Using hepatitis C and B virus–infected donor organs for pediatric heart transplantation

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ABSTRACT

Objective: High-risk donors for patients with end-stage cardiac or pulmonary disease awaiting transplantation represent an opportunity for access to more organs and therefore can significantly decrease the waiting list mortality. The objective of this study is to investigate the use of hepatitis B virus core antibody positive or hepatitis C virus seropositive donors for pediatric heart transplantation.

Methods: Data were reviewed from the United Network of Organ Sharing database (June 2008 to June 2015). A total of 3 hepatitis C seropositive and 9 hepatitis B core antibody positive donor hearts were identified for transplantation. Factors of age, underlying diagnosis, transplant year, extracorporeal membrane oxygenation, inotrope support, hepatitis C virus serostatus, and hepatitis B virus surface antigen status were used for 2 separate propensity score models. Standardized difference was evaluated for these variables before and after match. Survival was compared between the matched cohorts.

Results: Post-transplant graft survivals for recipients of hepatitis C virus positive donors and hepatitis B virus core antibody positive donors were similar to matched recipients of hepatitis C virus negative and hepatitis B virus core antibody negative donors, respectively.

Conclusions: The study has a small cohort to derive any significant conclusions, but the results are encouraging and consistent with the current trends among adult thoracic and pediatric kidney transplantation and demonstrates that hepatitis C virus positive and hepatitis B virus core antibody positive donors are not often used for pediatric heart transplantation. (*J Thorac Cardiovasc Surg* 2019;158:548-53)

Survival curves for patients who received an HBV- or HBV+ heart.

Central Message

HBV- and HCV-infected donors are infrequently used for pediatric cardiac transplantation, and this should be evaluated in further studies given the recent advances in treatments of HBV and HCV.

Perspective

The statistical power of this study was limited by the small study cohort; however, the data from this study suggest that more research on post-transplant outcomes of cardiac transplant patients with HBV- and HCV-infected donors is warranted to investigate a new method of expanding the current cardiac donor pool, considering the improved treatment options for HBV and HCV.

See Commentary on page 554.

The current shortage of thoracic donors results in a significant increase in waitlist mortality each year.^{1,2} However, the use of hepatitis C virus seropositive (HCV+) and hepatitis B virus surface antigen positive (HBV+) donors

has been a recently demonstrated strategy to expand the current adult thoracic donor pool because of the improvements in treatment options for hepatitis B virus (HBV) and hepatitis C virus (HCV), and by limiting HCV+ donors to high-risk candidates.³⁻⁵ Although the outcomes of using HCV+ and HBV+ donors for adult thoracic transplantation have been investigated, their use for pediatric thoracic transplantation has not been reported. A pediatric study observed similar post-transplant patient and graft survival among recipients who received an HBV- or HBV+ kidney.⁶ The purpose of this study was to investigate the post-transplant outcomes of pediatric heart transplant recipients who received an HBV core positive (HBVcAB+) or HCV+ donor heart or lung.

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Abbreviations and Acronyms	
HBV (+/-)	= hepatitis B virus surface antigen (positive/negative)
HBVcAB (+/-)	= hepatitis B virus core antibody (positive/negative)
HCV (+/-)	= hepatitis C virus (seropositive/seronegative)
PSM	= propensity score model
UNOS	= United Network for Organ Sharing

MATERIALS AND METHODS

Data

The data used for this study were obtained from the United Network for Organ Sharing (UNOS), a US private nonprofit organization that administers the Organ Procurement and Transplantation Network. The Organ Procurement and Transplantation Network was established by the US Congress under the National Organ Transplant Act of 1984 and requires submission of data on all solid organ transplants in the United States. The UNOS Standard Transplant Analysis and Research dataset contains data on all transplants in the United States and was used in this study. The institutional review board at Cincinnati Children’s Hospital waived full review of this project because of the de-identified nature of the UNOS dataset.

The UNOS database from June 2008 to June 2015 was used to identify pediatric (<18 years) heart, lung, and heart–lung transplant recipients (Figure 1). A total of 3 infants were identified who received HCV+ donor hearts and 9 infants and children who received

HBVcAB+ donor hearts. Two separate propensity score models (PSMs) for the HCV cohort and HBV cohort were conducted (1:3)⁷ to match recipients with HCV+ or HBVcAB+ donors to recipients with HCV- and HBVcAB- donors, based on factors of age, underlying cause for transplant, transplant year, extracorporeal membrane oxygenation, inotrope support, HCV serostatus (only for HCV cohort), and HBV surface antigen status (only for HBV cohort). Data were sampled without replacement when creating both PSMs. Standardized differences were evaluated for the variables that were used in the PSMs before and after match (Figure 2). The distribution of baseline characteristics between treated and untreated subjects in the matched sample was analyzed for the HCV cohort and HBV cohort. Patient post-transplant survival was defined as the time from transplantation to date of death or last alive follow-up.

