Pediatric Anesthesia and Critical Care Journal 2021;9(2):94-102
doi:10.14587/paccj.2021.16

PACCJ

Bivalirudin for cardiac catheterization in a pediatric patient with religious objection to the use of porcine-derived heparin

A. Caskey[1], C. McKee[2], J. D. Tobias[2]

[1]Heritage College of Osteopathic Medicine – Dublin Campus, Dublin, Ohio and Ohio University, USA
[2]Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital and the Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA

Corresponding author: J. D. Tobias, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital and the Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA. E-mail: Joseph.Tobias@nationwidechildrens.org

Keypoints

1. Various religions hold tenets regarding the consumption or utilization of animal-derived products, which may impact medical care when selecting animal-derived medications and products. As unfractionated heparin is porcine-derived, it may be objectionable to patients of specific religious groups.
2. Bivalirudin is a synthetic direct thrombin inhibitor that is related to hirudin. It was developed to provide an alternative anticoagulant to heparin in patients with heparin-induced thrombocytopenia or heparin resistance.
3. Although it is not currently FDA-approved for use in pediatric patients, there is significant anecdotal clinical experience with its use during cardiac catherterization, cardiac surgery requiring cardiopulmonary bypass, and during extracorporeal support procedures.
4. Although it provides effective anticoagulation, concerns with bivalirudin include identification of the optimal mode to monitor and adjust dosing, need to adjust dosing in patients with renal insufficiency or failure, and the lack of a rapid reversal agent.

Abstract

Various clinical scenarios may require the short or long-term administration of agents to provide anticoagulation. In the vast majority of scenarios and clinical situations, heparin remains the agent of choice. However, patient concerns or conditions such as heparin-induced thrombocytopenia (HIT) or religious concerns regarding the use of porcine-derived medications may require the use of alternative anticoagulants. We present the use of bivalirudin for anticoagulation during a cardiac catheterization procedure in a 9-year-old patient of the Islamic faith who requested no porcine-derived medications. Basic principles of bivalirudin are discussed, previous reports of its use during cardiac catheterization reviewed, and clinical guidelines for its use in this clinical scenario presented.

Keywords

anticoagulation, heparin, bivalirudin

Introduction

Various religions hold tenets regarding the consumption or utilization of animal-derived products, which may impact medical care when selecting animal-derived medications and products. Gelatin capsules, surfactants, surgical implants, and specific medications may be derived from porcine or bovine material.[1-4] One commonly used medication that is frequently porcine derived is heparin.[5] Heparin, a glycosaminoglycan produced by basophils and mast cells in all mammals, is a naturally occurring anticoagulant. This makes it convenient for pharmaceutical companies to extract heparin from various animals (porcine, bovine, and ovine).

The original clinically available heparin products from the 1930s were from a bovine source (cow lung). Although this a 50-60 year history of the safe use of bovine-derived heparin, due to concerns of the theoretical transmission of spongiform encephalopathy agents, bovine lung heparin was voluntarily removed from the US market by manufacturers in the late 1990s and replaced by porcine heparin. Despite this, bovine mucosa heparin drug products remain available and manufactured in various South American countries including Brazil and Argentina. However, in light of concerns over future global heparin supply shortages, the FDA has begun to encourage bovine derived heparin as purification processes for removing potential pathologic prions continue to advance.[6]

The advances in the development of synthetic heparins (fondaparinux) have been extensive, but manufacturing cost, availability, and the inability to quickly reverse these synthetic variants with protamine sulfate remain disadvantages to their use for acute anticoagulation.[7] As unfractionated heparin (UFH) may be porcine-derived, it may pose dilemmas with caring for patients of certain religious groups. We present the use of bivalirudin for anticoagulation during a cardiac catheterization procedure in a 9-year-old patient of the Islamic faith who requested no porcine-derived medications. Basic principles of bivalirudin are discussed, previous reports of its use during cardiac catheterization reviewed, and clinical guidelines for its use in this clinical scenario presented.

