

Bivalirudin in Venovenous Extracorporeal Membrane Oxygenation

Aman Jyoti, MD; Arun Maheshwari, MD; Elvin Daniel, MD; Amit Motihar, DNB;
Rajpal Singh Bhathiwal, PGDPT; Deevakar Sharma, PGDPT

Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi, India

Abstract: Optimal anticoagulation plays a pivotal role in successful outcome of extracorporeal membrane oxygenation (ECMO). Heparin has been the anticoagulant of choice owing to its advantages like easy monitoring and reversibility. However, if heparin resistance is encountered, one has to decide whether to treat heparin resistance with fresh-frozen plasma or antithrombin concentrates or to choose one of the heparin alternatives for anticoagulation. We report a case of heparin resistance resulting from antithrombin III deficiency in a patient on venovenous ECMO, in which anticoagulation was managed with bivalirudin. The dose of

bivalirudin for anticoagulation in ECMO has not been standardized and different authors have reported different doses. We found a bivalirudin dose of .1–.2 mg/kg/h to be adequate to maintain a target activated clotting time of 200–220 seconds. Platelet counts were stable throughout and no major bleeding or thrombotic complications took place. We found bivalirudin to be a feasible and effective anticoagulant and safe to use for long durations in ECMO without any major complications. **Keywords:** antithrombin III deficiency, bivalirudin, extracorporeal membrane oxygenation, heparin resistance. *JECT. 2014;46:94–97*

Optimum anticoagulation during extracorporeal membrane oxygenation (ECMO) is vital for a successful outcome. Unfractionated heparin (UFH) is used as an agent of first choice for anticoagulation during ECMO. We encountered heparin resistance resulting from antithrombin III (ATIII) deficiency in a case of acute hypoxic respiratory failure on venovenous ECMO. Instead of using fresh-frozen plasma (FFP) or ATIII concentrates to correct heparin resistance, we used direct thrombin inhibitor (DTI) bivalirudin for anticoagulation. Repeated transfusions of FFP were not preferred as a result of concerns of fluid overload and risk of transfusion-associated acute lung injury in already compromised lungs. We preferred bivalirudin over ATIII concentrates as a result of high cost and unavailability of the latter.

CASE REPORT

A 54-year-old male patient presented with symptoms of fever, cough, sore throat, and breathlessness for

4 days. Examination was unremarkable except tachycardia (115 beats/min), tachypnea (30 breaths/min), fever (oral temperature 38.4°C), and coarse crepitations in bilateral basal lung zones. Arterial blood gas analysis showed low partial pressure of oxygen (46 mmHg [6 kPa] on room air) with mild alkalosis (pH 7.45) and a mild decrease in partial pressure of carbon dioxide (30 mmHg [3.99 kPa]). Bilateral lower zone infiltrates could be seen on chest radiography. Hematology revealed leukopenia ($3.6 \times 10^9/L$) and normal platelet count. Procalcitonin level was mildly elevated (.15 µg/L). Infection with H1N1 influenza A (2009) virus was confirmed with reverse transcriptase polymerase chain reaction analysis. Cardiac function was found to be normal according to transthoracic echocardiography.

Initially oxygenation was managed with noninvasive ventilatory support but as a result of continuous deterioration, he was put on invasive ventilation 6 days after admission. Initially he was managed with pressure control ventilation but hypoxia persisted despite maximum ventilatory support, leading to institution of high-frequency oscillatory ventilation (HFOV). Oxygenation did not improve on HFOV and he started retaining carbon dioxide. His Murray score exceeded 3.0 and he was put on venovenous ECMO support (pump by Medos delta-stream, MEDOS Medizintechnik AG, Stolberg, Germany; oxygenator by Medos hilite, MEDOS Medizintechnik AG)

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Address correspondence to: Aman Jyoti, MD, Department of Cardiac Anaesthesia, Dharma Vira Heart Centre, Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi-110060, India. E-mail: drajyoti@gmail.com
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1 day after invasive ventilation as per institutional protocol. Venous cannulae (Edwards Lifesciences, Irvine, CA) were inserted percutaneously under fluoroscopic guidance. A 28-Fr cannula was inserted through the right femoral vein and placed in the inferior vena cava to drain the blood and a 16-Fr cannula was inserted through the right internal jugular vein and positioned in the right atrium just above the tricuspid valve. Initially ECMO flow rates were set high (5–6 L/min) and FiO₂ set at 100%. Sweep gas flow was used in 1:1 ratio. Lungs were given rest using low tidal volumes (3–4 mL/kg), low FiO₂ (30–40%), low rates (8–10/min), and a positive end expiratory pressure of 8–10 mmHg.