Statistical Analysis

Continuous variables were summarized as medians with interquartile range. Categorical variables were summarized as counts with percentages. Continuous data were compared using nonparametric tests (Kruskal–Wallis test and Mann–Whitney *U* test). Categorical data were compared using the chi-square test. Survival curves were estimated using the Kaplan–Meier method, and differences in the curves were assessed with a stratified log-rank test. Statistical analyses were performed using IBM SPSS Statistics 21 software (IBM Corp, Armonk, NY).

RESULTS

All recipient baseline characteristics between the treated and untreated patients in the matched HCV cohort (Table 1) and the HBV cohort (Table 2) were similar (*P* > .05). No HCV+ or HBVcAB+ donors were reported for pediatric lung or heart–lung transplantation. Three HCV seronegative recipients received an HCV+ donor

FIGURE 1. Consort diagram showing patient distribution for the study. HBV, Hepatitis B virus; HCV, hepatitis C virus.

FIGURE 2. Dot-plot showing standardized difference for different variables before and after matching ([A] HCV and [B] HBV groups). *ECMO*, Extracorporeal membrane oxygenation; *HCV*, hepatitis C virus; *DIAG*, diagnosis; *HBV*, hepatitis B virus.

heart (Table 3). Post-transplant graft survival for recipients of HCV+ donors ($n = 3$) was similar to recipients of HCV- donors ($n = 9$; 5-year survival: 67% vs 88%, $P = .48$) (Figure 3). Of the 3 recipients who received an HCV+ heart, 1 patient died of respiratory failure. Nine HBVcAB+ donor hearts were accepted for HBVcAB and HBV surface antigen negative recipients (Table 1). Post-transplant graft survival for recipients of HBVcAB+ donors ($n = 9$) was similar to recipients with HBVcAB- donors ($n = 27$; 5-year survival: 87% vs 91%, $P = .79$) (Figure 3). Of the 9 recipients who received an HBVcAB+ organ, 1 recipient died of multiple system organ failure. The 2 recipients (1 HCV+ donor and 1 HBV+ donor) who died after transplantation had congenital heart disease. There were 2203 potential donors who were HCV+ or HBVcAB+ and were not used for pediatric thoracic transplantation within the study period.

DISCUSSION

The use of HCV+ and HBV+ donors as a strategy to expand the current thoracic donor pool has been demonstrated in adult thoracic transplantation.³⁻⁵ However, the use of HCV+ and HBV+ donors for pediatric cardiac transplantation has been under-investigated.

In addition to our findings and the current literature, the recent approval of ledipasvir/sofosbuvir and sofosbuvir for the definitive treatment of pediatric HCV further

TABLE 1. Characteristics of recipients who received a hepatitis B virus core antibody negative or positive donor at transplant in the matched hepatitis B virus cohort

Transplant recipient variables	Cases (9)	Unmatched control (2667)	<i>P</i> value	Matched control (27)	<i>P</i> value
Age (y), median [IQR]	7 [4-11]		.363	10 [5-14]	.615
Gender, n (%)			.108		.177
Female	6 (67%)	1226 (46%)		11 (41%)	
Male	3 (33%)	1441 (54%)		16 (60%)	
Thoracic diagnosis, n (%)			.319		.209
Cardiomyopathy	5 (56%)	1345 (50.4%)		18 (67%)	
Congenital heart disease	3 (33%)	1118 (41.9%)		9 (33%)	
Other	1 (11%)	57 (2.1%)		0 (0%)	
Extracorporeal membrane oxygenation support, n (%)			n/a		n/a
No		2530 (95%)			
Yes	9 (100%)	137 (5%)		27 (100%)	
Inotrope support, n (%)			0		1.000
No	8 (89%)	1286 (48%)		24 (89%)	
Yes	1 (11%)	1381 (52%)		3 (11%)	
Chronic steroid use, n (%)			.291		.801
No	8 (89%)	2362 (88%)		22 (82%)	
Yes	1 (11%)	264 (10%)		4 (15%)	
Unknown	0 (0%)	41 (2%)		1 (4%)	

IQR, Interquartile range; n/a, not available.

TABLE 2. Characteristics of recipients who received a hepatitis C virus negative or positive donor at transplant in the matched hepatitis C virus cohort

Transplant recipient variables	Cases (3)	Unmatched control (2691)	P value	Matched control (9)	P value
Age (y), median [IQR]	0* [0-0]		.982	0 [0-0]	1.000
Gender, n (%)			.793		.157
Female	2 (67%)	1099 (41%)		2 (22%)	
Male	1 (33%)	1592 (59%)		7 (78%)	
Thoracic diagnosis, n (%)					n/a
Congenital heart disease		1133 (42%)			
Cardiomyopathy		1332 (49%)			
Other	3 (100%)	88 (4%)	.246	9 (100%)	
Extracorporeal membrane oxygenation support, n (%)			n/a		n/a
Yes		137 (5%)			
No	3 (100%)	2554 (94%)		9 (100%)	
Inotrope support, n (%)			.593		1.000
No	1 (33%)	1405 (52%)		3 (33%)	
Yes	2 (67%)	1310 (48%)		6 (67%)	
Chronic steroid use, n (%)			.822		.513
No	3 (100%)	2427 (90%)		6 (67%)	
Yes	0 (0%)	223 (8%)		2 (22%)	
Unknown	0 (0%)	41 (2%)		1 (11%)	

