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Editorial

The Emerging Role of Bivalirudin for Therapeutic Anticoagulation in Patients With Coronavirus Disease 2019 Requiring Extracorporeal Membrane Oxygenation Support: Is It Time to Change the Routine Practice?

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) can be helpful in patients presenting with life-threatening refractory hypoxemia secondary to acute respiratory distress syndrome (ARDS) for different reasons, including infection with the novel coronavirus disease 2019 (COVID-19). Systemic anticoagulation is challenging in the latter because of the associated hypercoagulable status in COVID-19 patients.[1]

Heparin commonly is used for therapeutic anticoagulation during the use of ECMO. Heparin-induced thrombocytopenia (HIT) can be challenging in patients with COVID-19 receiving ECMO support.[2]

Bivalirudin, a direct thrombin inhibitor administered by continuous infusion, is a synthetic congener of the naturally occurring hirudin, secreted in the saliva of the blood-sucking leech *Hirudo medicinalis*. The United States Food and Drug Administration approved using bivalirudin as an anticoagulant in patients undergoing percutaneous coronary intervention. It emerges as an off-label alternative anticoagulant for postcardiotomy ECMO, with particular concerns about avoiding areas of blood stagnation to reduce the risk of ECMO circuit and intracardiac thrombosis.[3,4]

Bivalirudin has been described for anticoagulation in 99 out of 142 patients with ARDS treated with ECMO at a referral North Italian center over 11 years from 2009; 45% of them had influenza A virus subtype H1N1 or COVID-19 pneumonia.[5] Seelhammer et al also reported the feasibility of using bivalirudin for maintaining anticoagulation during the use of ECMO in a patient with COVID-19.[6]

In this issue of the *Journal of Cardiothoracic Vascular Anesthesia*, Trigonis et al[7] presented the results of a retrospective case-control comparative study on the efficacy and safety of protocol-based therapeutic anticoagulation using different bivalirudin dosing rates in 42 patients receiving venovenous (VV) ECMO secondary to non-COVID-19 and COVID-19 infection. The main objective of this single-center study was to better describe the pharmacology of bivalirudin in patients with COVID-19 receiving ECMO support compared to the non-COVID patient group.[7] This study was based on the need to test the efficacy of using bivalirudin for anticoagulation in patients with COVID-19 receiving VV ECMO.

Compared with the non-COVID-19 group, patients in the COVID-19 group received higher median and maximum bivalirudin infusion rates to achieve consistent activated partial thromboplastin time (aPTT) levels at a greater frequency than the non-COVID patient group despite using the same anticoagulation protocol.[7]

In this study,[7] the authors collected the data from patients over 1 year, starting from June 2019. Of note, the first case of COVID-19 infection was identified in the United States, the authors' center-based country, on January 22, 2020. This study did not include any randomization or blinding.

Another retrospective study in the United States included a single group of 33 patients with COVID-19 receiving bivalirudin while on ECMO over 9 months from February 2020.[8] The 2 studies[7,8] had similar institutional protocols for changing the rate of bivalirudin infusion and a therapeutic target of aPTT of 60- to-80 seconds, but with different aPTT ranges for changing the bivalirudin infusion rate. Compared with Bissell et al,[8] patients in the study of Trigonis et al[7] needed lower peak bivalirudin infusion rates to maintain the target aPTT (0.08 *v* 0.36 μg/kg/h, respectively) and had higher ECMO survival rate (84% *v* 52%, respectively), more prolonged stays in the intensive care unit (median 29 *v* 25 days, respectively), and a higher incidence of bleeding complications (21% *v* 12%, respectively). The former study included more patients. The vast difference between the peak infusion rates of bivalirudin

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Table 1
The ELSO Criteria for Identifying Major and Minor Bleeding Events

Severity of Bleeding	Criteria
Major bleeding	Clinically overt bleeding is associated with any of the following: Hemoglobin falls of at least 2 g/dL in 24 hours A greater than 20 mL/kg over 24 hours Transfusion requirement of 1 or more 10 mL/kg PRBC transfusions over that same period Retroperitoneal bleeding. Pulmonary bleeding. Intracranial bleeding. Bleeding that requires surgical intervention.
Minor bleeding	A less than 20 mL/kg/d requires transfusion of one 10 mL/kg PRBCs transfusion or less.

