Antithrombotic regimens in patients awaiting heart transplant: a single-center experience

Tomasz Urbanowicz[1], Anna Olasińska-Wiśniewska[1], Veronica Cassadei[1], Ewa Straburzyńska-Migaj[2], Piotr Buczkowski[1], Marek Jemielity[1]

1 Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, Poznań, Poland
2 1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Introduction Patients with congestive heart failure are at high risk of death and 1.4% to 2.4% annual risk of stroke. The latter substantially increases with atrial fibrillation and other risk factors included in the CHA_2DS_2-VASc score.[1-3] Nowadays, non–vitamin K antagonist oral anticoagulants (NOACs) are the recommended drug class in this population.[4] Their major disadvantage is the immediate reversal of the antithrombotic effect in urgent surgery.

We present a single-center approach to antithrombotic and antiplatelet therapy in patients awaiting and undergoing heart transplant (HTx).

Methods Between the years 2017 and 2019, 84 patients were put on a waiting list for HTx in our Department of Cardiac Surgery and Transplantology. Twenty of them (17 men and 3 women; mean [SD] age, 44 [13] years) underwent HTx. They were referred for this procedure because of dilated (10 [50%]), ischemic (9 [45%]), and hypertrophic (1 [5%]) cardiomyopathy. Three patients (15%) were treated with dabigatran for chronic atrial fibrillation; the mean CHA_2DS_2-VASc score was 2.3, and the mean HAS-BLED score was 1.3. In the study group, there was no history of major bleeding, end-stage kidney disease (mean [SD] serum creatinine level, 156 [43] μmol/l), or liver dysfunction (mean [SD] aspartate aminotransferase level, 56 [13] IU/l).

Statistical analysis Data were entered and analysed using the Statview 5.0 software (SAS Institute, Inc., Cary, North Carolina, United States).

Ethics The study was approved by an ethics committee and all patients provided written informed consent.

Results and discussion All the study patients had HTx performed using the Lower–Shumway technique after a mean (SD) number of 256 (140) days of being put on the waiting list for transplant. The mean (SD) cold ischemia time was 218 (38) minutes, and the mean (SD) cross-clamping time was 181 (30) minutes. There was no perioperative death in the study group.

Non–vitamin K oral anticoagulants Two men with chronic atrial fibrillation, the first (36 years) diagnosed with ischemic cardiomyopathy and the second (48 years) with dilated cardiomyopathy, were transferred into the operation room 22 and 18 hours after receiving the last dose of dabigatran, respectively. Owing to a relatively short half-time of dabigatran elimination in the plasma (7 to 9 hours), we decided not to administer a reversal agent. A 43-year-old patient with dilated cardiomyopathy and atrial fibrillation received 5 g of idarucizumab (Praxbind, Boehringer Ingelheim Pharma, Ingelheim, Germany). The mean postoperative drainage volume in those men was 634 ml and 579 ml, respectively. Neither pericardial nor pleural fluids were detected during the postoperative hospital stay.

Oral anticoagulants (warfarin) There were 5 patients (25%) treated with warfarin: 3 (15%) with a mechanical valve prosthesis and 2 (10%) receiving mechanical paracorporeal circulatory support.

Correspondence to:
Tomasz Urbanowicz, MD, Department of Cardiac Surgery and Transplantology, Poznań University of Medical Sciences, ul. Długa 1/2, 61-848 Poznań, Poland, phone: +48 61 854 92 10, email: tk.urbanowicz@gmail.com
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TABLE 1 Postoperative characteristics of patients undergoing heart transplant by preoperative anticoagulation therapy received

Characteristic		Warfarin (n = 5)	NOAC (n = 3)	Antiplatelets (n = 5)	LMWH and bivalirudin (n = 7)
INR before HTx		2.8 (0.2)	1.1 (0.1)	1.1 (0.15)	1.1 (0.13)
Blood products required per patient, units	FFP	8 (2)	8 (2)	10 (2)	8 (3)
	Platelets	10	10	10	10
Postoperative drainage volume, ml		712 (53)	579; 634; 538[a]	690 (123)	710 (145)
PCC per patient, units		4 (2)	–	–	–
Patients receiving idarucizumab (2.5 g twice daily)		–	1	–	–
Patients not receiving idarucizumab		–	2	–	–