Case report

Review of this case and presentation in this format followed guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient was a 9-year-old, 30.6 kilogram female child who presented with increased cyanosis and clubbing for a Fontan fenestration closure. Her prior cardiac medical history included double outlet right ventricle (DORV), pulmonary stenosis, right ventricular hypoplasia, dextro-transposition of the great arteries (d-TGA), and large subpulmonic ventricular septal defect (VSD). Prior surgical procedures included bidirectional Glenn procedure, fenestrated extracardiac Fontan, tricuspid valve repair, pulmonary valve over-sewing, and patch augmentation of the pulmonary arteries. She developed atrial flutter following Fontan palliation which was controlled with amiodarone. Additional past surgical history included gastrostomy tube placement and dorsal rhizotomy. Additional past medical history and comorbid conditions included cerebral vascular events following her previous cardiac surgery, a seizure disorder, IVC thrombus requiring long term anticoagulation with coumadin, spastic quadriplegic cerebral palsy, developmental delay, cognitive impairment, mixed receptive-expressive language disorder, and muscle spasticity. At the time of cardiac catheterization procedure, medications included baclofen (30 mg by mouth every day), levetiracetam (800 mg by mouth every day), lisinopril (2 mg by mouth every day), and melatonin (2 mg by mouth every night). Physical examination revealed a normal pulmonary exam and airway with no loose teeth. The cardiovascular exam revealed a regular rhythm with cyanosis and clubbing. As the patient followed the Islamic faith, they requested no porcine-derived medications including heparin. The patient was admitted the day before the procedure in anticipation of the need to bridge anticoagulation with bivalirudin. However, as the international normalized ratio (INR) was 1.7 even after

holding the warfarin for 2 days, it was decided that pre-operative bridging was not indicated. The patient was held *nil per os* after midnight and transported to the cardiac catheterization suite where standard American Society of Anesthesiologists' monitors were placed. Anesthesia was induced with intravenous fentanyl (25 µg), propofol (20 mg), midazolam (2 mg), and lidocaine (30 mg). Neuromuscular blockade was provided with intravenous rocuronium (30 mg). Intravenous cefazolin (1500 mg) was administered for antimicrobial prophylaxis. Direct laryngoscopy provided a Cormack-Lehane grade 1 view and the trachea was intubated with a 5.5 mm cuffed endotracheal tube without difficulty. Bivalirudin was administered intravenously for anticoagulation during the procedure (0.25 mg/kg bolus followed by an infusion starting at 0.25 mg/kg/hour) with a proposed activated clotting time (ACT) goal of >250 seconds. The infusion rate was down titrated to 0.125 mg/kg/hour when the patient's first ACT was 322 seconds, an hour after the bolus and initiation of the initial infusion rate. The infusion rate was subsequently increased to 0.2 mg/kg/hour, approximately 25 minutes later when the ACT had decreased to 255 seconds. The infusion was held constant at 0.2 mg/kg/hour. The ACT was 251 seconds, 2 hours after the start of the infusion. The cardiac catheterization ablation procedure lasted approximately 3 hours. Postoperative anti-emetic medication included intravenous dexamethasone (4 mg) and ondansetron (4 mg). Postoperative analgesia therapy was provided with intravenous acetaminophen (450 mg). Residual neuromuscular blockade was reversed with sugammadex (75 mg) and the patient's trachea was extubated in the operating room. She was transported to the cardiothoracic intensive care unit (CTICU). In consultation with hematology, the bivalirudin infusion (0.2 mg/kg/hr) was continued in the CTICU to bridge anticoagulation until a therapeutic prothrombin time (PT)/INR was achieved with oral coumadin with an INR goal of 2.5-3.0. Coumadin (3 mg every night) was started the day after surgery and increased to 4 mg every night, 6 days post-surgery as the INR remained at 2.1 while bridging with bivalirudin. Bivalirudin was discontinued 7 days post-procedure with an INR at 2.8. The patient remained hemodynamically stable throughout the post-operative course and was discharged home 8 days after the procedure with an INR at 2.2.

