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Effect of Induction Therapy on Graft Survival in Primary Pediatric Heart Transplantation: A propensity score analysis of the UNOS database

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Abstract

Background—The use of induction therapy in pediatric heart transplantation has increased. The aim of this study was to investigate the effects of induction therapy on graft survival.

Methods—The United Network for Organ Sharing database was queried for isolated pediatric heart transplants from January 1, 1994 to December 31, 2013. Propensity scores for induction treatment were calculated by estimating probability of induction using a logistic regression model. Transplants were then matched between induction treatment groups based upon the propensity score, reducing potential biases. Using only propensity score matched transplants, the effect of induction therapy on graft survival was investigated using Cox-proportional hazards. Sub-group analyses were performed based upon age, race, recipient cardiac diagnosis, HLA and recipient panel-reactive antibody.

Results—Of 4565 pediatric primary heart transplants from 1994 to 2013, 3741 had complete data for the propensity score calculation. There were 2792 transplants successfully matched

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(induction n=1396, no induction n=1396). There were no significant differences in transplant and pretransplant covariates between induction and no induction groups. In the Cox-proportional hazards model, the use of induction of was not associated with graft loss (HR = 0.88; 95% CI: 0.75-1.01; p=0.07). In sub-group analyses, induction therapy may be associated with improved survival in patients with PRA >50% (HR=0.57; 95% CI: 0.34 – 0.97) and congenital heart disease (HR=0.78; 95% CI: 0.64-0.96).

Conclusion—Induction therapy is not associated with improved graft survival in primary pediatric heart transplantation. However, in pediatric heart transplant recipients with PRA>50% or congenital heart disease, induction therapy is associated with improved survival.

Introduction

The use of induction therapy has increased in pediatric heart transplant recipients. While, there are a multitude of induction agents, the most common induction agents are anti-thymocyte antibodies or IL-2 receptor antibodies. Induction therapy has been associated with decreased rejection in the first posttransplant year and death due to rejection.¹⁻⁴ Also, the use of induction therapy has been described as a successful method to lead to avoidance of steroids.⁵ An association between induction therapy and infection or posttransplant lymphoproliferative disorder has not been established in pediatric heart transplantation.⁶ The decrease in rejection and lack of association with possible complications has led to increasing use of induction therapy. Little is known, however, of the effect of induction therapy on overall graft survival in pediatric heart transplant recipients. This study aimed to investigate the association between induction therapy and graft survival in pediatric heart transplantation.

Materials and Methods

A retrospective analysis was performed using data obtained from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) files. Heart transplants performed in the United States from January 1, 1994 to December 31, 2013 were included in the analysis. The database was queried for pediatric heart transplants (age <18 years). Transplants were included if they had valid reporting of the use of induction therapy. Transplants were excluded if they were age 18 or older, were not isolated heart transplantation, or were retransplantations. The primary endpoint was graft survival, with graft loss being defined as patient death or retransplantation. The Medical University of South Carolina Institutional Review Board approved the study. For the purposes of the study, induction therapy was defined as immunosuppressant medications given during the immediate posttransplant time period (started <1 week posttransplant) that would not be part of maintenance therapy. For the purposes of this study, steroids were not considered induction therapy.

Statistical Analysis

In order to reduce bias from the observational study design, propensity scores were employed. Using multiple pretransplant variables, logistic regression models were used to assign the probability of receiving induction therapy (Table 1). Due to the increase in use of

induction in more recent years, year of transplant was used in the propensity score. Transplants were then 1:1 matched between each treatment group (induction vs. no induction), using a “greedy” propensity score algorithm.⁷ Acceptable matches were defined as transplants that had a difference between propensity scores of less than 0.2 times the standard deviation of propensity scores for the entire cohort. Only transplants that were successfully matched were used in the assessment of induction on graft survival.

