Use of Apixaban in Children Awaiting Heart Transplantation

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Abstract

Objective The use of apixaban in the pediatric cardiac population is expanding. We describe our apixaban dosing and monitoring strategy in children and young adults awaiting heart transplantation, along with outcomes related to bleeding and thrombosis during wait-list and early post-transplant periods. *Methods* This study is a retrospective, single center analysis of all patients receiving apixaban while awaiting cardiac transplantation. Weight-based dosing was monitored with peak drug-specific anti-Xa chromogenic analysis. Significant post-operative bleeding defined by chest tube output or need for surgical intervention. *Results* From September 2020 through December 2022, 19 patients, median age 13.5 years (6.1, 15.8 years), weighing 48.9 kg (15.4, 67.6) received apixaban while awaiting transplant. Indication for apixaban was prophylaxis (n=18, 3 with ventricular assist devices) and treatment of thrombus (n=1). There were no clinically relevant non-major or major bleeding, nor thrombotic events while awaiting transplant. The median time from last apixaban dose to arrival in the operating room was 23.2 hours (15.6-33.8), with median random apixaban level of 37 ng/ml (28.3, 59), 6.3 hours (4.8, 8.4) prior to arrival in the operating room. 32% of patients had significant post-operative bleeding based on chest tube output post-transplant or need for intervention. No patients meeting criteria for significant postoperative bleeding were thought to be attributable to apixaban. *Conclusion* Careful use of apixaban can be safe and effective while awaiting heart transplant. There was no appreciable increase in perioperative bleeding. The use of apixaban is promising in providing safe, predictable and efficacious anticoagulation while avoiding additional patient stressors.

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Abbreviations Key:

LMWH	Low Molecular Weight Heparin
DOAC	Direct Oral Anticoagulant
FDA	Food and Drug Administration
OR	Operating Room
CICU	Cardiac Intensive Care Unit
UNOS	United Network for Organ Sharing
VAD	Ventricular Assist Device
HM3	HeartMate 3
ASA	Aspirin
ECMO	Extracorporeal Membrane Oxygenation

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Methods

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Conclusion

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Introduction

Thromboembolic events in children with congenital or acquired heart disease are a significant concern for pediatric cardiologists. Thromboembolic event rates are elevated in this population due to a multitude of factors including disruption of laminar blood flow, endothelial disruption, presence of central venous catheters, surgical introduction of foreign materials, iatrogenic and clinical coagulopathies from hepatic congestion, and hypoperfusion in the setting of abnormal cardiac function [1]. Unfortunately, a subset of these patients progress towards the need for cardiac transplantation, with continued needs for thromboembolic treatments and prophylaxis.

Traditionally, anticoagulation therapy has consisted of either low molecular weight heparin (LMWH) or oral vitamin K antagonists (i.e. warfarin). Guidelines have been established regarding the use of these agents for

prophylaxis in children with heart disease [2] and in those awaiting heart transplantation [3]. However, these therapies have their downsides. Warfarin requires frequent monitoring with serum levels greatly affected by changes in diet, hepatic function and interactions with other medications. LMWH requires twice-daily subcutaneous injections, along with serum monitoring requiring venipuncture, both of which are a challenge in the pediatric population.

Direct oral anticoagulants (DOACs), which include the direct thrombin inhibitor dabigatran and factor Xa inhibitors (Apixaban, Rivaroxaban, Edoxaban), have recently become the anticoagulants of choice in adults with acquired non-valvar cardiac disease, such as atrial fibrillation [4], left ventricular thrombus after myocardial infarction and adults with congenital heart disease [5-7]. In pediatrics, DOACs are increasingly being considered given the upside of less frequent monitoring and oral administration [8], in addition to their independence of antithrombin III and linear dose response [9]. Apixaban, a direct, reversible inhibitor of factor Xa, is of particular interest in ongoing pediatric trials [10-11]. There is emerging evidence in adults to suggest apixaban is more efficacious than rivaroxaban, the only currently Food and Drug Administration (FDA) approved factor Xa inhibitor in the pediatric population [12].

