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Antithrombotic strategies in children receiving long-term Berlin Heart EXCOR ventricular assist device therapy

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BACKGROUND: Thromboembolic events while receiving ventricular assist device (VAD) support remain a significant cause of morbidity and mortality despite standard anti-coagulation and anti-platelet therapies. The use of bivalirudin and epoprostenol infusions as an alternate anti-thrombotic (AT) regimen in pediatric VAD patients was reviewed.

METHODS: This was a retrospective record review of 6 pediatric patients (aged $\leq$17 years) at 2 institutions treated with bivalirudin and epoprostenol infusions while being supported with the Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany) VAD.

RESULTS: Six patients (age, 0.8–14 years; weight, 6.7–29.7 kg) were treated. Diagnoses included cardiomyopathy in 2 and congenital heart disease in 4. VAD support was left VAD in 2 and bi-VAD in 4, with duration of support of 21 to 155 days. Three patients required extracorporeal membrane oxygenation before VAD support. Bivalirudin/epoprostenol was used after recurrent thromboses on conventional medication in 3 patients, heparin-induced thrombocytopenia in 2, and in 1 patient considered high risk with a prosthetic mitral valve. The bivalirudin dose was titrated to partial thromboplastin time (PTT) of 1.5- to 2-times baseline (0.1–0.8 mg/kg/hour); the epoprostenol dose was 2 to 10 ng/kg/min. Additional anti-platelet agents included acetylsalicylic acid, dipyridamole, and clopidogrel in 5 patients each. No bleeding complications occurred. One patient sustained a cerebrovascular infarct on therapy, with subsequent complete recovery. No other complications occurred. Five patients underwent successful transplantation, and 1 patient died of multisystem organ failure.

CONCLUSIONS: This report provides data on estimated safety and efficacy of bivalirudin and epoprostenol as an AT strategy in pediatric patients on extended VAD support. The short drug half-life and predictable AT response facilitated conversion to standard AT regimens at the time of transplantation (heparin-induced thrombocytopenia–negative patients). These agents should be considered for management of pediatric VAD patients when standard regimens fail.

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Mechanical circulatory support with ventricular assist devices (VADs) has evolved in the pediatric population as an accepted modality for the failing heart refractory to maximal medical and surgical management. Despite refinements in anti-thrombotic (AT) management, clinically significant thromboembolic events continue to be a devastating complication.[1] Conventional anticoagulation regimens include unfractionated heparin, low-molecular-weight heparin, or warfarin, with the addition of anti-platelet agents (dipyridamole, acetylsalicylic acid, or clopidogrel), but as

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yet, there are no standardized treatment guidelines for pediatric patients.[2] In addition, patients diagnosed with heparin-induced thrombocytopenia (HIT) with thrombosis or isolated HIT with normal renal function should not receive unfractionated heparin or low-molecular-weight heparin.[3]

Bivalirudin, a direct thrombin inhibitor, has become an accepted alternative in patients requiring anti-coagulation in the setting of HIT or for use during percutaneous coronary interventions. Epoprostenol is a synthetic prostacyclin analog that inhibits platelet aggregation and has been used in HIT-positive patients undergoing cardiopulmonary bypass (CPB).[4,5] This study reports the estimated safety and efficacy of the combination of bivalirudin and epoprostenol infusions as an alternate AT regimen for VAD support from the combined pediatric experience at 2 institutions.

Methods

After Institutional Review Board approval, a retrospective review of all patients aged $\leq$17 years treated with the combination of bivalirudin and epoprostenol (bivalirudin/epoprostenol) infusions while being supported with the Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany) VAD was conducted at the University of Alberta Hospital, Edmonton, Alberta, Canada ($n = 1$) and Mount Sinai Medical Center-New York University, New York, New York ($n = 5$). Clinical and laboratory data collected included patient demographics, diagnosis, device type, surgical procedure(s) before VAD implant, prior AT management, AT strategy at transplant (if different), complications (safety), and outcome (efficacy).