Discussion

The direct-thrombin inhibitors (DTIs) were introduced into clinical practice in 1909 with the availability of hirudin, the first parental anticoagulant.[8,9] Hirudin is a natural thrombin inhibitor, which is produced by the salivary gland of the leech.[8] Although hirudin was used for anticoagulation during hemodialysis, heparin became available in the early 1950s and has subsequently become the most commonly used agent for parenteral anticoagulation. Although hirudin is no longer available, lepirudin subsequently became available. It is a recombinant form of hirudin (r-hirudin) that forms an irreversible (1:1) complex with thrombin.[10] Unlike heparin, lepirudin also inhibits clot-bound thrombin, including thrombin on fibrin independent of antithrombin III (ATIII).[10] Although clinical trials have demonstrated its efficacy to provide anticoagulation, allergic reactions ranging from urticaria to hemodynamic instability have been reported.[11-13] Anaphylactoid reactions may occur regardless of previous exposure. However, as re-exposure is associated with a greater risk, it is recommended that exposure to lepirudin be limited to a single exposure whenever clinically feasible.

Bivalirudin is a synthetic DTI that is related to hirudin. It was developed in the early 1990s and acquired its first FDA-approval for percutaneous transluminal coronary angioplasty (PTCA) in 2000 under the brand name Angiomax® by The Medicines Company (Parsippany, NJ).[9] It is a 20-amino acid synthetic peptide consisting of a 12-amino acid carboxy-terminal segment (dodecapeptide) derived from natural hirudin residues 53-64, a tetrapeptide amino-terminal segment, and a connecting tetraglycine spacer segment.[14] Like lepirudin, bivalirudin is a bivalent DTI binding both free circulating (solu-

ble) and clot-bound (fibrin-bound) thrombin independent of ATIII. The amino-terminal segment electively binds to the catalytic site of thrombin and the carboxyl-terminal portion binds to the fibrinogen site on thrombin. Anticoagulation is achieved through specific and reversible interaction with the catalytic site of thrombin responsible for converting fibrinogen to fibrin, a terminal step in the coagulation cascade. The half-life of bivalirudin is only 25 minutes, and it is predominantly (80%) eliminated through proteolytic cleavage within the plasma. A minority (20%) is excreted by the kidneys. Despite limited dependence on renal excretion, its clearance is reduced by ~80% in patients with renal failure.[15]

Bivalirudin was originally developed with the goal of providing a safe alternative anticoagulant when heparin use is contraindicated, including HIT or heparin resistance.[16,17] Bivalirudin received its first FDA-approved indication in 2000 for anticoagulation during PTCA following the Bivalirudin Angioplasty Trial (BAT).[9] The Bivalirudin Angioplasty Study from 2001 reanalyzed the same data from the BAT study comparing high-dose UFH (175 units/kg bolus followed by an infusion of 15 units/kg/hr) to bivalirudin (1.0 mg/kg bolus followed by an infusion of 2.5 mg/kg/hr) during coronary angioplasty in adults with unstable angina.[18] The composite endpoints of death, myocardial infarction (MI), or the need for surgical revascularization were significantly lower ($p<0.039$) in bivalirudin-treated patients with an associated reduction in major bleeding complications ($p<0.001$).[18]

The first pilot study on dosing, the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trials (CACHET) determined that that the most effective dosing of bivalirudin was a 0.75 mg/kg bolus dose followed by an infusion of 1.75 mg/kg/hr during the span of percutaneous coronary intervention (PCI).[19] This subsequently became the FDA-approved dosage and is still the most employed dosing regimen today in routine clinical practice. Since its initial success in PTCA for unstable angina, bivalirudin use in adults has expanded to other surgical and interventional scenarios including PCI for ST-elevated myocardial infarction (STEMI) and cardiopulmonary bypass (CPB), as well as patients with a history of HIT.[20-25] Although PCI remains the only FDA-approved indication for anticoagulation with bivalirudin, the applications and safety of bivalirudin in on-pump and off-pump coronary artery bypass graft (CABG) surgery, acute coronary syndrome (ACS), transcatheter valve intervention, extracorporeal membrane oxygenation (ECMO), and deep vein thrombosis (DVT) prophylaxis has seen increased use.[26-30]