Initially UFH was used for anticoagulation to maintain a target activated clotting time (ACT) in the range of 200–220 seconds and activated partial thromboplastin time (APTT) in a range of 60–80 seconds. High heparin requirement (>30 IU/kg/h) with frequent supplemental boluses (4000–8000 IU) was noticed. Small clots were seen on the surface of oxygenator as a result of which oxygenator was changed. ATIII levels were assessed, which showed only 31% activity. We switched to DTI bivalirudin (Bivaflo; Sun Pharmaceuticals Industries Ltd., Mumbai, India) for anticoagulation. Initially a dose of .6 mg/kg/h was used and titrated according to ACT and APTT. The average dose of bivalirudin used was .1–.2 mg/kg/h (Figure 1). Target ACT and APTT were managed easily with bivalirudin and no supplemental boluses were needed (Figure 2). Total duration of ECMO was 552 hours and platelet counts were stable throughout (Figure 1). Platelet transfusion was not required during ECMO.

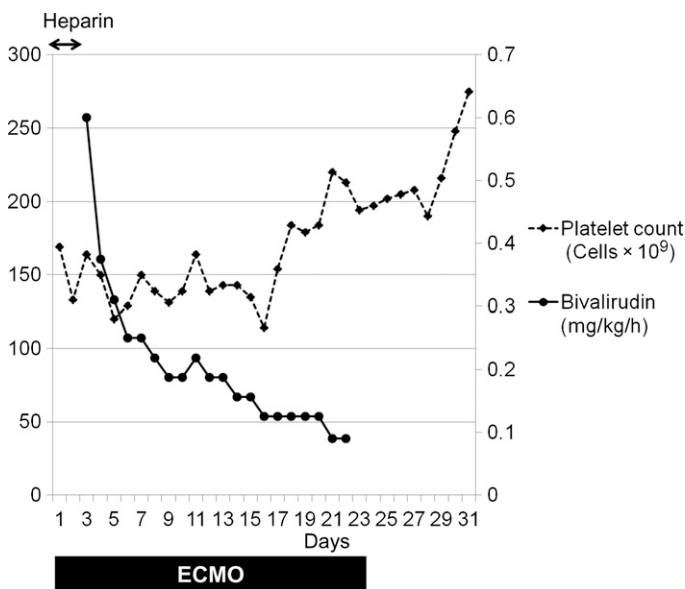


Figure 1. Bivalirudin dosage and platelet counts during extracorporeal membrane oxygenation. ECMO, extracorporeal membrane oxygenation.

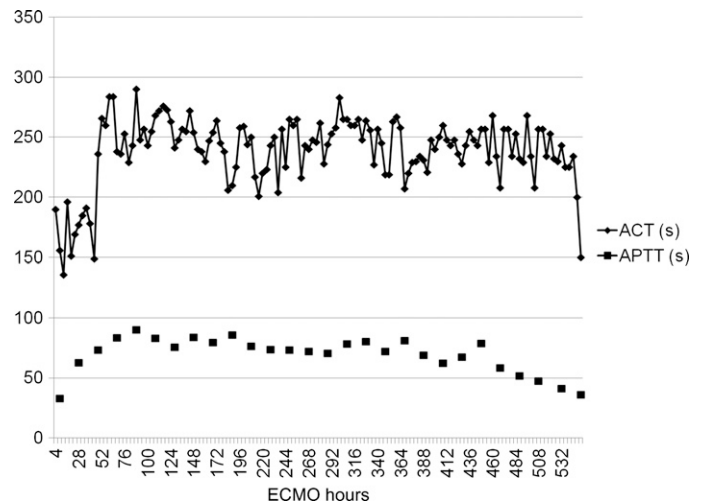


Figure 2. Activated clotting time and activated partial thromboplastin time during extracorporeal membrane oxygenation. ACT, activated clotting time; APTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation.

International normalized ratio remained high during ECMO and D-dimers were also raised. The patient had blood-tinged endotracheal secretions but no major bleeding episode took place. Bronchoscopy at this time did not reveal any focal bleeding. Seven units of FFP were transfused during the entire period of ECMO to correct this coagulation factor abnormality. There was no bleeding from cannulae or indwelling catheter sites.

His baseline hemoglobin (Hb) was low (80 g/L) and with add-on hemolysis caused by ECMO, we had to transfuse multiple units of packed red blood cells (PRBCs) to maintain the oxygen-carrying capacity of blood. Approximately 175 mL of PRBCs were transfused per day to maintain Hb above 80 g/L.

The patient was kept under sedation throughout ECMO and muscle relaxants were given for the initial few days because neck movements were interfering with the pump flow. The patient had a secondary lower respiratory tract infection and transient bloodstream infection during ECMO, which was controlled with appropriate antibiotics.