In this study, we describe our use of apixaban in children and young adults awaiting heart transplantation, including outcomes related to bleeding and thrombosis during wait-list and early post-transplant periods.

Materials and Methods

Our study is a retrospective, single-center analysis of all patients who received apixaban while listed for cardiac transplantation at Boston Children's Hospital. Data was obtained from review of the electronic medical record upon approval by the Boston Children's institutional review board (IRB-P00037911). This study was performed in line with the principles of the Declaration of Helsinki. No patients meeting this criteria were excluded from the study. Data collected included patient demographics, pertinent medical history and baseline laboratory results. Apixaban dosing was weight-based with dose adjustment to the nearest 0.625mg BID (1/4 of a 2.5mg pill) based on available formulation. Apixaban serum levels were obtained using drug-specific anti-Xa chromogenic STA® Liquid Anti-Xa with apixaban Calibrator and Controls (Diagnostica Stago Inc, Asnieres-sur-Seine, France) [13] with reportable range of <23ng/ml - 500ng/ml. analysis. Goal apixaban levels were extrapolated from adult studies [14, 15] and center experience: standard risk prophylaxis 80-150ng/mL, standard risk prophylaxis or treatment of thrombosis 100-300ng/mL and high-risk prophylaxis (i.e. ventricular assist devices (VAD) or Kawasaki with giant coronary aneurysm) 200-300ng/mL. Prior to the availability of apixaban level testing, low molecular weight heparin anti-Xa levels were followed with goal therapeutic level of greater than 1.5 units/mL and a maximum level reported of the assay of 2.0 units/ml.

Our institutional protocol included holding apixaban upon notification of organ acceptance. Arrival to the operating room (OR) was determined as documented in the anesthesia record. Significant bleeding was defined by one of four criteria: an average chest tube output upon arrival to the cardiac intensive care unit (CICU) of> 10mL/kg/hour for the first 2 hours,> 5mL/kg/hour over the first 4 hours, need for surgical re-exploration due to complications from bleeding, or clinical diagnosis of cardiac tamponade. Medians were calculated for all continuous variables with 25^{th} and 75^{th} percent quartiles reported.

Results

Between September 2020 and December 2022, a total of 19 patients (Table 1) were identified as having received apixaban at the time of transplantation (42% male, median 13.5 years of age). Of those, 13 patients had congenital heart disease, with the remainder having cardiomyopathy. Sixteen of the 19 patients were listed United Network for Organ Sharing (UNOS) Status 1A, of which 3 patients were supported with a HeartMate 3 (HM3, Abbott, Chicago, IL), 2 patients were Status 1B, and 1 patient was Status 2. Fifteen patients were maintained on inotropic support with milrinone infusions in inpatient and outpatient settings. For 13 patients, apixaban was administered in 3 patients for prophylaxis due to history of previous thrombus, 4 patients with severe ventricular dysfunction with ejection fraction <30%, and 6 patients for the presence of a central venous line in single ventricle palliation. Therapeutic levels were targeted in 6 patients for active thrombus treatment or presence of VAD. All patients had normal kidney function at the time of transplant

based on serum blood urea nitrogen and creatinine levels.

Median length of apixaban therapy prior to transplantation was 114.6 days (Table 2). Dosing ranged from 0.625mg twice daily to 7.5mg twice daily. In addition, the 3 patients on HM3 VAD and 1 patient with a bioprosthetic mitral valve received concomitant antiplatelet therapy with aspirin (ASA). There were no clinically relevant bleeding, including no major bleeding, or thrombotic events while awaiting transplant. The median time from last apixaban dose to arrival to the OR was 23.2 hours. The median apixaban level prior to OR arrival was 37ng/mL, obtained 6.2 hours prior to OR arrival. Apixaban level testing was not obtained immediately prior to transfer to the OR in 3 patients. The median chest tube output in the CICU post-operatively was 1.9mL/kg/hr and 1.8mL/kg/hr for the first 2 and 4 post-operative hours respectively.