IQR, Interquartile range; n/a, not available. *Standardized data only have ages in years, and for patients aged less than 1 year, “0” is provided.

suggests that HCV+ donors may be considered for pediatric cardiac transplantation.⁸ In a previous clinical study, these treatments have been observed to eliminate HCV from patients with HCV genotype 1.⁹ A recent cardiac transplantation study reported successful clearance of HCV in HCV-naïve recipients who received an HCV-infected donor heart and who were on a 12-week

ledipasvir/sofosbuvir or sofosbuvir/velpatasvir treatment plan.⁸ One of the patients had a previous HCV infection, which was cleared successfully even before transplantation.⁸ Harvoni (Gilead, Foster City, Calif) and Sovaldi (Gilead) mark the first direct-acting antiviral treatments for pediatric patients with HCV. In the event of HCV transmission, these definitive treatments may be able to

TABLE 3. Recipient age, transplant year, diagnosis, years survived post-transplant, patient status at post-transplant time point, and cause of death for pediatric recipients who had a hepatitis C virus positive or hepatitis B virus core antibody positive donor

Donor	Recipient age (y)	Transplant year	Recipient diagnosis	Years post-transplant	Patient status at years post-transplant	Primary cause of death
HCV+	0.58	2009	CHD	5.91	Alive	
HCV+	0.25	2013	CHD	1.91	Alive	
HCV+	0.34	2014	CHD	0.38	Dead	RF
HBVcAB+	7	2008	CHD	6.25	Alive	
HBVcAB+	4	2009	CHD	6.04	Alive	
HBVcAB+	0.75	2011	CM	4	Alive	
HBVcAB+	5	2011	CM	3.99	Alive	
HBVcAB+	0.5	2011	CM	2.87	Alive	
HBVcAB+	10	2014	CHD	0.42	Dead	MOF
HBVcAB+	14	2014	CHD	1	Alive	
HBVcAB+	17	2014	CHD	0.67	Alive	
HBVcAB+	11	2015	CM	0.49	Alive	

HCV+, Hepatitis C seropositive; CHD, congenital heart disease; RF, respiratory failure; HBVcAB+, hepatitis B core antibody positive; CM, cardiomyopathy; MOF, multiple organ failure.

FIGURE 3. Kaplan–Meier survival curves (A) for pediatric recipients who received an HBVcAB- or HBVcAB+ donor heart and (B) for pediatric recipients who received an HCV- or HCV+ donor heart. *HBV*, Hepatitis B virus; *HCV*, hepatitis C virus; *HEPC*, hepatitis C.

eliminate HCV, suggesting that we may be able to use HCV+ donors more often. More research on the use of these treatments in cardiac transplantation is necessary to learn more about long-term outcomes. These 2 treatments could help maximize donor use and improve post-transplant survival among pediatric thoracic transplant recipients.

Study Limitations

The UNOS dataset was missing vital variables, such as donor nucleic acid amplification testing, recipient HBV surface antibody status, and whether or not prophylaxis was administered. Rates of seroconversion and virus transmission of HCV and HBV in recipients who received an HCV+ or HBVcAB+ organ could not be measured because the recipient HCV serology and HBVcAB post-transplant statuses, HCV+ polymerase chain reaction results, and whether a patient received antiviral therapy were not reported in the dataset. More cases (HCV+ and HBVcAB+) would strengthen the statistical power of our study and allow for better estimations of the Kaplan–Meier survival curve. Half of the transplant surgeries were performed during the most recent 2 years of the study, which limits the ability to evaluate mid- to long-term follow-up.

CONCLUSIONS

This is the only study that has investigated the use of HCV+ and HBVcAB+ donors for pediatric cardiac transplantation within the last 7 years. Keeping in mind that the conclusions of this study are based on 12 HCV+ or HCVcAB+ matched patients, this study is consistent with the current trends among adult thoracic³⁻⁵ and pediatric kidney transplantation,⁶ and demonstrates that HCV+ and HBVcAB+ donors are not often used for transplantation. Although the results are encouraging in this small cohort, more studies under protocol are needed along with effective communication about safety with the

parents before considering HCV+ or HBVcAB+ donors for pediatric cardiac transplantation, given the restricted donor pool and improved treatment options for both HCV and HBV.

Conflict of Interest Statement

L.D-I. receives grants from Merck, Chimerix, AnsanBio-Pharma, Astellas, Roche, and Viracor. All other authors have nothing to disclose with regard to commercial support.

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