The growing anecdotal reports and clinical experience have expanded to include the pediatric population, most commonly in those with confirmed or suspected HIT, ATIII deficiency, or hypersensitivity to heparin or pork products, requiring cardiac catheterization or surgery for congenital heart disease using CPB.[20,31-33] The first successful use of bivalirudin for anticoagulation in the pediatric population was published in 2006 and included a 2-month old infant with ATIII deficiency who required a stent placement to correct stenosis of a previously placed conduit between the right ventricle and pulmonary trunk.[31] Two additional case reports and a large cohort case series have since been published on bivalirudin use during pediatric cardiac catheterization.[32-34] Streiff et al. described the successful use of bivalirudin in a 4-year old male with a history of complex congenital heart disease and HIT who required anticoagulation during two separate cardiac catheterizations 3 months apart.[32] While both procedures were successful, the first and second case both required increasing bivalirudin infusion due to inadequate ACT and clotting in access sheaths, respectively.[32] The authors noted the difficulty in monitoring and dosing of bivalirudin during cardiac catheterization as there is a lack of well-established evidence-based medicine for age-specific dosing regimens and monitoring techniques. The 106-patient study by Forbes et al. in 2011 is the only study to examine bivalirudin pharmacokinetics (PK) and pharmacodynamics

(PD) in pediatric patients undergoing cardiac catheterization.[34] The study monitored PK/PD data (ACT, steady-state concentration, max concentration, clearance, and half-life) in the neonate to 16-year-old pediatric age range undergoing PCI procedures. The safety endpoints included bleeding and thrombotic events. The PK/PD outcomes performed similar to adults and there was no increased risk in either safety endpoint.[34] This led the authors to conclude that bivalirudin was safe and its pharmacologic effects predictable in pediatric patients undergoing PCI procedures.

In addition to its use for pediatric cardiac catheterization, there has been expanded anecdotal clinical experience with bivalirudin for anticoagulation during pediatric cardiac surgery, largely for children with HIT, as well as a recent randomized controlled trial.[35-42] The first reported use in cardiac surgery included a 5-year-old child with HIT requiring CPB during orthotopic heart transplantation.[35] Bivalirudin dosing included an initial bolus dose of 0.15 mg/kg followed by an infusion at 0.25 mg/kg/hr. Despite this, the authors noted the need for several additional bolus doses and a rapid increase in the infusion rate to achieve and sustain their target ACT >400 seconds. The post-operative course was reported to be without any thrombotic events or major bleeding. Following this, six additional cases regarding bivalirudin use during pediatric CPB have been reported.[36-41] Although bivalirudin was successful without thrombotic or bleeding complications, many of the authors expressed the need for a standardized, evidence-based medicine protocol for bivalirudin use during CPB, were concerned over inconsistencies in using ACT to monitor anticoagulation during surgery, and noted variable approaches to minimize postoperative bleeding (including the use of tranexamic acid and modified ultrafiltration). This initial work led to a prospective, randomized study in 2018 directly comparing heparin to bivalirudin for anticoagulation during cardiac surgery in pediatric patients ranging in age from 1 to 12 years.[42] The trial evaluated the dose of heparin or bivalirudin required to achieve an ACT greater than 480 seconds during CPB in two groups of 25 pediatric patients. Bivalirudin dosing requirements included a bolus dose of 1.7 ± 0.2 mg/kg followed by an infusion at 3.0 ± 0.7 mg/kg/hr (comparably higher than routine dosing in adults of 1 mg/kg bolus followed by an infusion of 2.5 mg/kg/hr).[42] Anticoagulation was evaluated using the Sonoclot Coagulation and Platelet Function Analyzer (Sienco Inc., Arvada, CO). Heparin was judged to be more effective in regard to the 3 endpoints evaluated including the prolongation of clot formation, decreased stable thrombus formation, and inhibition of platelet function. Bivalirudin required frequent additional boluses (n=13, 54.2%) compared to heparin (n=1, 3.9%), which led to a prolongation of the overall surgical time in the bivalirudin group. In addition, the ACT remained elevated in bivalirudin patients for 2 hours postoperatively due to the lack of availability of a reversal agent. For the above reasons, the authors recommended that bivalirudin not be used routinely during CPB in infants and children unless there is a contraindication to heparin. Similar findings were noted in a more recent report from 2021.[43] Over the past decade, reports of bivalirudin use in pediatrics continue to expand into other procedures including ECMO, ventricular assist device (VAD) implantation, and DVT treatment.[44,45] Four case reports outline the novel use of bivalirudin in combination with tissue plasminogen activator (tPA) as thrombolytic therapy in pediatric patients.[46-49]