In total, 6 patients met our definition for significant post-operative bleeding, including 1 patient for chest tube output$>$ 10mL/kg/hour for the first two hours, 4 patients for chest tube output $>$ 5mL/kg/hour over the first 4 hours, and 1 patient requiring re-intervention for hemodynamically significant bleeding. No patients developed tamponade. All 6 of these patients had palliated complex congenital heart disease (Table 3) with a median of 3.5 sternotomies per patient (3, 4.8) and median age of 6.1 years (3.6, 13.1). Additionally, 3 patients had anti-Xa levels post-operatively $<$0.2 units/ml, an average of 10 hours after arrival to the intensive care unit. This confirms no measurable residual effect of apixaban.

A number of adverse postoperative events deserve further description. As seen in Table 3, Patient 6 developed severe primary graft dysfunction requiring extracorporeal membrane oxygenation (ECMO) in the first 12 postoperative hours. This patient was the only to receive a reversal agent recombinant Factor Xa (andexanet alfa) in addition to protamine, despite no notable increase in operative bleeding or difficulties achieving hemostasis. Reason for administration of recombinant Factor Xa was that it was thought to help establish hemostasis in a patient with previous sternotomies and it was made readily available for administration. Notably, pre-operative apixaban level was low at 28.4ng/ml. While on ECMO, patient underwent cardiac catheterization demonstrating multiple diffuse pulmonary embolism. This patient developed gross hemolysis, with multi-organ failure and subsequent redirection of care and death on post-operative day 7. Patient 12 required re-exploration for bleeding after development of acute postoperative thrombosis in the reconstructed systemic venous system requiring trans-catheter stent placement near a fresh suture line. It was thought at the time the significant bleeding was mechanical in origin post-stent placement, not related to anticoagulation. Patient 14 was managed on HM3 ventricular assist device with apixaban and ASA prophylaxis pre-transplant without significant complications. Postoperatively, he was noted to have severe global neurologic injury unrelated to bleeding or thrombosis and not left to be attributable to apixaban, resulting in death.

Discussion

In this retrospective analysis, we demonstrate that the use of apixaban for prophylactic and therapeutic indications can be safe and effective in patients awaiting heart transplantation. We report no significant preoperative bleeding or thrombotic complications while receiving apixaban therapy. Postoperatively the rate of major bleeding was comparable to that previous reported, given patient complexity and likely unrelated to our anticoagulation strategy. The benefit of DOAC therapy includes reliability, predictability, ease of oral administration and the need for less frequent monitoring. In total, apixaban therapy accounted for 2 178 patient days in our patient population, all of whom would have otherwise received twice daily LMWH injections, or associated rigorous monitoring and dosing parameters of vitamin K antagonists.

Apixaban levels are not routinely recommended for monitoring therapy in adult patients. However, given the lack of apixaban data in pediatrics, and our use of apixaban in a high-risk population, intermittent monitoring may help guide management and reduce the risk of complications from bleeding or thrombosis while receiving apixaban. Most importantly, baseline peak and random apixaban levels allow for assessment of drug clearance prior to invasive procedures, such as heart transplantation. Drug monitoring is also beneficial for identifying causality in situations with significant post-operative bleeding. While our center can receive same day results for apixaban levels, we do realize that is not an option at all institutions. The described prophylactic and therapeutic apixaban levels have been demonstrated to have appropriate efficacy, safety, and low events rates

in an analysis 219 pediatric patients from our institution [16], along with a large meta-analysis in adults [17]. It has been demonstrated that chromogenic anti-factor Xa assay calibrated with heparin standards shows a correlation between apixaban levels and LMWH levels [18]. These previously described findings correlate with our experience as well, with goal LMWH of greater than 1.5units/mL suggesting appropriate apixaban anticoagulation.

We acknowledge the seemingly high percentage of significant post-operative bleeding. Unfortunately, there is no standard definition of what should be considered significant postoperative bleeding in patients requiring cardiopulmonary bypass. The limited pediatric literature available is applicable to infants under the age of 1 year, where the author also highlights the discrepancy in definitions used for other studies [19]. Looking at the rates of significant post-operative bleeding, our rate of 32% appears to correlate with what has been described from previously published studies in pediatric patients requiring cardiopulmonary bypass, with incidence ranging from 21.5% to 42% [20-24]. These studies all utilize different values based on chest tube output in the intensive care unit for their definition of significant bleeding. We utilized a more stringent definition of significant bleeding in our study. If we were to utilize the definitions described in the above studies, our rate of significant bleeding would range from 10.5% to 32%. Additionally, these patients have a high prevalence of previous sternotomies, presence of cyanosis, and hemodilution from cardiopulmonary bypass [25].