Developed from The ELSO Anticoagulation Guideline.[9]
Abbreviations: ELSO, extracorporeal life support organization; PRBC, packed red blood cell.

in these 2 studies[7,8] raises a concern on the need for a well-designed dose-response study to evaluate the optimum infusion rate to maintain the balance between the risks of thrombosis and bleeding.

The incidence of intracranial, intraocular, and gastrointestinal bleeding, defined as an acute blood loss for which the patient was transfused for hemoglobin level less than 7 g/dL or associated hemodynamic compromise, and deep venous thrombosis were similar in the 2 groups.[7]

However, caution should be exercised in interpreting the safety of using bivalirudin in patients with COVID-19. First, this study[7] was not powered to test the incidence of bivalirudin-induced complications. Second, the authors did not consider the Extracorporeal Life Support Organization criteria for identifying major and minor bleeding events (Table 1). Third, no data is available on the volume of blood derivatives transfused or the rates of significant circuit or component clots, necessitating a change of the ECMO circuit or circuit component.

Bivalirudin would be a good alternative to heparin use during the use of ECMO in patients with HIT[3,10]; however, in the study of Trigonis et al,[7] patients were not tested for HIT as bivalirudin was used routinely for all patients receiving ECMO at the authors' center. That would limit the generalizability of the present results among different worldwide centers where the use of bivalirudin is only limited to the patients with HIT because of its high cost.

Several previous studies compared the use of unfractionated heparin and bivalirudin for anticoagulation during the use of ECMO, but they have variable designs and numbers of included patients.[11-13] Seelhammer et al[14] demonstrated a lower mortality rate in the adult group receiving bivalirudin than the use of heparin for anticoagulation in a large retrospective study, including 424 patients requiring ECMO in which 21% were pediatric. However, this difference was not reported among pediatric patients. Rivosecchi et al[15] reported significant decreases in the incidence of major bleeding events and ECMO circuit thrombotic complications and volume of packed red blood cells, fresh frozen plasma, and platelet transfusion in 133 patients who received bivalirudin for anticoagulation during the use of ECMO compared with 162 patients who received heparin. Smaller studies failed to report similar differences in terms of bleeding or thrombotic complications.[11-12]

Future research also needs to consider the concern on the reported resistance to bivalirudin in patients receiving ECMO.[15]

The authors also reported double the cost of using bivalirudin in patients with COVID-19 in addition to the expected added costs of longer times on using ECMO and intensive care unit stays than those patients with non-COVID-19 ARDS.[7] Ranucci et al demonstrated that compared with heparin use, there was a trend toward a lower cost of using bivalirudin in adults and a statistically significantly lower cost in pediatric patients receiving postcardiotomy ECMO.[16] A cost-analysis study is needed to define the affordability of routine using bivalirudin anticoagulation for ECMO patients with COVID-19.

The aPTT is widely accepted as the standard test to monitor bivalirudin therapy during the use of ECMO. Thromboelastometry (ROTEM)-included-intrinsic (INTEM) coagulation pathway had a moderate correlation with simultaneously measured aPTT with bivalirudin anticoagulation in pediatric patients on either ECMO or a ventricular assist device.[17] Contradictory discordance between the 2 methods was reported in critically ill adult patients receiving ECMO support.[18] The role of using rotational thromboelastrometry to monitor bivalirudin therapy for adult patients with COVID-19 on ECMO is unclear.

In conclusion, although using bivalirudin has merit in maintaining therapeutic anticoagulation in patients with COVID-19 who need ECMO support, it might be a bit early to change the routine use of unfractionated heparin for patients without HIT. Larger prospective randomized-controlled studies are required to corroborate the findings of Trigonis et al[7] and confirm the safety and efficacy of bivalirudin compared with heparin in patients with COVID-19 receiving ECMO support.