Although it provides effective anticoagulation, concerns with bivalirudin include identification of the optimal mode to monitor and adjust dosing as well as the lack of a rapid reversal agent. Unlike the reversibility of heparin with protamine, there is no reversal agent for bivalirudin. Once the need for anticoagulation has ceased, the bivalirudin infusion is discontinued and its effects allowed to dissipate, generally over 2 hours. Approximately 20% of bivalirudin is excreted via the kidney; the remainder is eliminated by proteolytic enzymatic degradation. Elimination can be accelerated by ultrafil-

tration after separation from CPB.[50] Bivalirudin prolongs the activated partial thromboplastin time (aPPT), thrombin time (TT), ACT, and to a lesser degree PT/INR. As a rapid point-of-care test, the ACT has been used most commonly to monitor anticoagulation during bivalirudin administration. While bivalirudin concentration is positively correlated with an increase in ACT, it does not demonstrate a linear dose-response relationship. ACT values exceeding 350 seconds were shown to not accurately reflect increasing doses of bivalirudin.[51] In addition, ACT has been shown to poorly differentiate between common low-dose (0.75 mg/kg bolus, 1.75 mg/kg/hr) and high-dose (1 mg/kg bolus, 2.5 mg/kg/hr) bivalirudin regimens.[51] The dose-response correlation declines even further at higher concentrations, notably in the case of pediatric patients and CPB.[20] Monitoring methods that have been shown to have more sensitivity and a greater range of measurement have been suggested for routine use, such as ecarin clotting time (ECT), but none are FDA-approved or widely available.[52]

In summary, we report the use of bivalirudin in a 9-year-old patient of Islamic faith who requested no porcine-derived medications including heparin. Bivalirudin, a DTI, has seen increased use in clinical practice over the past two decades, particularly in patients with contraindications to heparin, most commonly HIT. Although it is not currently FDA-approved for use in pediatric patients, there is a large amount of anecdotal experience reported in the literature to provide safety data and dosing guidelines. Current point-of-care monitoring techniques require sound clinical judgment and awareness of limitations. Cardiac catheterization and cardiac surgery requiring CPB remain the most common scenarios in pediatrics where bivalirudin is employed, with other surgical procedures being increasingly explored in the past decade. As experience with bivalirudin among pediatric patients increases, it may be appropriately used outside the context of HIT, as in unique cases of the request of no porcine-derived medications due to religious convictions.

