Postoperative Complications Associated With Perioperative Sirolimus Prior to Pediatric Cardiac Retransplantation

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OBJECTIVES: Sirolimus has been used in pediatric cardiac transplantation for the past decade for chronic renal dysfunction, recurrent rejection, and/or coronary allograft vasculopathy. There has been concern regarding the effect of sirolimus on wound healing and other postoperative complications. To date, the pediatric literature on its use is limited and has not specifically addressed its use in the perioperative period following repeat cardiac transplantation.

METHODS: We compared the patients in our institution who received sirolimus before repeat cardiac transplantation to those in the same era who did not receive sirolimus.

RESULTS: Of the 5 patients in the study group, 5 (100%) developed pleural effusions vs 1 (17%) in the control group ($p=0.013$). There was no increase in mortality in the sirolimus group, and there were no significant differences in renal dysfunction, serious bacterial infection, rejection, or postoperative length of stay.

CONCLUSIONS: In this small data set, there was a statistically significant increase in pleural effusions in patients on sirolimus. Further study is needed to develop an appropriate strategy to avoid postoperative complications in this patient population.

INDEX TERMS: heart transplantation, pediatrics, postoperative complications, sirolimus

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INTRODUCTION

Sirolimus, an inhibitor of mammalian target of rapamycin, has been used in pediatric cardiac transplantation in the past decade; however, it is only used in approximately 10% of pediatric patients 1 year after transplantation.¹ Sirolimus is used to slow the progression of cardiac allograft vasculopathy (CAV),² mitigate rejection,³ and improve renal dysfunction by substituting sirolimus for calcineurin inhibitors⁴ in some studies or minimizing calcineurin inhibitor dosage in others.^{5,6} Although small pediatric studies in this population have replicated the beneficial effects on rejection⁷ and renal function,^{5,6} the data regarding sirolimus use in the pediatric cardiac transplant population remain limited.^{5–8}

Sirolimus has a side effect profile that includes hyperlipidemia and hypertriglyceridemia,³ as well as thrombocytopenia, leucopenia, anemia,⁹ and noninfectious pneumonitis.¹⁰ There is increased concern regarding wound healing complications, such as wound dehiscence, in-

creased perigraft fluid collection, anastomotic complications, wound infections, and pleural effusions.^{11–13} Because of wound healing complications, it has been recommended that sirolimus be discontinued several weeks prior to a planned surgery. However, when sirolimus is used for patients awaiting cardiac retransplantation, it is impossible to know when a donor organ will become available. If the clinician wishes to mitigate the risks of perioperative complications by pre-emptively discontinuing the drug, the patient may be at an increased risk for advancing CAV or renal dysfunction while awaiting retransplantation.

To date, there are no pediatric studies specifically evaluating the complications of ongoing sirolimus use in patients undergoing surgery for retransplantation. The objective of this study is to review postoperative complications and rejection data in pediatric and young adult patients undergoing cardiac retransplantation or ventricular assist device (VAD) placement while receiving sirolimus.

Table 1. Age, Sex, and Comorbidities

Patient	Age at Prior Tx	Prior Tx Indication	Age at Study Period, yr	Sex	BMI	Comorbidity	Sirolimus Length, days
Control 1*	4 yr	CAV	15	M	27.3	CRI	
Control 2	6 mo	DCM	8	M	24.1		
Control 3	8 yr	RCM	19	F	32.7		
Control 4	13 yr	TOF	20	M	19.8	CRI	
Control 5	3 yr	RCM	12	M	27.0		
Control 6	14 yr	CAS	22	M	31.9		
Control group			Median, 17		Median, 27.2		
Sirolimus 1†	4 yr	CAV	15	M	32.2	CRI	785
Sirolimus 2	3 yr	DCM	21	M	18.3	CRI	1195
Sirolimus 3	14 yr	DCM	21	F	22.8	PHTN	846
Sirolimus 4	6 yr	CAV	14	F	20.5	IDDM	933
Sirolimus 5	4 yr	RCM	15	M	17.0		4004
Sirolimus group			Median, 15		Median, 20.5		Median, 933