To assess associations between graft survival and induction therapy, a Cox proportional hazard model was constructed. To account for matched pairs, robust standard errors were employed.⁸ Covariates in the model included: transplant year, recipient on extra-corporeal membrane oxygenation (ECMO), recipient on ventricular assist device, underlying cardiac diagnosis, recipients most recent PRA, recipient age, recipient gender, recipient race, recipient on inotropes, recipient on mechanical ventilation, degree of donor: recipient HLA matching, crossmatch results and recipient renal function. P-values less than 0.05 were considered statistically significant. Secondary endpoint was 1-year survival, assessed by logistic regression analysis with the same covariates employed in the Cox regression analysis.

When comparing transplant demographic and other descriptive data between induction and no induction groups, standardized differences were employed. The standardized difference is the difference in the sample means divided by the pooled standard deviation. It is impervious to sample size and is not the product of significance testing based on hypotheses about populations; since the goal is to examine differences between samples (not populations), p-values comparing pre- and post-match balance are intentionally not reported. As such, small standardized differences indicate that there are little differences between populations.

Subgroup Analyses

Subgroup analyses were performed based upon recipient age, recipient race, degree of HLA matching, recipient cardiac diagnosis and recipient PRA at time of transplant. For age, transplants were divided into the following categories: <1 year, 1-10, 11-17. For race, recipients were divided into Caucasian versus non-Caucasian. Cardiac diagnosis was divided into the categories: cardiomyopathy, congenital heart disease or other. Degree of donor:recipient HLA matching was divided into the following 3 groups: no match, low match (1-2 out of 6 possible matches), high match (3-6 matches).⁹ Recipient PRA was divided into the following 3 groups: <10%, 10-50%, and >50%. In each subgroup (ie transplant with PRA >50%), propensity matching was performed as previously described, as was the association between induction therapy and graft survival with Cox proportional hazard models. A hazard ratio was considered statistically significant if the 95% confidence interval did not include 1.0.

Treatment Analysis

Given the large time period in which the study encompasses, 2 subsequent analysis of treatment were undertaken. In the first analysis, only induction agents that are used frequently in the current era were considered induction agents (IL-2 receptor antibodies, anti-thymocyte antibodies) and everyone else was considered to have not been induced. The

second analysis compared survival between patients who received IL-2 receptor antibodies versus anti-thymocyte antibodies. In each treatment analysis, propensity score matching and cox regression analysis was performed as previously outlined.

Results

There were 4565 pediatric primary heart transplants from 1994 to 2013 in the UNOS database. Mean age for all primary heart transplants was 6.43 years $\pm$ 6.23, 2015 (43.9%) were female, 2387 (52.0%) had cardiomyopathy, 2032 (44.3%) had a congenital heart defect. Of the 4565 transplants, 1813 (39.7%) received induction therapy. Induction therapy continued to increase in use with each subsequent year, with approximately 5% of transplants receiving induction in 1994 and 50% of transplants being induced in 2013. The most common induction agents were: anti-thymocyte antibodies (rabbit or equine) (942), Basiliximab (505), Daclizumab (245), and OKT3 (137).

Of the 4565 primary transplants, 3741 (81.9%) had sufficient data to calculate a propensity score. The variables used in the propensity model are summarized in table 1, the logistic regression model was significant compared to intercept-only model ($p < 0.01$). In using the matching algorithm, 2792 (61.2%) were successfully matched. (table 2) The transplants which were not matched ($n=949$) were not matched, as these transplants were ones in which the patients' propensity score indicated that they were either extremely likely to receive induction therapy, or extremely unlikely to receive induction therapy. For the 3741 transplants with sufficient data for propensity score calculation, mean age was 6.61 years $\pm$ 6.25, 43.6% were female, 52.3% had cardiomyopathy and 39.2% received induction therapy. As matching occurred in a 1:1 fashion between treatment groups, both induction and no-induction groups had 1396 transplants after propensity score matching. Table 3 compares the patient characteristics between induction and no induction in all 4565 transplants, as well as those that were successfully matched. In the postmatched cohort, patient characteristics are not clinically different between groups, indicated by the low standardized differences.