References

1. Sattar SP, Ahmed MS, Majeed F, Petty F. Inert medication ingredients causing nonadherence due to religious beliefs. Ann Pharmacother. 2004;38:621-4.
2. Sattar SP, Ahmed MS, Madison J, et al. Patient and physician attitudes to using medications with religiously forbidden ingredients. Ann Pharmacother. 2004;38:1830-5.
3. Gatrad AR, Mynors G, Hunt P, Sheikh A. Patient choice in medicine taking: religious sensitivities must be respected. Arch Dis Child. 2005;90:983-4.
4. Enoch S, Shaaban H, Dunn KW. Informed consent should be obtained from patients to use products (skin substitutes) and dressings containing biological material. J Med Ethics. 2005;31:2-6.
5. Datz H, Syed A, Alsuhebani M, Tumin D, Tobias JD. Religious-related concerns and animal-derived medications during anesthetic care. Anaesth Pain Intensive. Care 2018;22:247-50.
6. Andrews O, Bett C, Shu Q, Kaelber N, Asher D, Keire D, Gregori L. Processing bovine intestinal mucosa to active heparin removes spiked BSE agent. Biologicals. 2020;67:56-61.
7. Nahain AA, Ignjatovic V, Monagle P, Tsanaktsidis J, Ferro V. Heparin mimetics with anticoagulant activity. Med Res Rev. 2018;38:1582-1613.
8. Greinacher A, Lubenow N. Recombinant hirudin in clinical practice: focus on lepirudin. Circulation. 2001;103:1479-84.
9. Markwardt F. Hirudin as alternative anticoagulant—a historical review. Semin Thromb Hemost. 2002;28:405-14.
10. Petros S. Lepirudin in the management of patients with heparin-induced thrombocytopenia. Biologics. 2008;2:481-90.
11. Bircher AJ, Czendlik CH, Messmer SL, Müller P, Howald H. Acute urticaria caused by subcutaneous recombinant hirudin: evidence for an IgG-mediated

hypersensitivity reaction. J Allergy Clin Immunol. 1996;98:994-6.

12. Badger NO, Butler K, Hallman LC. Excessive anticoagulation and anaphylactic reaction after rechallenge with lepirudin in a patient with heparin induced thrombocytopenia. Pharmacotherapy. 2004;24:1800-3.
13. Greinacher A, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. Circulation. 2003;108:2062-5.
14. Warkentin TE, Koster A. Bivalirudin: a review. Expert Opin Pharmacother. 2005;6:1349-71.
15. Chew DP, Bhatt DL, Kimball W, Henry TD, Berger P, McCullough PA, Feit F, Bittl JA, Lincoff AM. Bivalirudin provides increasing benefit with decreasing renal function: a meta-analysis of randomized trials. Am J Cardiol. 2003;15;92:919-23.
16. Seybert AL. Bivalirudin administration during percutaneous coronary intervention: emphasis on high-risk patients. Pharmacotherapy. 2002;22:112S-18S.
17. McNair E, Marcoux JA, Bally C, Gamble J, Thomson D. Bivalirudin as an adjunctive anticoagulant to heparin in the treatment of heparin resistance during cardiopulmonary bypass-assisted cardiac surgery. Perfusion. 2016;31:189-99.
18. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. Am Heart J. 2001;142:952-9.
19. Lincoff AM, Kleiman NS, Kottke-Marchant K, Maierson ES, Maresh K, Wolski KE, Topol EJ. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). Am Heart J. 2002;143:847-53.
20. Zaleski KL, DiNardo JA, Nasr VG. Bivalirudin for pediatric procedural Anticoagulation: A Narrative Review. Anesth Analg. 2019;128:43-55.
21. Smedira NG, Dyke CM, Koster A, Jurmann M, Bhatia DS, Hu T, McCarthy HL 2nd, Lincoff AM, Spiess BD, Aronson S. Anticoagulation with bivalirudin for off-pump coronary artery bypass grafting: the results of the Evolution-Off study. J Thorac Cardiovasc Surg. 2006;131:686-92.
22. Dyke CM, Smedira NG, Koster A, Aronson S, McCarthy HL 2nd, Kirshner R, Lincoff AM, Spiess BD. A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. J Thorac Cardiovasc Surg. 2006;131:533-9.
23. Augoustides JG. Update in hematology: heparin-induced thrombocytopenia and bivalirudin. J Cardiothorac Vasc Anesth. 2011;25:371-5.
24. Koster A, Dyke CM, Aldea G, Smedira NG, McCarthy HL 2nd, Aronson S, Hetzer R, Avery E, Spiess B, Lincoff AM. 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.
25. Dyke CM, Aldea G, Koster A, Smedira N, Avery E, Aronson S, Spiess BD, Lincoff AM. Off-pump coronary artery bypass with bivalirudin for patients with heparin-induced thrombocytopenia or antiplatelet factor four/heparin antibodies. Ann Thorac Surg. 2007;84:836-9.
26. Van De Car DA, Rao SV, Ohman EM. Bivalirudin: a review of the pharmacology and clinical application. Expert Rev Cardiovasc Ther. 2010;8:1673-81.
27. Kini A, Yu J, Cohen MG, et al. Effect of bivalirudin on aortic valve intervention outcomes study: a two-centre registry study comparing bivalirudin and unfractionated heparin in balloon aortic valvuloplasty. EuroIntervention. 2014;10:312–9.

