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Case Report

Bivalirudin Anticoagulation for an Infant with Hyperbilirubinemia and Elevated Plasma-Free Hemoglobin on ECMO

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Abstract: Heparin has been used for decades as an anticoagulant in patients on mechanical circulatory support, which includes extracorporeal membrane oxygenation (ECMO) and ventricular assist devices. Bivalirudin is a direct thrombin inhibitor that can be used as an alternative anticoagulant in neonates and infants demonstrating inaccurate heparin monitoring. We report a case of a 2-month-old male child who was placed on ECMO for severe acute respiratory distress syndrome. His ECMO course was complicated by severe hemolysis and hyperbilirubinemia, which precluded accurate monitoring of heparin activity. Bivalirudin was successfully used for anticoagulation in this patient. **Keywords:** extracorporeal membrane oxygenation, bivalirudin, heparin, partial thromboplastin time, heparin anti-Xa level. *J Extra Corpor Technol. 2019;51:26–8*

Mechanical circulatory support with ventricular assist devices or extracorporeal membrane oxygenation (ECMO) in pediatric patients with cardiorespiratory failure, end-stage heart failure, and congenital heart disease has been well described (1). Adequate anticoagulation is the cornerstone of successful outcomes in these patients. Heparin has, for decades, been established as the anticoagulant of choice for mechanical circulatory support and has been the standard of care for anticoagulation in these patients. Heparin anticoagulation has its inherent problems, which includes platelet consumption and/or activation. In addition, it occasionally may lead to a life-threatening immunologically or non-immunologically mediated thrombocytopenia.

A known complication of ECMO is ongoing hemolysis resulting from shear forces on red blood cells in the mechanical circuit (2). Elevated plasma-free hemoglobin and hyperbilirubinemia, as a consequence of hemolysis, could affect unfractionated heparin therapy monitoring with heparin anti-Xa assay and activated partial thromboplastin time (aPTT) during in vitro analysis (2), thus making heparin unreliable for anticoagulation in this setting.

Bivalirudin, with the trade name Angiomax® (The Medicines Company, Parsippany, NJ), is a short-acting, direct thrombin inhibitor that has been used successfully for anticoagulation in patients on ECMO (1). However, its value in the setting of elevated plasma-free hemoglobin and hyperbilirubinemia has not been previously described. We encountered unreliable heparin monitoring in a patient on ECMO complicated by severe hemolysis and consequently high plasma-free hemoglobin and hyperbilirubinemia. Subsequently, we switched the anticoagulant from heparin to bivalirudin and successfully achieved a level of therapeutic, consistent, safe anticoagulation.

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CASE

A 2-month-old, full-term, unimmunized male infant was admitted to the pediatric intensive care unit with

respiratory syncytial virus bronchiolitis and respiratory distress. The patient was initially placed on noninvasive positive pressure ventilation for 24 hours, but developed hypoxic and hypercarbic respiratory failure. The patient was intubated on hospital day #2 and placed on conventional mechanical ventilation. The patient progressed to acute respiratory distress syndrome, with respiratory cultures positive for *Hemophilus influenza* and *Moraxella catarrhalis*, and was transitioned to a high-frequency oscillator (8.0 hertz, amplitude 33 cm H_2O, mean airway pressure 28.0 cm H_2O, inspiratory time 33%, and 20 L/min of bias flow on 100% FiO_2) for persistent hypoxemia and hypercarbia. Rapidly worsening hemodynamics leads to a brief 2-minute period of cardiac arrest. Return of spontaneous circulation was achieved and the patient was emergently cannulated for venoarterial ECMO using a ROTAFLOW pump (Maquet, Rastatt, Germany), QUADROX-iD pediatric oxygenator (Maquet, Germany), and a heparin-coated circuit with CARMEDA® Bioactive Surface (Carmeda AB, Uppland Vasby, Sweden). Arterial access for ECMO was an eight-French Bio-Medicus™ cannula (Medtronic, Minneapolis, MN) in the right carotid artery and venous access was achieved with a 12-French Bio-Medicus™ cannula (Medtronic) in the right internal jugular vein. An ECMO blood flow of 120 mL/kg/min was achieved and inotropic support was weaned off in a few hours.