For the entire cohort ($n=4565$), median graft survival was 13.1 years (95% CI: 12.1-13.7 years). In the individual propensity score matched groups, median survival was not estimable due to high levels of censoring; therefore, 1, 5 and 10 year survival are reported (figure 1). In the induction cohort ($n=1396$), 1 year survival was 91%, 5 year was 76% and 10 years was 61%. In the induction cohort there were 361 graft losses, with 187 (52%) having a reported cause; 38 from primary graft failure, 53 acute rejection, 56 chronic rejection/coronary artery disease, and 40 other. In the no induction cohort, 1 year survival was 88%, 5 years was 72% and 10 years was 56%. In the no induction cohort there were 507 graft losses, with only 204 (40%) having a reported cause; 41 primary graft failure, 46 acute rejection, 82 chronic rejection/coronary artery disease, and 35 other. The unadjusted difference in survival was statistically significant in univariate log-rank testing ($p=0.01$). However, in the Cox proportional hazards model the use of induction was not statistically associated with graft loss (HR = 0.88; 95% CI: 0.75-1.01; $p=0.07$). In logistic regression analysis, 1-year survival was not associated with induction (OR 1.18, 95% CI 0.96-1.5, $p=0.11$).

When performing sub-group analyses, 1462 of the 2387 (61%) transplants with recipient underlying diagnosis of cardiomyopathy were able to be matched. After controlling for previously mentioned covariates in the Cox-proportional hazards model, induction therapy was not associated with graft loss within this group (HR=0.88 95% CI 0.7-1.1) (table 4). Table 4 summarizes the results of the sub-group analyses for congenital heart disease, degree of HLA matching, race, and PRA. Of note, the only 2 groups that had hazard ratios with 95% confidence intervals that did not include 1.0 were recipients with congenital heart disease and recipients with a PRA >50%. In the congenital heart disease cohort, the hazard ratio for graft loss in those who received induction was 0.78 (95% CI 0.64-0.96), indicating that induction therapy was associated with decreased graft loss (figure 2). In the PRA > 50% cohort, the hazard ratio for those who received induction was 0.57 (95% CI 0.34-0.97), also indicating that induction therapy was associated with decreased graft loss (figure 3). However, in the PRA <10% and PRA 10-50% subgroups, there was no survival benefit associated with induction. The congenital heart disease cohort were more likely to have a PRA >50% compared to cardiomyopathy (odds ratio 8.8, 95% CI 7.1-10.4, p<0.01) and other diagnosis (OR 6.1, 95% CI 1.64-10.55, p<0.01). Approximately 5% of the congenital heart disease patients had PRA >50%.

Treatment Analysis

In the analysis of comparing patients who received contemporary induction agents (IL-2 receptor antibodies and/or anti-thymocyte antibodies) versus other induction agents or no induction (no induction), there were 2588 successfully matched transplants. In univariate analysis, there was improved survival with modern induction compared to no induction. (figure 4). However, in Cox hazard regression analysis, there was no association between contemporary induction and graft loss (HR=0.94, 95% CI 0.8-1.1, p=0.49).

When comparing patients who received anti-thymocyte antibodies versus those who received IL-2 receptor antibodies, 1070 transplants were able to be propensity score matched (535 per treatment arm). The median survival for the T-cell cohort was 14.8 years versus 10.5 years for the IL-2 receptor blockers (p=0.09). (figure 5) In Cox hazards model, the IL-2 receptor blocker antibodies were more likely to suffer from graft loss compared to the anti-thymocyte antibody cohort (HR=1.34, 95% CI 1.02-1.76, p=0.03).