We do acknowledge that this lack of a formal definition is a limitation to our retrospective analysis given the subjectivity of formulating our own definition. This definition was determined in discussion with a multidisciplinary team including cardiac anesthesiologists, cardiac surgeons, transplant cardiologists and cardiac intensivists at our institution. Further analysis shows that in 3 of the 5 patients defined as having significant post-operative bleeding by chest tube output, anti-Xa heparin levels obtained within the first 18 hours post-operatively were under 0.2units/mL. This further supports the idea that, in those patients, there was little to no appreciable apixaban effect remaining post-operatively, based on available serum testing.

After extensive institutional review, we did not attribute any of the mortalities described to the use of apixaban pre-transplant. As described, one patient, later noted to have pulmonary emboli while on ECMO, received recombinant Factor Xa prophylactically early in our use of apixaban. Given this potential complication we advise against empiric use of recombinant Factor Xa in the absence of life threatening bleeding, as reversal can be a potential trigger of thrombosis. Data from a recent meta-analysis on reflex thrombosis secondary to reversal showed a rate of thromboembolism after utilization of andexanet alfa of 10.7% [26], making this a well-described and not insignificant complication. No other patients required recombinant Factor Xa.

We recognize there are several limitations to our study, including the previously mentioned lack of definition for post-operative bleeding, as well as potential inability to monitor apixaban levels promptly. Lastly, our single center cohort was small, retrospective and descriptive in nature. We hope that our experience can lead to randomized controlled studies comparing apixaban use to the more traditional anticoagulants.

Conflict of Interest: The authors have no disclosures to report.

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Tables

TABLE 1 Demographics.

Age at Transplant (years)	13.5 (6.1, 15.8)*
Sex (Male) (N%)	42%
Race (White, Black, Hispanic, Other, Declined) (N)	9/3/2/2/3
Weight (kg)	48.9 (15.4, 67.6)*
Body Mass Index (kg/m^2)	19 (15.5, 27.1)*
Congenital Heart Disease (N%)	68%
UNOS Listing (1A, 1B, 2)	16/2/1
Inotropic Support (Milrinone) (N%)	79%
Mechanical Circulatory Support (N%)	16%
Blood Urea Nitrogen At Transplant (mg/dL)	16 (12.5, 18)*
Serum Creatinine At Transplant (mg/dL)	0.6 (0.4, 0.7)*
United Network for Organ Sharing, UNOS. *Median values with 25th and 75th interquartile range.	United Network for Or

TABLE 2 Apixaban Dosing, Monitoring, and Peri-operative Management	TABLE 2 Apixaban Dosing, Monitoring, ar
Length of Apixaban Therapy Pre-Transplant (days)	Length of Apixaban Therapy Pre-Transplar
Prophylaxis Indication (N%)	Prophylaxis Indication (N%)
Concomitant Aspirin use (N%)	Concomitant Aspirin use (N%)
Time from Last Dose to OR Arrival (hours)	Time from Last Dose to OR Arrival (hours
Pre-OR Apixaban Level (ng/mL)	Pre-OR Apixaban Level (ng/mL)
Time from Last Level to OR Arrival (hours)	Time from Last Level to OR Arrival (hours
Chest Tube Out (mL/kg/hr)	Chest Tube Out (mL/kg/hr)
	First 2 Post-Operative Hours
	First 4 Post-Operative Hours
Patients Requiring Re-Operation for Bleeding (N%)	Patients Requiring Re-Operation for Bleedi
Significant Post-Operative Bleeding (N%)	Significant Post-Operative Bleeding (N%)
Operating Room, OR. *Median values with 25th and 75th interquartile range.	Operating Room, OR. *Median values with

TABLE 3 Key Demographic and Clinical Data for Patients Receiving Apixaban Prior to Undergoing Heart Transplantation.

Patient (years)