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Maintenance steroid use at 30 days post-transplant and outcomes of pediatric heart transplantation: A propensity matched analysis of the Pediatric Heart Transplant Study database

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BACKGROUND: Maintenance steroid (MS) use in pediatric heart transplantation is variable. The purpose of this study was to evaluate the impact of MS use on graft outcomes.

METHODS: All patients <18 years old in the Pediatric Heart Transplant Study database at the time of first heart transplant between 1993 and 2011 who survived ≥30 days post-transplant and were from centers with a protocolized approach to MS use were included ($N = 2{,}178$). Patients were grouped by MS use at 30 days post-transplant as MS+ or MS− (no MS use). Propensity score analysis was used to generate matched groups of MS+ and MS− patients based on pre-transplant and peri-transplant factors. Kaplan-Meier survival analysis was used to compare freedom from graft loss, graft loss secondary to rejection, rejection, rejection with severe hemodynamic compromise (RSHC), malignancy, and infection between groups.

RESULTS: Of patients, 1,393 (64%) were MS+ and 785 (36%) were MS−. There were 315 MS− patients who had propensity matched MS+ controls. Kaplan-Meier estimates showed no difference in graft loss ($p = 0.9$) or graft loss secondary to rejection ($p = 0.09$). At 1 year post-transplant, there was no difference in freedom from rejection ($p = 0.15$) or malignancy ($p = 0.07$), but there was lower freedom from RSHC and infection in the MS− group ($p = 0.05$ and $p = 0.02$, respectively).

CONCLUSIONS: MS use at 30 days post-transplant was not associated with enhanced graft survival after pediatric heart transplant. MS− patients had a higher incidence of RSHC and infection. These risks should be taken into consideration when determining MS use for pediatric recipients of heart transplants.
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The use of steroids as part of a maintenance immunosuppression regimen is common in most pediatric heart transplant centers. Efforts are usually made to try to wean off maintenance steroids (MS) by the end of the first

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post-transplant year; however, the International Society for Heart and Lung Transplantation (ISHLT) registry reported that 63% of pediatric recipients of heart transplants received MS at 1 year after transplantation.[1] Although there are concerns about rejection after withdrawal of MS in patients on triple-drug immunosuppression, multiple single-center reports of experience with steroid avoidance protocols are available, with some studies reporting long-term follow-up with survival equivalent to what has been reported in national registries.[2–8] Most of these single-center reports used induction therapy with high-dose steroids and anti-thymocyte globulin, with variable timing and dosing of each medication, and maintenance immunosuppression typically involved cyclosporine alone or in combination with azathioprine.[4–7] Singh et al[9] reported a short-term study showing an acceptable incidence of acute rejection and excellent survival in a dual-center steroid avoidance protocol that included only non-sensitized, low-risk patients. Univariate analysis of the ISHLT registry showed that patients taking MS at 1 year had worse conditional 1-year survival.[1] Our initial analysis of graft survival based on the use of MS in the United Network for Organ Sharing database showed no difference in graft survival after controlling for pre-transplant risk factors.[10] However, this analysis was limited by inadequate data on rejection and comorbidities. The purpose of this study was to determine if MS use in pediatric recipients of heart transplants resulted in a difference in graft and patient outcomes. Our hypothesis was that there would be no difference in graft survival or in the incidence of rejection between patients who received MS and patients who did not receive MS at 30 days post-transplant as part of their maintenance immunosuppression regimen, whereas the incidence of post-transplant comorbidities would be higher in patients receiving MS.

Methods

Patient Data and Study Population

The Pediatric Heart Transplant Study (PHTS) is an organization of 42 centers in the United States, Canada, and the United Kingdom with a centralized, prospective, multicenter, event-driven database. The database contains information about each patient from the time of listing and throughout the post-transplant period. The study centers require institutional review board approval to participate in the PHTS. Confirmation of institutional review board approval for each institution is kept on file at the PHTS data collection center.

All children <18 years old who underwent a first heart transplant between 1993 and 2011 were retrospectively identified from the PHTS database. Patients surviving until 30 days post-transplantation were included; multiorgan transplants were excluded from the analysis. Patients were divided into 2 groups based on MS use. Patients taking MS at 30 days post-transplant were defined as MS+, and patients not taking MS at 30 days post-transplant were defined as MS−.

Because of concern that some recipients perceived to be at higher risk of poor outcomes may be preferentially treated with a MS+ regimen and that patients perceived to be at lower risk may be treated with a MS− regimen, we determined which centers had a protocolized approach to MS use. We carefully investigated the use of MS at each institution using cumulative distribution function curve analysis. We were able to categorize hospitals into 1 of 4 groups: (1) all patients received steroids at 30 days across the time period of the study, (2) all patients did not receive steroids at 30 days across the time period of the study, (3) the use of steroids was changed (the hospital switched from steroids to not steroids or vice versa) at a specific calendar date, or (4) the use of steroids at 30 days had no clear pattern. The study was restricted to the first 3 groups.

Because of significant differences in baseline characteristics between the MS+ and MS− groups and to avoid potential selection bias, a propensity score matched pair analysis was performed with the maximum allowable difference in propensity score for matching being ≤ 0.05. All patients from MS+ institutions, MS− institutions, and "change in protocol institutions" were included in propensity matching; patients from "variable protocol institutions" were excluded. Multivariate logistic regression was used to identify the significant covariates to enter the model. Based on results of logistic regression, the following risk factors appeared to be significant ($p \leq 0.05$) and considered for propensity match analysis: age, ischemic time, era of transplant (1993–2000 vs 2001–2011), race, history of previous cardiac surgery, diagnosis of congenital heart disease, weight of donor, history of shock, donor age, abnormal donor echocardiography, infection within 30 days, rejection and infection within 30 days, positive crossmatch, panel reactive antibodies, use and type of induction therapy, and use and type of calcineurin inhibitor. Specifically, each patient who received MS at 30 days post -transplant was randomly matched to 1 patient who did not receive MS with the closest propensity score. This 1:1 matching resulted in 315 MS+ patients and 315 MS− patients.

Data Analysis

The primary outcome was graft survival conditional on patients being alive 30 days post-transplant. Secondary outcomes included time to graft loss secondary to rejection, time to first rejection episode, time to rejection with severe hemodynamic compromise (RSHC), time to a diagnosis of malignancy, and time to first treated infection. Graft loss was defined as retransplantation or death. As in previous PHTS publications, the standard PHTS definition of rejection as "an event leading to augmentation of immunotherapy" was used for this study.[11–15] RSHC was defined as an episode of rejection requiring inotropic support, as in previous PHTS reports.[14,16] Infection was defined as an infectious process requiring intravenous therapy or potentially life-threatening infections requiring oral therapy.[17]

Non-parametric estimates of freedom from event and survival were obtained using Kaplan-Meier methods and the log-rank test to compare the propensity matched MS+ and MS− groups for differences in the incidence of graft loss, graft loss secondary to rejection, rejection, RSHC, malignancy, and infection. Data were insufficient to analyze the effect of MS use on hypertension and diabetes. Because MS use is most common in the first post-transplant year, outcome variables not directly evaluating graft survival were analyzed at 1 year post-transplant.

Continuous variables are reported as median (range) and were compared using the Kruskal-Wallis test. Dichotomous and ordinal variables were compared by the chi-square test. All p-values are 2-sided. All statistics were performed using SAS software version 9.3 (SAS Institute, Inc, Cary, NC).

Results

There were 3,495 patients alive 30 days post-transplant during the study period, with 2,349 (67%) MS+ and