Discussion

Induction therapy has gained popularity, being used in 50% or more of pediatric primary transplants since 2010 up from 3% in 1994. This may be in part by a rising population of transplants in highly HLA sensitized patients.¹⁰ Despite the rising popularity of induction therapy, there have been very few studies investigating the effects of induction on overall graft survival in pediatric heart transplant. To the authors' knowledge, this study represents the first study to employ propensity scores, therefore reducing potential biases, to assess the association of induction with graft survival in pediatric heart transplantation. Our findings indicate that induction therapy does not significantly improve overall graft survival in primary pediatric heart transplant recipients. However, recipients that had congenital heart disease or PRA > 50% may have improved survival with induction therapy.

While association between induction therapy and PTLT, rejection and infection have been well studied, induction and overall graft survival has been less studied. Boucek et al studied 461 pediatric transplant recipients in the Pediatric Heart Transplant Study database, 206 of whom had received induction therapy.² They concluded that induction therapy was associated with reduction in overall mortality and death due to rejection. Also, the authors stated anti-thymocyte antibodies had improved graft survival compared to OKT3. Our study suggests that when induction therapies are grouped together, induction therapy does not improve survival. Also, when we analyzed for contemporary induction agents (IL-2 receptor antibodies and anti-thymocyte antibodies) compared to less common induction agents or no induction, there was no survival benefit noted. We did find a survival benefit in anti-thymocyte antibodies compared to IL-2 receptor antibodies. The finding of improved survival in the anti-thymocyte cohort should be interpreted with caution. Similar to the Boucek et al, this comparison is based upon a small number of transplant (535 in each treatment arm). Therefore, this should be the focus of future studies, in possibly larger datasets such as the ISHLT registry.

Our study indicates that 2 subpopulations have improved graft survival when receiving induction therapy, recipients with PRA > 50% and patients with congenital heart disease. Both of these populations are at risk for early rejection.¹¹ Elevated PRA and congenital heart disease have also been associated with worse posttransplant survival.^{12,13} Early rejection has been associated with worse long-term graft survival.^{2,14-16} Induction therapy has been shown to decrease the risk of early rejection in pediatric heart transplantation.¹⁷ The survival curves in both populations show that the majority of survival benefit is in the first posttransplant year. Performing such an analysis was significantly limited in the current database by the large amount of missing reports of early rejection (30-35%). Therefore, further analysis of associations between induction and early rejection should be performed using databases with more robust reporting of early rejection, such as the PHTS database.

Limitations

In order to appropriately perform propensity score matching, all induction agents were grouped together. It is a possibility that certain induction agents are more efficacious and may provide a graft survival benefit. Also, while propensity scores assist in reducing potential biases associated with observational study designs, many transplants in the UNOS database had missing data that was required for the propensity score calculation and therefore had to be excluded from our analyses; future work might attempt to determine whether such cases could be included in these types of studies using strategies such as multiple imputation. The exclusion of multiple transplants through propensity score matching does lead to possible exclusion of data points that could alter the results. Therefore indicating that future trials investigating the effect of induction on transplant survival should be done through a randomized clinical trial. Future studies of observational datasets should concentrate on contemporary induction agents (Thymoglobulin) only. However, given the large amount of excluded transplants for propensity matching all induction agents were investigated together. The CHD and PRA>50% are colinear, (ie the PRA>50% is more likely to have CHD). Therefore, benefits in CHD group could be from the CHD subgroup with PRA>50%. In order to reduce this bias, PRA group was controlled for in all Cox

proportional hazard models. Propensity scores help reduce biases from known and measured variables; however, unmeasured variables that could affect outcomes are not able to be adjusted for and may introduce unintended biases. Future work might also examine whether induction may be beneficial for patients receiving multiple transplants.

Conclusions

In the general population of pediatric heart transplant recipients, induction therapy is not associated with significantly improved graft survival. However, in recipients with PRA > 50% and congenital heart disease, induction therapy may be associated with graft survival. Therefore, indicating that induction therapy may be best employed in subgroup of patients. There is a possible survival benefit of anti-thymocyte antibodies compared to IL-2 receptor antibodies. This information may help guide individual institutions on when to use induction therapy. These findings should be investigated further through clinical trials.