The patient started showing clinical and radiological improvement in both lungs in the second week on ECMO. Weaning from ECMO was proceeded gradually and ECMO support was withdrawn after 23 days. Venous cannulae were removed 1 hour after stopping bivalirudin and a pressure bandage was applied to the cannulae site to prevent any bleeding. ACT decreased to 150 seconds 4 hours after stopping bivalirudin infusion. No bleeding complication took place from the site of venous cannulation. Ventilatory support was removed in the next 10 days. The patient was neurologically intact and had no cognitive dysfunction. He was discharged to home 4 weeks after removing ECMO.

DISCUSSION

Conventionally UFH has been the anticoagulant of choice in ECMO as a result of its benefits like easy monitoring and titration, presence of an antidote, low cost, and familiarity with its use. However, along with these benefits, it also carries certain serious limitations like heparin-induced thrombocytopenia (HIT) (1). Moreover, heparin does not provide effective anticoagulation in cases of ATIII deficiency. Reduced plasma antithrombin may result from congenital deficiency or arise secondarily from a range of disorders such as liver dysfunction, sepsis, or as a result of interventions such as major surgery or cardiopulmonary bypass. We had no evidence regarding a congenital cause of ATIII deficiency in our patient; hence, we suspect a multitude of acquired causes behind this deficiency, which include treatment with heparin, presence of inflammatory focus in the body, and dilution from the ECMO circuit.

Usually heparin resistance resulting from ATIII deficiency is treated using either ATIII concentrates or FFP transfusion. Repeated administration of FFPs may increase incidence of transfusion-related complications and there may be some risk of bleeding with administration of ATIII concentrates (2,3). High cost and unavailability of ATIII concentrate can prohibit its use in certain cases. Instead of choosing between these two options, we preferred to use one of the heparin alternatives to minimize the transfusion-related complications.

Alternatives to heparin include ancrod, danaparoid, fondaparinux, low-molecular-weight heparins (LMWH), platelet receptor inhibitors, and DTIs. Ancrod cleaves fibrinogen and patients anticoagulated in this fashion bleed more and require more cryoprecipitate and FFP compared with heparin-anticoagulated patients (4). Danaparoid has a relatively long half-life of approximately 24 hours and severe bleeding resulting in death has been reported with its use (5). Fondaparinux and LMWH have a long half-life. Among the DTIs, hirudin and argatroban have a long half-life as compared with bivalirudin; hence, we opted to use bivalirudin for anticoagulation in our patient.

Bivalirudin is a short-acting reversible DTI with a short half-life (25 minutes) and has been used for anticoagulation during cardiac surgery in patients with HIT although there is very limited experience with its use in patients with ATIII deficiency (6,7). There is only one report mentioning bivalirudin use in ATIII deficiency for anticoagulation in a pediatric patient undergoing interventional cardiac catheterization (8). There is no standard protocol regarding the dose of bivalirudin for anticoagulation in ECMO. Different doses have been reported varying from .5 mg/kg/h by Koster et al. to .025 mg/kg/h by Piery et al., but frequent dosage corrections have been reported for lower-end doses (9,10). We found a dose of .1–.2 mg/kg/h to be adequate

to maintain a target ACT of 200–220 seconds with no requirement for supplemental boluses.

The major hindrance in bivalirudin use is anticoagulation monitoring. Various methods used for this purpose include ACT, APTT, ecarin clotting time, and chromogenic antifactor IIa assay (11,12). The latter two tests are not easily available, so ACT and APTT are used mostly for monitoring the anticoagulation effect of bivalirudin. Pieri et al. (9) observed significantly higher APTT variations in a heparin group as compared with a bivalirudin group. Similar to their observation, we too observed relatively stable ACT and APTT values with bivalirudin.

The total transfusion requirement is significantly decreased with bivalirudin as compared with heparin, which is evident from a study by Ranucci et al. (13) in postcardiotomy ECMO cases. In our case, platelet counts remained markedly stable throughout ECMO. No platelet transfusions were administered and no major bleeding episode took place. There is no recommendation regarding the duration for safe use of bivalirudin. Manufacturers have recommended bivalirudin only for duration of 20 hours (in cases of acute coronary syndrome). No studies have attributed any adverse effects to prolonged use of bivalirudin (9,13). We used bivalirudin infusion for 21 days without any complication.

