectrum of patients' representative?	Is the control definition adequate?	Is non-exposed cohort from the same community?	Comparability of cases and controls on the basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate	Were both groups assessed in the same manner?	Was follow-up long enough?	Adequacy of follow up
Teruya (2014)	Retrospective cohort	Somewhat representative of the average, consecutive patients were selected	NA	NA	NA	Yes, secure record were used	NA	NA	NA	Yes	Yes
Yu (2017)	Prospective controlled Cohort	Somewhat representative of the average	Yes	Yes, patients requiring ECLS admitted to a different hospital with the same level of care	Yes	Yes	Yes	No	Yes	Yes	Yes

Abbreviations.-, ECLS: Extracorporeal life support ECMO: extracorporeal membrane oxygenation, ECRP: Extracorporeal cardiopulmonary resuscitation, ICU: Intensive care unit, NA: Not applicable, NR: Not reported, PICU: Pediatric intensive care unit,

are depicted on Supplemental figs. 1, 2 and 3.

4. Discussion

4.1. Main findings

To our knowledge this is the first systematic and meta-analysis review to evaluate correlations of routinely measured laboratory tests in children on ECMO as well as their prediction of mortality, thrombosis and bleeding.

We found that the only laboratory test that showed strong correlation with heparin infusion dose was Anti-Xa ($r = 0.61$, 0.25–0.82). Based on this, Anti-Xa seems like the most suitable test to monitor heparin anticoagulation during ECMO in this population.

Data were sparse regarding clinical complications (hemorrhagic and thrombotic) and mortality. Unfortunately, none of the evaluated laboratory tests showed significant correlation with hemorrhagic and thrombotic complications.

4.2. Limitations and strengths

During the development of this systematic review several measures were undertaken in order to reduce bias and error while strengthening its quality. These measures included: predefined protocol-driven procedures, comprehensive literature search, study selection by independent reviewers and providing quantitative synthesis of the evidence.

There are significant limitations that have to be considered. Even when some pooled estimates present low or no statistical heterogeneity, there are important clinical differences that should be addressed. In terms of population, most of the included studies combined neonatal and pediatric populations (only 2 studies exclusively evaluated newborns). Neonates have age –dependent outcomes as well as coagulation factor levels, notably factor VIII and von-Willebrand factor activities [18]. In addition, they have wide variability of renal clearance and unique physiologic responses to sepsis, inflammatory reaction to ECMO and require repeated blood product transfusions. Additionally, one of the studies reviewed laboratory data from autopsies and it is possible that this population of patients, who died after ECMO, differed significantly from ECMO survivors [19]. In terms of the laboratory test evaluated, we have to acknowledge the potential significant differences between specific centres. This could significantly increase heterogeneity and limit the extrapolation of our results. A clear example is aPTT, it is well known that there is no standardization for this test, it can change depending on reagents and instruments used [20]. Unfortunately, the included studies did not provide enough information for us to adjust our analysis. With respect to the ECMO modality, most of the studies included patients with cardiac and respiratory indications for ECMO, leading to the use of Venous –venous (VV) and Venous-Arterial (VA) ECMO. A recently published systematic review in adults showed lower rates of complication in VV ECMO compared to previous reports using mixed population or VA exclusively [21,22]. They hypothesized that added to the mortality associated to the original indication for ECMO initiation, the cannulation procedure and the length of treatment may have a significant detrimental impact [22].

4.3. Implications for practice and research

The correlation data synthesized in this review suggest that in children on ECMO, anti-Xa levels may be the best test to assess heparin activity. However, these data do not allow prescription as to how much heparin activity may be needed for a given patient circumstance and we found no correlation between anti-Xa levels with thrombotic complications, hemorrhagic complications, or death. These results raise serious concerns about our current ability in clinical practice to monitor the anticoagulation in these patients as well as to prevent bleeding and

Table 3
Correlation between tests and heparin infusion dose.

Test 1	Test 2	Number of studies	Correlation r	95% CI	Interpretation
Anti-Xa	ACT	6	0.28	0.07; 0.50	Weak
Anti-Xa	Heparin dose[b]	4	0.61	0.25; 0.82	Strong
Anti-Xa	aPTT	5	0.32	0.16; 0.50	Weak
Anti-Xa	TEG-R	1	0.57	0.27; 0.77	Moderate
ACT	Heparin dose[+]	5	0.06	(−0.10;0.21	Very weak
ACT	aPTT	2	0.56	0.45; 0.65	Moderate
ACT	TEG	2	0.33	0.07; 0.55	Weak
ACT	Platelet count[a]	1	0.11	(−0.28; 0.47	Very weak
aPTT	Heparin dose[b]	3	0.21	0.08;0.47	Weak
aPTT	TEG-R	2	0.31	0.18; 0.43	Weak

[a] Log platelet count.
[b] Unit/kg/h.

hemorrhagic complications.

Unfortunately, the quality of the available evidence is low due to the observational nature of the evidence and imprecision (sparse data) [23]. Even in adults there are limited data comparing the laboratory tests to monitor anticoagulation during ECMO and the results are inconsistent [24,25].

The current status of the evidence challenges the creation of anticoagulation guidelines. As new studies become available, including randomized controlled trials (RCT), new systematic reviews and meta-analyses should be performed to include these data and improve reliability of present estimations [23].

5. Conclusions

Thrombosis and hemorrhage remain common complications of ECMO that lead to increased morbidity and mortality. Despite widespread use, the interpretation of standard unfractioned heparin monitoring tests in ECMO patients is complicated by limited correlation to each other and with the heparin dose being infused. Based on current evidence, Anti-Xa is the only laboratory test that shows strong correlation with unfractioned heparin infusion dose and seems like the most suitable test for monitoring of anticoagulation with unfractioned heparin in children on ECMO.

Further research is needed to determine the optimal anticoagulation regimen and monitoring strategy.

Funding source

No external funding for this manuscript.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.05.006.

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