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Abbreviations

ECMO	extracorporeal membrane oxygenation
PRA	panel reactive antibody
HLA	human leukocyte antigen
HR	hazard ratio
PTLD	post-transplant lymphoproliferative disorder
PHTS	Pediatric Heart Transplant Study

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Figure 1.

Kaplan-Meier curve of graft survival comparing patients who received induction (solid line) versus those who did not receive induction (dashed line). Overall there was no difference in graft survival between groups ($p=0.09$)

Figure 2.

Kaplan-Meier curve of graft survival comparing congenital heart disease patients who received induction (solid line) versus those who did not receive induction (dashed line). Induction was association with reduced risk of graft loss, HR=0.78 (95% CI 0.64-0.96).

Figure 3.

Kaplan-Meier curve of graft survival comparing transplant recipients with a PRA>50% who received induction (solid) versus those who did not receive induction (dashed line). Induction was association with reduced risk of graft loss, HR=0.57 (95% CI 0.34-0.97).

Figure 4.

Kaplan-Meier curve of graft survival comparing transplant recipients who received contemporary induction agents (anti-thymocyte antibodies/IL-2 receptor antibodies versus other induction agents or no induction). Contemporary agents are demonstrated by the solid line, all or agents or no agents are represented by the dashed line. There was no association between contemporary induction and graft loss (HR=0.94, 95% CI 0.8-1.1, p=0.49)

Figure 5.

Kaplan-Meier curve of graft survival comparing transplant recipients who received IL-2 receptor antibodies (dashed line) versus anti-thymocyte antibodies (solid line). IL-2 receptor antibodies cohort was more likely to suffer from graft loss compared to the anti-thymocyte antibody cohort (HR=1.34, 95%CI 1.02-1.76, $p=0.03$).

Table 1

Variables Used in Propensity Score Model

<i>Recipient Variables</i>
Blood Type
Clinical Infection
Cardiac Diagnosis
Ethnicity
Gender
Prior Cardiac Surgeries
Mechanical Ventilation at Time of Transplant
Age
Inotropes at time of transplant
Ischemic Time
PRA (most recent to transplant)
ECMO at time of transplant
VAD at time of transplant
Creatinine Clearance
<i>Donor Variables</i>
Blood Type
Clinical Infection
Cause of Death
Ethnicity
Gender
Age
Creatinine Clearance
<i>Transplant Variables</i>
Year
HLA Match
Donor:Recipient Weight Ratio

Table 2

Comparison of Patient Excluded from Propensity Score Model, Matched Transplants and Nonmatched transplants

Variable	Excluded from Propensity Score Model due to missingness (n=824)	Included in Propensity Score Model		
		Total (n=3741)	Matched (n=2792)	Not matched (n=949)
Female	45.27%	43.57%	44.23%	41.62%
Caucasian	84.47%	83.43%	81.70%	88.51%
Congenital Heart Disease	44.96%	44.16%	44.09%	44.36%
Negative Crossmatch	88.35%	85.70%	84.78%	88.41%
HLA Matches (3 or more)	12.86%	14.19%	14.43%	13.49%
Recipient off vent	82.16%	83.16%	15.94%	19.49%
Not on ECMO	94.30%	94.84%	95.70%	92.31%
Not receiving inotropes	51.82%	50.41%	49.75%	52.37%
Age (mean, years)	5.72	6.61	6.63	6.54
Donor Weight Ratio (mean)	1.43	1.38	1.39	1.31
Donor Creatinine Clearance (mean)	121.94	128.29	127.94	129.32
Ischemic Time (mean, hours)	3.73	3.62	3.66	3.50
PRA (mean, percent)	9.02%	9.32%	9.93%	7.52%