VAD implantation

The decision to implant LVAD vs biventricular (BiVAD) support was made by the managing physicians.

AT therapy

Patients who initially received conventional AT regimens were treated according to the recommendations of the Edmonton Antithrombotic Protocol,[6] including therapeutic monitoring with anti-Xa levels, thromboelastography (TEG, Haemonetics Corporation, Niles, IL) and Platelet Mapping Assay (Haemonetics Corp, Braintree, MA) with arachidonic acid and adenosine diphosphate as agonists. Additional hematologic monitoring included platelet count, prothrombin time/PTT, and AT levels at the discretion of the managing physicians. Patients converted from the Edmonton Protocol to bivalirudin were treated as outlined in Table 1.

Epoprostenol

All patients were initiated on a dose of 2 ng/kg/min after VAD implant (Table 1). Those patients without pulmonary hypertension had few dosage adjustments (dose increased to 4 ng/kg/min in Patient 4 due to increased fibrin deposits). Patients with elevated pulmonary artery pressures had incremental dose increases to reach a therapeutic dose of 20 ng/kg/min or until hypotension was seen (Patients 2 and 3). All patients received additional anti-platelet agents, as reported in Table 4.

Frequency of TEG and Platelet Mapping studies was at the discretion of the managing physicians following guidelines from the Edmonton Antithrombotic Protocol.[6] In general, TEG is recommended every 24 hours in the first 2 weeks after implant, twice weekly in the next week, and once weekly thereafter. If, at any time after the first 2 weeks, the AT status becomes unstable, the TEG should be performed daily until the patient and/or AT status is again stable. Similarly, Platelet Mapping studies are recommended every 2 days in the first week after implant, twice weekly the following week, and weekly thereafter.

Table 1 Bivalirudin Dosing Guidelines for Ventricular Assist Device Patients Failing the Edmonton Protocol

1. Before administration: Baseline aPTT/PT, serum creatinine, estimated GFR (Schwartz formula)
2. Initial infusion rate:
   - Normal renal function: 0.5 mg/kg/hour
   - GFR 30-60 ml/min: 0.3 mg/kg/hour
   - GFR $<$30 ml/min: 0.2 mg/kg/hour
   - Renal replacement therapy: 0.1 mg/kg/hour
3. Monitoring:
   a. aPTT: 2 hours after initiation of therapy (target aPTT 1.5–2-times baseline or 60-90; ACT 180-220 seconds)
   b. Once target achieved: monitoring every day before noon (consider reducing frequency to weekly once stable with no dosage adjustments)
   c. Monitor aPTT 2 hours after dose change, immediately before resuming therapy if infusionhas been held or if thromboembolism or hemorrhage suspected
4. Dose titration
   No loading dose
   - aPTT $<$60 Increase dose 20%
   - aPTT 60-90 No change
   - aPTT $>$90 Hold infusion 1 hour and restart at 50% prior dose
5. Antiplatelet therapy
   - Intravenous epoprostenol 2-20 ng/kg/min
   - Clopidogrel 1-2 mg/kg/day
   - Dipyridamole 0.5 mg/kg/dose every 12 hours
   - Omega 3 fatty acid supplementation to food (canola or fish oil)

ACT, activated clotting time; aPTT, activated partial thromboplastin time; GFR, glomerular filtration rate; PT, prothrombin time.

Results

Six pediatric VAD patients received bivalirudin/epoprostenol infusions, and their demographics are reported in Table 2. Bivalirudin and epoprostenol were used after conventional AT therapy failed in 3 patients, consisting of rapid and recurrent VAD thrombosis or clinical thromboembolism. In 2 patients, bivalirudin/epoprostenol was used due to HIT. Patient 4 was initiated directly on therapy with bivalirudin/epoprostenol in the absence of HIT or previous AT therapy failure because the managing physicians felt there was a high risk of prosthetic mitral valve thrombosis due to the unloading effect of the LVAD and reduced transmitral flow. In addition, the team had gained experience with this regimen in 3 previous patients.