Critical Care

LETTER

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Comments on 'Comparison of anticoagulation strategies for veno-venous ECMO support in acute respiratory failure': the bitter truth about unfractionated heparin monitoring assays

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To the editor,

We read with interest the article by Benjamin Seeliger et al. [1] in which the authors compared two different anticoagulation strategies defined as high-dose (HD) heparinization and low-dose (LD) heparinization. They report a lower rate of ECMO oxygenator change and thromboembolic events, in the HD group as compared to LD group.

1. The limits of activated clotting time (ACT) and partial thromboplastin time (PTT) to monitor ECMO anticoagulation.

LD and HD heparinization were defined using different anticoagulation monitoring assays—PTT and ACT respectively—leading to a possible classification bias. These assays are known to be poorly correlated to heparin concentration, to heparin anti-FXa and to each other [2].

Notably, the mean PTT values in the HD and LD groups [48 s (IQR 41–57) vs 38 s (IQR 34–42)] were overlapped for 25% of patients despite a significant difference in heparin dose. This underlines the poor correlation between heparin concentration and the monitoring assays used. Moreover, the difference in mean PTT is uninterpretable without providing for each PTT assay, the heparin therapeutic range is corresponding to the anti-FXa range of 0.3–0.7 UI/ml [3].

Furthermore, the accuracy of PTT and even worse of ACT are sensitive to several analytical limitations, and biological factors (thrombocytopenia, coagulation factor deficiencies, etc.) unrelated to heparin therapy are commonly observed during ECMO support [2, 4].

In addition, the ELSO recommends that ACT or PTT should not be used in isolation for heparin monitoring due to their limitations [5].

2. The observed differences in thrombotic events cannot be explained by the difference in heparin dosage alone.

The transfusion strategies in both centers differed significantly and should not be ignored in the analyses. Patients in the LD heparinization group received more platelet concentrates and more prothrombin complex concentrates, in line with the liberal transfusion practices in this

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center. However, these confounders were not included in the multivariate analysis.

Since the baseline coagulation covariates (fibrinogen, d-dimers, antithrombin) included in the model are likely to fluctuate daily during ECMO, they should be analyzed as time-varying covariates in the multivariate model. ACT and PTT may have similar variations, so it would be more informative to analyse them as time-dependent covariates in a multivariate model to explain thrombotic and bleeding complications.

In conclusion, this study has compared the ECMO management procedures of two centers beyond heparinization alone, in two different populations with a methodology that may lead to misinterpretation.

Authors' response

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To the editor,

We thank *Moussa* et al. for their comments on our article, addressing the issue of heparin monitoring and potential confounders.

Concerning the monitoring of heparin, we agree that APTT and ACT poorly correlate with each other and with anti-Xa levels in critically ill patients. Our own group recently confirmed this observation using two modern ACT devices with different detection methods [6]. As outlined in the current paper, we employed additional anti-Xa measurements whenever APTT or ACT was inconsistent with heparin dose or clinical picture. The main study result was a significant difference in heparin dose (17,495 vs 11,185 IU/d, $p < 0.001$) and a remarkable difference in the risk of oxygenator change between the two centers.

An intriguing question is why most centers, despite ELSO recommendations and the well-known limitations of APTT/ACT, still use these assays in the majority of patients [7]. Is it ignorance and lethargy that anti-Xa assays have not been adopted more completely? Or is it their longer turnaround time, higher cost and lack of 24/7 availability? It must be acknowledged that anti-Xa assays do not measure heparin *concentration* but just one of its pharmacodynamic, antithrombin-dependent *effects*. Different anti-Xa assays (with or without addition of exogenous antithrombin) do not measure the same in critically ill patients with low antithrombin [8]. Neither do anti-Xa assays reflect the important effects heparin has on other coagulation enzymes and the expression of tissue factor and tissue factor pathway inhibitor [9]. Proof is lacking that anti-Xa monitoring improves the outcome of ECMO patients. So-called global hemostasis assays may possibly better reflect the complex alterations of hemostasis and guide the use of heparin and blood components [10].

Concerning the transfusion strategy as a potential confounder, we agree with *Moussa* et al. and concluded already in our paper that prospective studies with predefined transfusion strategies are needed. We do not agree that transfusions could have been simply included as covariates in our analysis. The dilemma is that transfusion, for example, of platelets, may potentially prevent bleeding but is also done because of already existing bleeding.

In conclusion, our retrospective comparison of real-world data from two centers found lower rates of oxygenator change and thromboembolic complications in the center employing higher doses of heparin. Patient baseline characteristics were unlikely to explain this difference. Because of other potential confounders (e.g. transfusion strategy), confirmation from prospective studies is required.

Abbreviations

Anti-FXa: Antifactor Xa; ECMO: Extracorporeal membrane oxygenation; ELSO: Extracorporeal life support organization; IQR: Interquartile range.

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MDM and OAA write the manuscript; ER and AV performed critical review of the manuscript. All authors read and approved the final manuscript.

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