Conflict of Interest

None.

Mohamed R. El Tahan, MD*
*Anesthesiology Department, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

References

1 Guo Z, Sun L, Li B, et al. Anticoagulation management in severe coronavirus disease 2019 patients on extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth 2021;35:389–97.
2 Bidar F, Hékimian G, Martin-Toutain I, et al. Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: Two case reports. J Artif Organs 2021;24:277–81.

3 Erdoes G, Ortmann E, Martinez Lopez De Arroyabe B, et al. Role of bivalirudin for anticoagulation in adult perioperative cardiothoracic practice. J Cardiothorac Vasc Anesth 2020;4:2207–14.
4 Ranucci M. Bivalirudin and post-cardiotomy ECMO: A word of caution. Crit Care 2012;16:427.
5 Pieri M, Donatelli V, Calabrò MG, et al. Eleven years of venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: From H1N1 to SARS-CoV-2. Experience and perspectives of a national referral center. J Cardiothorac Vasc Anesth 2021;S1053-0770(21)00842-9.
6 Seelhammer TG, Rowse P, Yalamuri S. Bivalirudin for maintenance anticoagulation during venovenous extracorporeal membrane oxygenation for COVID-19. J Cardiothorac Vasc Anesth 2021;35:1149–53.
7 Trigonis R, Smith N, Porter S, et al. Efficacy of bivalirudin for therapeutic anticoagulation in COVID-19 patients requiring ECMO support. J Cardiothorac Vasc Anesth 2022;36:414–8.
8 Bissell BD, Gabbard T, Sheridan EA, et al. Evaluation of bivalirudin as the primary anticoagulant in patients receiving extracorporeal membrane oxygenation for SARS-CoV-2-associated acute respiratory failure. Ann Pharmacother 2021 Jul 29:10600280211036151. https://doi.org/10.1177/10600280211036151;Online ahead of print.
9 Lequier L, Annich G, Al-Ibrahim O, et al. The ELSO Anticoagulation Guideline. Available at: https://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents.pdf. Accessed October 31, 2021.
10 Brown MA, Najam F, Pocock ES, et al. A comparison of bivalirudin and heparin for patients on extracorporeal membrane oxygenation. Thromb Res 2020;190:76–8.
11 Kaseer H, Soto-Arenall M, Sanghavi D, et al. Heparin vs. bivalirudin anticoagulation for extracorporeal membrane oxygenation. J Card Surg 2020;35:779–86.
12 Giuliano K, Bigelow BF, Etchill EW, et al. Extracorporeal membrane oxygenation complications in heparin- and bivalirudin-treated patients. Crit Care Explor 2021;3:e0485.
13 Berlioz B, Kaseer HS, Sanghavi DK, et al. Bivalirudin resistance in a patient on venovenous extracorporeal membrane oxygenation with a therapeutic response to argatroban. BMJ Case Rep 2020;13:e232262.
14 Seelhammer TG, Bohman JK, Schulte PJ, et al. Comparison of bivalirudin versus heparin for maintenance systemic anticoagulation during adult and pediatric extracorporeal membrane oxygenation. Crit Care Med 2021;49:1481–92.
15 Rivosecchi RM, Arakelians AR, Ryan J, et al. Comparison of anticoagulation strategies in patients requiring venovenous extracorporeal membrane oxygenation: Heparin versus Bivalirudin. Crit Care Med 2021;49:1129–36.
16 Ranucci M, Ballotta A, Kandil H, et al. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. Crit Care 2011;15:R275.
17 Teruya J, Hensch L, Bruzdoski K, et al. Monitoring bivalirudin therapy in children on extracorporeal circulatory support devices: Thromboelastometry versus routine coagulation testing. Thromb Res 2020;186:54–7.
18 Prakash S, Wiersema UF, Bihari S, et al. Discordance between ROTEM® clotting time and conventional tests during unfractionated heparin-based anticoagulation in intensive care patients on extracorporeal membrane oxygenation. Anaesth Intensive Care 2016;44:85–92.