Some precautions should be observed while using bivalirudin for cardiopulmonary bypass (CPB) or ECMO. Blood stagnation in the circuit must be avoided because the rapid cleavage of bivalirudin may result in thrombosis. During ECMO, leaving a minimal degree of intracardiac blood flow may help in preventing stagnation of blood in cardiac chambers. If there is any echocardiographic evidence of a “smoke effect” within one or more cardiac chambers, bivalirudin should be replaced by standard heparin anticoagulation (14).

Mateen et al. (15) have reported 50% incidence of severe neurological sequelae in a study of 87 patients who underwent ECMO. Diagnoses included subarachnoid hemorrhage, ischemic watershed infarctions, hypoxic–ischemic encephalopathy, unexplained coma, and brain death. They attributed these outcomes to the precipitating event, which led to ECMO or ECMO itself. Polito et al. have identified certain risk factors for neurological sequelae during ECMO, which may be compounded by anticoagulation. They have advised better anticoagulation management in these patients to minimize neurological sequelae (16). Although previous studies have reported no significant difference regarding thromboembolic phenomena in bivalirudin versus heparin groups, yet a trend toward less thromboembolic events can be seen in the bivalirudin group (9,13). More randomized controlled trials are warranted to explore the incidence of thromboembolic events with different anticoagulants in ECMO or CPB patient populations.

CONCLUSION

Our results are from one case study and these results may not be appropriate for all patients on ECMO. We found bivalirudin as a feasible and effective anticoagulant for ECMO. We used it safely for a long duration without encountering thrombocytopenia or other major complications. It is cost-effective as compared with ATIII concentrates and can be considered as an alternative to heparin in cases of heparin resistance or HIT. Dosage requirements decrease over time during infusions used for prolonged time. A dose of .1–2 mg/kg/h was found to be effective for adequate anticoagulation in ECMO with no noticeable side effects. However, more studies are required to ascertain bivalirudin dosage in this subset of patients.

REFERENCES

1. Poncz M. Mechanistic basis of heparin-induced thrombocytopenia. *Semin Thorac Cardiovasc Surg.* 2005;17:73–9.
2. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: A review. *Chest.* 2004;126:249–58.
3. Avidan MS, Levy JH, Scholz J, et al. A phase III, double-blind, placebo-controlled, multicenter study on the efficacy of recombinant human antithrombin in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass. *Anesthesiology.* 2005;102:276–84.
4. Zulys VJ, Teasdale SJ, Michel ER, et al. Ancrod (Arvin) as an alternative to heparin anticoagulation for cardiopulmonary bypass. *Anesthesiology.* 1989;71:870–7.
5. Tardy-Poncet B, Tardy B, Reynaud J, et al. Efficacy and safety of danaparoid sodium (ORG 10172) in critically ill patients with heparin-associated thrombocytopenia. *Chest.* 1999;115:1616–20.
6. Dyke CM, Aldea G, Koster A, et al. Off-pump coronary artery bypass with bivalirudin for patients with heparin-induced thrombocytopenia or antiplatelet factor four/heparin antibodies. *Thorac Surg.* 2007;84:836–9.
7. Koster A, Dyke CM, Aldea G, et al. Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: Results of the CHOOSE-ON Trial. *Ann Thorac Surg.* 2007;83:572–7.
8. Zamora R. Successful anticoagulation with bivalirudin in antithrombin-deficient pediatric patient undergoing stent placement. *Catheter Cardiovasc Interv.* 2006;68:292–5.
9. Pieri M, Agracheva N, Bonaveglio E, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: A case-control study. *J Cardiothorac Vasc Anesth.* 2013;27:30–4.
10. Koster A, Weng Y, Bottcher W, et al. Successful use of bivalirudin as anticoagulant for ECMO in a patient with acute HIT. *Ann Thorac Surg.* 2007;83:1865–7.
11. Koster A, Chew D, Grundel M, et al. Bivalirudin monitored with the ecarin clotting time for anticoagulation during cardiopulmonary bypass. *Anesth Analg.* 2003;96:383–6.
12. Salemi A, Agrawal YP, Fontes MA. An assay to monitor bivalirudin levels on cardiopulmonary bypass. *Ann Thorac Surg.* 2011;92:332–4.
13. Ranucci M, Ballotta A, Kandil H, et al. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. *Crit Care.* 2011;15:R275.
14. Ranucci M. Bivalirudin and post-cardiotomy ECMO: A word of caution. *Crit Care.* 2012;16:427.
15. Mateen FJ, Muralidharan R, Shinohara RT, et al. Neurological injury in adults treated with extracorporeal membrane oxygenation. *Arch Neurol.* 2011;68:1543–9.
16. Polito A, Barrett CS, Wypij D, et al. Neurologic complications in neonates supported with extracorporeal membrane oxygenation. An analysis of ELSO registry data. *Intensive Care Med.* 2013;39:1594–601.