Initial anticoagulation with systemic heparin was commenced at 18 units/kg/h on cannulation for ECMO. The goals of anticoagulation were heparin anti-Xa assay levels .3–.5 IU/mL, aPTT 60–80 seconds, and activated clotting time (ACT) 180–200 seconds. Heparin was titrated up to 60 units/kg/h before reaching ACTs of 180–200 seconds using the i-STAT® Kaolin ACT (Abbot Point of Care Inc., Princeton, NJ), 12 hours after cannulation. The initial antithrombin III (AT) level was 35%, and the patient received 65 units/kg of AT concentrate, Thrombate III (Grifols, Research Triangle Park, NC). The repeat AT level, 12 hours after Thrombate III administration, was 49%, and the aPTT value at that same time was greater than 180 seconds. Despite the high dose of heparin and Thrombate III administration, heparin anti-Xa assay levels remained lower than .1 IU/mL and aPTT levels were consistently greater than 150 seconds. Laboratory work on day #2 of ECMO revealed a progressive increase in plasma-free hemoglobin, from 85 mg/dL to a peak of 388 mg/dL (normal range 0–9.7 mg/dL). Total serum bilirubin also increased from a baseline of 1.3 mg/dL to a peak of 18.2 mg/dL. These laboratory values, along with an elevated lactate dehydrogenase, were indicative of severe hemolysis. The patient's renal function remained normal with a blood urea nitrogen of 9 mg/dL (normal range 4–19 mg/dL) and creatinine .23 mg/dL (normal range .16–.39 mg/dL). Determination and reliability of the heparin effect was a challenge, and the risk of bleeding increased with escalating doses of heparin, although the patient did not have any episodes of bleeding. Therefore, 35 hours after ECMO cannulation, anticoagulation was changed to bivalirudin with a starting dose of .3 mg/kg/h. The first aPTT level, 4 hours after initiation, was 96 seconds. Bivalirudin was titrated to achieve target aPTT goals and values of 60–80 seconds were consistently achieved, starting 11 hours after switching to bivalirudin and throughout the remainder of the patients' ECMO course (Figure 1). Anticoagulation during this period was reliably achieved with bivalirudin, even in the presence of high bilirubin and plasma-free hemoglobin levels. Ultimately, the underlying cause of hemolysis was identified as cannula malposition with very high ECMO negative inlet pressure after bedside venous cannula manipulation resulted in a dramatic decrease in negative inlet pressure. Following the cannula adjustment, the hemolysis resolved on day #4. The patient's clinical condition improved and he was successfully decannulated after 5 days on ECMO.

DISCUSSION

Heparin is an indirect anticoagulant requiring AT for significant therapeutic effect. The binding of heparin to AT increases its action 10,000 fold (3). Heparin has notable advantages, which include easy reversibility, well-established titration protocols for therapeutic effect, and low cost (4). However, heparin use has many challenges, which include heparin resistance, usually in the setting of low AT levels (1). This is frequently encountered in neonates because of their relative inability to produce sufficient quantities of AT (3). Also, the AT–heparin complex does not inhibit thrombin already bound to a clot or the surface of the circuit (3). Heparin may cause heparin-induced thrombocytopenia, which has potentially severe consequences such as thrombosis and bleeding (4).

The use of bivalirudin as an anticoagulant in patients on ECMO has been well described (4). It appears to have

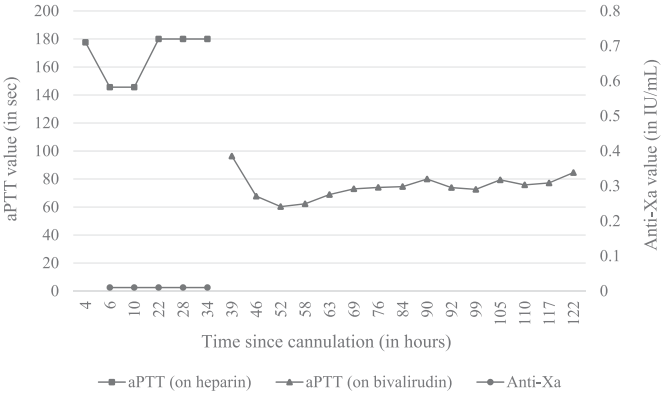

Figure 1. Anticoagulation values on ECMO.

comparable efficacy and incidence of complications when compared with heparin (1). Bivalirudin is a short-acting, direct thrombin inhibitor which works independently of AT on both circulating and clot-bound thrombin (5). It has a rapid onset of action and a short half-life, 25 minutes in the presence of normal renal function (6). Its elimination is mostly achieved by proteolytic cleavage, about 80%, and to a minor extent by renal excretion, about 20% (5). Its pharmacokinetics clearly gives it an advantage over other direct thrombin inhibitors in clinical use, such as argatroban and lepirudin, both of which have considerably longer half-lives and may accumulate, in patients with hepatic and renal dysfunction (7,8). Bivalirudin additionally can be reversed using recombinant factor VII more reliably than argatroban and lepirudin (7,8).

