



ORIGINAL CLINICAL SCIENCE

Amiodarone use in patients listed for heart transplant is associated with increased 1-year post-transplant mortality

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KEYWORDS:

heart transplant;
pre-transplant;
graft dysfunction;
antiarrhythmics;
outcomes

BACKGROUND: Pre-transplant amiodarone use has been postulated as a risk factor for morbidity and mortality after orthotopic heart transplantation (OHT). We assessed pre-OHT amiodarone use and tested the hypothesis that it is associated with impaired post-OHT outcomes.

METHODS: We performed a retrospective cohort analysis of adult OHT recipients from the registry of the International Society for Heart and Lung Transplantation (ISHLT). All patients had been transplanted between 2005 and 2013 and were stratified by pre-OHT amiodarone use. We derived propensity scores using logistic regression with amiodarone use as the dependent variable, and assessed the associations between amiodarone use and outcomes with Kaplan–Meier analysis after matching patients 1:1 based on propensity score, and with Cox regression with adjustment for propensity score.

RESULTS: Of the 14,944 OHT patients in the study cohort, 32% ($N = 4,752$) received pre-OHT amiodarone. Amiodarone use was higher in recent years (29% in 2005 to 2007, 32% in 2008 to 2010, 35% in 2011 to 2013). Amiodarone-treated patients were older and more frequently had a history of sudden cardiac death (27% vs 13%) and pre-OHT mechanical circulatory support. Key donor characteristics and allograft ischemia times were similar between groups. In propensity-matched analyses, amiodarone-treated patients had higher rates of cardiac reoperation (15% vs 13%) and permanent pacemaker (5% vs 3%) after OHT and before discharge. Amiodarone-treated patients also had higher 1-year mortality (hazard ratio 1.15, 95% confidence interval 1.02 to 1.30), but the risks of early graft failure, retransplantation and rehospitalization were similar between groups.

CONCLUSIONS: Amiodarone use before OHT was independently associated with increased 1-year mortality. The need for amiodarone therapy should be carefully and continuously assessed in patients awaiting OHT. J Heart Lung Transplant ■■■■:■:■■■–■■■

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Survival after heart transplantation in the current era is substantially better than survival in the early years of heart transplantation, and it continues to improve.^{1,2} This is

mostly due to improved survival in the first year after transplant; however, the risk of mortality remains highest early after transplant. Although early post-transplant mortality is affected by the transplant procedure and post-transplant care, it is increasingly recognized that donor and recipient characteristics and pre-transplant management also play an important role in in-hospital and post-discharge outcomes.

Some investigations have suggested that pre-transplant anti-arrhythmic therapy with amiodarone results in increased risk of primary graft dysfunction (PGD), early graft failure and increased mortality,^{3,4} whereas other studies showed no difference in peri-operative morbidity or mortality in those treated with amiodarone and those not receiving this therapy.^{5–7} However, these investigations included small numbers of patients, were mostly based on single-center experience, and reported on patients transplanted more than a decade ago. No large multicenter studies in the contemporary era have addressed this question.

We examined the data available in the scientific transplant registry of the International Society for Heart and Lung Transplantation (ISHLT) to assess the prevalence of amiodarone use before heart transplantation and clinical characteristics of patients treated with amiodarone. We then tested the hypothesis that pre-transplant amiodarone therapy is independently associated with increased post-transplant morbidity and mortality.

Methods

Data source

The ISHLT registry was the data source in this study. This database is populated by participating national and international organ transplant registries and collectives, and by individual transplant centers globally.⁸ History of taking amiodarone pre-transplant is reported (yes/no) in the registry.

Study population

The study population consisted of adult (age ≥ 18 years) recipients of orthotopic heart transplantation (OHT) included in the ISHLT registry with pre-transplant amiodarone use reported. Previous amiodarone use was defined as history of taking amiodarone before transplant. To study a contemporary cohort of transplant recipients in the current era of mechanical circulatory support and pre- and post-transplant management, we limited the study population to those who underwent transplantation from January 2005 to December 2013. We excluded patients with no information regarding pre-transplant amiodarone use, and patients with previous heart transplants, multi-organ transplants, heterotopic transplants or domino transplants. The institutional review board at Duke University granted an exemption from review for this study.

Outcomes

The primary outcome was time to all-cause death within 1-year after transplant. Secondary outcomes included early post-transplant outcomes, such as post-transplant time on inotropes, need for

reoperation, length of hospital stay, graft failure and pacemaker implant before hospital discharge. Post-transplant time on inotropes was defined as the number of days that inotropes were used after transplantation before discharge, and length of stay as number of days between transplant and hospital discharge among those who were discharged alive. Need for reoperation or permanent pacemaker between transplant and hospital discharge were categorized as yes, no or unknown. We examined both graft failure at hospital discharge and 30-day death or retransplant due to graft failure. Graft failure at hospital discharge was based on a report by treating centers. The outcome of 30-day death or retransplant due to graft failure was termed “early graft failure” in the ISHLT 32nd Adult Heart Transplant Report on early graft failure.¹ This definition is stricter than most definitions of PGD, which may include graft dysfunction after 30 days. We also examined 1-year rehospitalization, retransplant or need for permanent pacemaker.

Statistical analyses

Groups were stratified by previous amiodarone use. We described baseline characteristics of heart transplant recipients and organ donors using frequency and percent for categorical variables and median and 25th and 75th percentiles (interquartile range) for continuous variables. Categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test, and continuous variables were compared using Wilcoxon’s rank-sum test. We calculated the prevalence of pre-transplant amiodarone use by year of transplant, and assessed for trend using the Cochran–Armitage test.

Given the non-randomized use of amiodarone, propensity score methodology was used to assess the association between amiodarone use and post-transplant clinical outcomes. The propensity score is the propensity from 0 to 1 of receiving a treatment (in this case amiodarone) given a set of known variables (in this case other baseline characteristics included in the ISHLT registry database), and is used to adjust for potential selection bias, confounding and differences between treatment groups in observational studies.⁹ A propensity analysis was performed using a logistic regression model, with amiodarone use as the outcome of interest. Candidate variables used to construct the logistic model included are indicated in Table 1. Using a backwards selection cut-off alpha level of 0.20, previous malignancy, drug-treated hypertension and angina were removed from the model. Based on this final model, a propensity score was computed for each transplant recipient. For each transplant recipient with amiodarone use, a transplant recipient with no amiodarone use was selected, using a greedy 5 \rightarrow 1-digit matching algorithm. This algorithm matches recipients from the 2 amiodarone groups who have similar propensity scores, first matching on 5 digits of the propensity score, then 4 digits for cases that did not match, and so on to 1-digit matching. Of the 4,752 amiodarone transplant recipients, 4,633 were propensity-matched to non-amiodarone transplant recipients. This resulted in a total propensity-matched cohort of 9,266 transplants. Covariates used in the calculation of the propensity scores after matching were assessed for balance between amiodarone groups.

The Kaplan–Meier method was used to produce estimates of patient survival stratified by amiodarone use for the entire cohort (unadjusted), and also for the propensity-matched cohort. In addition, Cox proportional hazards regression was used to assess the relationship between amiodarone use and mortality and morbidity outcomes, adjusting for recipient, donor and transplant

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