28. Lange P, Greif M, Bongiovanni D, et al. Bivalirudin vs heparin in patients who undergo transcatheter aortic valve implantation. Can J Cardiol. 2015;31:998–1003.
29. Dangas GD, Lefèvre T, Kupatt C, et al; BRAVO-3 Investigators. Bivalirudin versus heparin anticoagulation in transcatheter aortic valve replacement: the randomized BRAVO-3 trial. J Am Coll Cardiol. 2015;66:2860–8.
30. Janjua T, Nussbaum E, Lowary J, Babbini V. Bivalirudin as a bridge for anticoagulation in high risk neurosurgical patients with active DVT or high risk of thrombosis. Neurocrit Care. 2013;18:349-53.
31. Zamora R. Successful anticoagulation with bivalirudin in antithrombin-deficient pediatric patient undergoing stent placement. Catheter Cardiovasc Interv. 2006;68:292-5.
32. Streiff A, DiNardo J, Zaleski K. Titration of bivalirudin infusion in the pediatric cardiac catheterization laboratory: A Case Report. AA Pract. 2019;15;13:65-8.
33. Breinholt JP, Moffett BS, Texter KM, Ing FF. Successful use of bivalirudin for superior vena cava recanalization and stent placement in a child with heparin-induced thrombocytopenia. Pediatr Cardiol. 2008;29:804-7.
34. Forbes TJ, Hijazi ZM, Young G, Ringewald JM, Aquino PM, Vincent RN, Qureshi AM, Rome JJ, Rhodes JF Jr, Jones TK, Moskowitz WB, Holzer RJ, Zamora R. Pediatric catheterization laboratory anticoagulation with bivalirudin. Catheter Cardiovasc Interv. 2011;1;77:671-9.
35. Almond CS, Harrington J, Thiagarajan R, Duncan CN, LaPierre R, Halwick D, Blume ED, Del Nido PJ, Neufeld EJ, McGowan FX. Successful use of bivalirudin for cardiac transplantation in a child with heparin-induced thrombocytopenia. J Heart Lung Transplant. 2006;25:1376-9.
36. Gates R, Yost P, Parker B. The use of bivalirudin for cardiopulmonary bypass anticoagulation in pediatric heparin-induced thrombocytopenia patients. Artif Organs. 2010;34:667-9.
37. Dragomer D, Chalfant A, Biniwale R, Reemtsen B, Federman M. Novel techniques in the use of bivalirudin for cardiopulmonary bypass anticoagulation in a child with heparin-induced thrombocytopenia. Perfusion. 2011;26:516-8.
38. Faella KH, Whiting D, Fynn-Thompson F, Matte GS. Bivalirudin anticoagulation for a pediatric patient with heparin-induced thrombocytopenia and thrombosis requiring cardiopulmonary bypass for ventricular assist device placement. J Extra Corpor Technol. 2016;48:39-42.
39. Kamata M, Sebastian R, McConnell PI, Gomez D, Naguib A, Tobias JD. Perioperative care in an adolescent patient with heparin-induced thrombocytopenia for placement of a cardiac assist device and heart transplantation: case report and literature review. Int Med Case Rep J. 2017;14;10:55-63.
40. Bryant ME, Regan WL, Fynn-Thompson F, Hoganson D, Nasr VG, Zaleski K, Faella K, Matte GS. Comparison of two pediatric cases requiring the use of bivalirudin during cardiopulmonary bypass. Perfusion. 2018;33:525-32.
41. Argueta-Morales IR, Olsen MC, DeCampli WM, Munro HM, Felix DE. Alternative anticoagulation during cardiovascular procedures in pediatric patients with heparin-induced thrombocytopenia. J Extra Corpor Technol. 2012;44:69-74.
42. Hasija S, Talwar S, Makhija N, Chauhan S, Malhotra P, Chowdhury UK, Krishna NS, Sharma G. Randomized controlled trial of heparin versus bivalirudin anticoagulation in acyanotic children undergoing open heart surgery. J Cardiothorac Vasc Anesth. 2018;32:2633-40.
43. Wolstencroft P, Arnold P, Anderson BJ. Dose estimation for bivalirudin during pediatric cardiopulmonary bypass. Paediatr Anaesth. 2021;31:637-43.
44. Goswami D, DiGiusto M, Wadia R, Barnes S, Schwartz J, Steppan D, Nelson-McMillan K, Ringel