In our patient, with severe hyperbilirubinemia (peak of 18.2 mg/dL) and high plasma-free hemoglobin (peak of 388 mg/dL), aPTT was consistently greater than 150 seconds and heparin anti-Xa assay levels were less than .1 IU/mL. The effects from elevated plasma-free hemoglobin and hyperbilirubinemia on heparin anti-Xa assay levels in heparinized blood samples of ECMO patients have been studied and are consistent with the findings in in vitro studies (2). The reason for this is not completely understood but is related to the colorimetric assay for heparin anti-Xa being sensitive to high plasma-free hemoglobin and high bilirubin in the specimen in the presence of heparin (9). A previous in vitro study suggests that heparin anti-Xa activity is already underestimated by more than 10% in the presence of 6 mg/dL of bilirubin and 100 mg/dL of plasma-free hemoglobin (2). In addition, per package insert, anti-Xa rotachrom assay, which is used in our facility, is insensitive when bilirubin is greater than 6.6 mg/dL and plasma-free hemoglobin is greater than 200 mg/dL (9). Because the anti-Xa level was repeatedly less than .1 IU/mL, heparin dosing was titrated up, resulting in a further increase in the aPTT. Hyperbilirubinemia has also been shown to prolong aPTT usually at levels greater than 6 mg/dL through possible decrease in the activity of factors II, V, and VII (2). However, some reviewers believe the interference on coagulation testing from hyperbilirubinemia is due to spectral overlap and not its biologic properties (10).

After switching to bivalirudin, therapeutic goals of 60–80 seconds for aPTT on a dose range of .2–1 mg/kg/h were achieved without complications, bleeding or clot formation in the ECMO circuit. Bivalirudin appears to be an alternative anticoagulant with reliable monitoring in the setting of hyperbilirubinemia and high plasma-free hemoglobin. This added benefit of bivalirudin adds to the increasing body of evidence of comparable efficacy and complication rate with heparin and apparent advantages such as less need for AT.

REFERENCES

1. Nagle EL, Dager WE. Bivalirudin in pediatric patient maintained on extracorporeal life support. Pediatr Crit Care Med. 2013;14:182–8.
2. Kostousov V, Nguyen K, Hundalani SG, et al. The influence of free hemoglobin and bilirubin on heparin monitoring by activated partial thromboplastin time and anti-Xa assay. Arch Pathol Lab Med. 2014; 138:1503–6.
3. Oliver WC. Anticoagulation and coagulation management for ECMO. Semin Cardiothorac Vasc Anesth. 2009;13:154–75.
4. Sanfilippo F, Asmussen S, Maybauer M, et al. Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: A systematic review. J Intensive Care Med. 2017;32:312–9.
5. Bates SM, Neitz JI. The mechanism of action of thrombin inhibitors. J Invasive Cardiol. 2000;12(Suppl F):27F–32F.
6. Angiomax [Package Insert]. Parsippany, NJ: Medicines Company; 2016. Available at: https://web.archive.org/web/20120426012238/http://angiomax.com/Downloads/Angiomax_PI_2010_PN1601-12.pdf. Accessed August 2, 2018.
7. Cornell T, Wyrick P, Fleming G, et al. A case series describing the use of argatroban in patients on extracorporeal circulation. ASAIO J. 2007;53:460–3.
8. Drager WE, Gosselm RC, Yoshikawa R, et al. Use of lepuridin in continuous extracorporeal membrane oxygenation. Ann Pharmacother. 2004;38:598–601.
9. STA Rotachrom Heparin [Package Insert]. Parsippany, NJ: Diagnositica Stago; 2009.
10. Luppi G, Plebani M, Favaloro EJ. Interference in coagulation testing: Focus on spurious hemolysis, icterus, and lipemia. Semin Thromb Hemost. 2013;29:258–66.