Data are presented as number or mean (SD).

a Drainage volumes of 3 study patients

Abbreviations: FFP, fresh frozen plasma; HTx, heart transplant; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulant; PCC, prothrombin complex concentrate

Patients with a mechanical valve prosthesis treated with warfarin within the therapeutic range of the international normalized ratio (INR) on admission were transferred into the operation room without INR correction. The mean (SD) cold ischemia time was 238 (14) minutes. After protamine administration, the standard protocol of fresh frozen plasma and platelet concentrate infusion was augmented by prothrombin complex concentrate administration if needed. The mean (SD) postoperative drainage volume in this patient subgroup was 712 (53) ml (TABLE 1).

One patient developed heparin-induced thrombocytopenia after 2 weeks of unfractionated heparin infusion during intra-aortic balloon pump treatment before HTx, which was diagnosed based on a platelet count decrease from 361 to $64 \times 10^3/mm^3$. The patient had no thrombotic complications and was subsequently treated with bivalirudin infusion before and during surgery. After 1 week, the patient's platelet count increased to $153 \times 10^3/mm^3$. The bivalirudin infusion was adjusted following the activated clotting time.

Low-molecular-weight heparin Seven patients were treated with low-molecular-weight heparin. The therapy was not withdrawn prior to surgery due to its urgency. The mean (SD) postoperative drainage volume was 710 (145) ml.

Aspirin Five patients were receiving acetylsalicylic acid before HTx, as they were diagnosed with ischemic heart disease. The mean (SD) postoperative drainage volume in these patients was 690 (123) ml.

All study patients were treated with low-molecular-weight heparin during hospitalization and acetylsalicylic acid at a dose of 75 mg daily, which was initiated within 5 days after surgery. None of the patients required anticoagulation therapy. No bleeding complications were observed. We did not observe any differences between patient groups in terms of procedural complications.

Within the first postoperative year, patients were treated with standard triple immunosuppressive therapy including an calcineurin inhibitor, mycophenolate mofetil, and oral steroids.

Our study was a single-center analysis of antithrombotic regimens used in patients awaiting HTx. Patients qualified for HTx most often require oral anticoagulation or antiplatelet treatment.[5] Generally, both kinds of therapy should be interrupted in a planned manner before most of surgical procedures. However, HTx is performed on an urgent basis. Therefore, an optimal strategy of anticoagulation reversal should be implemented in the operating center in advance. The interruption of pharmacotherapy may increase the risk of either bleeding or thromboembolic events. These complications may be, however, related not only to drugs but also to preoperative factors, including kidney function or the EuroSCORE.[6]

Similar to coronary artery bypass grafting,[7] there is no need for aspirin withdrawal before HTx.

Warfarin therapy is still the first-choice treatment in many patients, including those with left ventricular assist device.[8] A 4-factor prothrombin complex concentrate is a useful drug for warfarin reversal, which, compared with fresh frozen plasma, may prevent volume overload and is recommended in clinical practice.[9]

There is currently an increasing number of patients on long-term NOAC therapy.[10] Discontinuation of each drug relates to its half-life, patients' kidney function and age, and is relatively

safe for approximately 2 half-lives of the drug prior to a surgical intervention.[9] Postponing surgery seems to be reasonable in most cases, but it is impossible in solid organ transplant. Therefore, a reversal agent, currently available for dabigatran, enables prompt patient preparation before HTx.[11]

Considering the availability of idarucizumab, the recommendations in our institution were altered for patients awaiting HTx, indicating the need for dabigatran use.

There is still lack of clear guidelines in the field of the antithrombotic regimen before HTx. Therefore, we believe that they should be implemented to increase patient safety. We compared complication rates in our study subgroups and did not find any significant differences in the postoperative drainage volumes and bleeding events. However, our observations are limited by the small number of patients included in the study. Nevertheless, the availability of a reversal agent is crucial when performing urgent surgery including HTx and, therefore, we encourage the use of dabigatran in the pre-HTx period.

Conclusions The antithrombotic regimens are particularly problematic in urgent cardiac surgery. The reversibility of NOAC activity using its specific antidote should be considered a possible and safe option in HTx procedures.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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