Table 3

Comparison of Induction vs. No Induction, pre and postpropensity matching

	PreMatching (n=4565)			PostMatching (n=2792)		
<i>Categorical Variable</i>	<i>No Induction (%)</i>	<i>Induction (%)</i>	<i>Difference (%)</i>	<i>No Induction (%)</i>	<i>Induction (%)</i>	<i>Difference (%)</i>
Female	42.77	45.77	3	43.55	44.91	1.36
Caucasian	85.4	80.58	4.82	81.81	81.59	0.22
Congenital Heart Disease	44.3	44.31	0.01	44.41	43.77	0.64
Negative Crossmatch	87.17	84.49	2.68	84.89	84.67	0.22
HLA Matches (3 or more)	14.12	13.68	0.44	14.54	14.33	0.21
Recipient off vent	82.37	84.01	1.64	83.95	84.17	0.22
Not on ECMO	94.26	95.56	1.3	95.92	95.49	0.43
Not receiving inotropes	51.11	49.91	1.2	49.64	49.86	0.22
<i>Continuous Variable</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Standardized Difference</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Standardized Difference</i>
Age	6.43 (6.23)	6.47 (6.19)	0.005	6.63 (6.28)	6.62 (6.25)	0.001
Donor Weight Ratio	1.36 (0.49)	1.40 (0.48)	0.074	1.39 (0.49)	1.38 (0.46)	0.008
Donor Creatinine Clearance	127.14 (76.64)	127.55 (72.35)	0.005	126.62 (72.01)	129.26 (73.41)	0.036
Recipient Creatinine Clearance	116.57 (57.50)	125.33 (69.07)	0.138	123.11 (58.97)	123.45 (58.52)	0.006
Ischemic Time	3.60 (1.28)	3.70 (1.25)	0.081	3.66 (1.29)	3.67 (1.23)	0.009
PRA	8.57 (21.50)	10.52 (24.12)	0.085	9.83 (23.37)	10.03 (23.38)	0.008

HLA=Human Leukocyte Antigen, PRA=panel-reactive antibody

of note, standardized difference (3rd and 6th column) is not the same as a p-value, low standardized difference indicates the populations were similar

Table 4Subgroup Analysis^{*} : Multivariable Cox Regression Analysis

Subgroup Description		Number of Pairs	Hazard Ratio for Induction Therapy	95% Confidence Interval
	Entire Cohort	1396	0.88	0.75-1.01
Cardiac Diagnosis	Cardiomyopathy	731	0.88	(0.70, 1.11)
	Congenital Heart Disease	605	0.78	(0.64, 0.96)
HLA Match	0	306	0.79	(0.57, 1.09)
	1-2	889	0.83	(0.68, 1.01)
	3	180	0.99	(0.61, 1.60)
PRA	<10%	1120	0.91	(0.76, 1.08)
	10-50%	147	0.86	(0.51, 1.45)
	>50%	102	0.57	(0.34, 0.97)
Race	White	1145	0.88	(0.75, 1.04)
	Nonwhite	216	0.83	(0.53, 1.32)
Age	<1 year	380	0.83	(0.62, 1.11)
	1-10 years	524	0.98	(0.76, 1.28)
	>10 years	482	0.94	(0.73, 1.23)

PRA=panel-reactive antibody, HLA=human leukocyte antibody, Bolded numbers represent hazard ratios that 95% CI did not include 1

^{*} Table 3 depicts results when subgroup analysis was performed. ie 1432 patients with cardiomyopathy were propensity score matched, ½ receiving induction (n=731); then induction therapy was inserted into the multivariable Cox regression with covariates previously mentioned. The hazard ratio reported is the hazard ratio for induction in that particular subgroup. ie in Cardiomyopathy the hazard ratio for graft loss with induction was 0.88 (95%CI 0.7-1.1), but in patients with congenital heart disease it was 0.78 (95%CI 0.64-0.96).