R, Steppan J. The use of bivalirudin in pediatric cardiac surgery and in the interventional cardiology suite. J Cardiothorac Vasc Anesth. 2020;34:2215-23.

45. O'Brien SH, Yee DL, Lira J, Goldenberg NA, Young G. UNBLOCK: an open-label, dose-finding, pharmacokinetic and safety study of bivalirudin in children with deep vein thrombosis. J Thromb Haemost. 2015;13:1615-22.
46. Regling K, Callaghan MU, Rajpurkar M. Bivalirudin during thrombolysis with catheter-directed tPA in a heparin-refractory patient: A case report. Pediatr Blood Cancer. 2020;67:e28094.
47. Samelson-Jones BJ, Acord MR, Raffini L. Comment on: Bivalirudin during thrombolysis with catheter-directed tPA in a heparin-refractory patient: A case report. Pediatr Blood Cancer. 2020;67:e28518.
48. Taha A, Rajgarhia A, Alsaleem M. Bivalirudin and thrombolytic therapy: a novel successful treatment of severe aortic arch thrombosis in a term neonate. BMJ Case Rep. 2021;18;14:e239535.
49. Machado DS, Tule M, Philip J, Wynn T, Lazarowicz M, Machuca T, Pipkin M, Alnuhaimat H, Ebraheem M, Peek G, Bleiweis M. Bivalirudin and alteplase for pulmonary embolism requiring veno-arterial extracorporeal membrane oxygenation in an adolescent. J Extra Corpor Technol. 2020;52:327-31.
50. Koster A, Buz S, Krabatsch T, Dehmel F, Kuppe H, Hetzer R, Aronson S, Dyke CM. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: assessment of different filtration strategies. J Card Surg. 2008;23:655-8.
51. Casserly IP, Kereiakes DJ, Gray WA, Gibson PH, Lauer MA, Reginelli JP, Moliterno DJ. Point-of-care ecarin clotting time versus activated clotting time in correlation with bivalirudin concentration. Thromb Res. 2004;113:115-21.
52. Zucker ML, Koster A, Prats J, Laduca FM. Sensitivity of a modified ACT test to levels of bivalirudin used during cardiac surgery. J Extra Corpor Technol. 2005;37:364-8.