CAS, congenital aortic stenosis; CAV, cardiac allograft vasculopathy; CRI, chronic renal insufficiency; DCM, dilated cardiomyopathy; IDDM, insulin-dependent diabetes mellitus; PHTN, pulmonary hypertension; RCM, restrictive cardiomyopathy; TOF, tetralogy of Fallot; Tx, transplant

*Ventricular assist device (VAD) patient at eventual retransplantation

†Placement of VAD

METHODS

The protocol for this retrospective analysis was approved by the Institutional Review Board at the Baylor College of Medicine, and written informed consent was not required for this retrospective chart review. Study data were retrieved from the institution's Pediatric Cardiac Transplantation Database as well as departmental and hospital records.

The study data include all patients at our institution who underwent repeat cardiac transplantation or VAD placement after cardiac transplantation between November 2004 and July 2011. This group was divided into study and control groups based on those who had received sirolimus for at least 90 days prior to operation and those who had not. The study group consisted of 5 patients, and the control group consisted of 6 patients. Four of the study group patients underwent retransplantation, and one of these patients underwent implantation of a VAD as a bridge to retransplantation.

The control group consisted of 6 retransplantation cases in the same time period. One of these patients was the VAD patient included in the study group who became a control at the time of retransplantation. Sirolimus was discontinued at VAD placement, and the patient had been off of sirolimus for 93 days prior to retransplantation.

Data collected for study and control groups included age, sex, body mass index (BMI), ad-

ditional comorbidities, and immunosuppressive regimen before and after operation. The outcomes identified include length of hospital stay and the following measures in the 90 days after operation: wound healing and infectious complications, rejection surveillance biopsy data, and presence of renal dysfunction. The charts were reviewed for the following wound healing complications: delayed sternal closure, wound dehiscence, and pleural effusions. Patients defined as having pleural effusions had this clinical entity listed as a problem in hospital notes and in chest x-ray reports for at least 4 consecutive days. Renal dysfunction was defined using RIFLE (risk, injury, failure, loss, end-stage) and pediatric RIFLE classifications.^{14,15}

Age and BMI were compared using the *t* test and the Mann-Whitney *U* test. Length of stay data in the study and control groups were compared using the Wilcoxon signed rank test. The remaining outcomes were compared using Fisher exact test.

RESULTS

Patient Demographics

The study group consisted of patients ages 14 to 21 years (median, 15) at the time of operation. The control group consisted of patients ages 8 to 22 years (median, 17). Patients in the study and control groups had median BMI values of 20.5 and 27.2, respectively. With respect to age and BMI, the groups were not significantly dif-

Table 2. Immunosuppressive Regimens

Patient	Corticosteroids		Cyclosporine		Tacrolimus		Mycophenolate		Azathioprine	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control 1*	+	+	+	+	–	–	–	+	–	–
Control 2	+	+	+	+	–	–	+	+	–	–
Control 3	+	+	+	+	–	–	–	+	–	–
Control 4	+	+	–	–	+	+	–	+	–	–
Control 5	+	+	+	+	–	–	–	+	–	–
Control 6	+	+	+	+	–	–	–	+	–	–
Sirolimus 1†	+	+	+	+	–	–	–	–	–	–
Sirolimus 2	+	+	+	–	–	+	–	+	–	–
Sirolimus 3	+	+	–	–	+	+	–	+	–	–
Sirolimus 4‡	+	+	+	+	–	–	–	–	–	–
Sirolimus 5	+	+	+	–	–	+	–	+	–	–

*Ventricular assist device (VAD) patient at eventual retransplantation

†Placement of VAD

‡This was the only patient who restarted sirolimus (4 days after operation)

ferent ($p>0.05$). Chronic renal insufficiency was previously present in two of the study patients and two of the control patients. Additionally, one study patient had reactive pulmonary hypertension and another had type 1 diabetes mellitus. Patient demographics and comorbidities are shown in Table 1.

All patients in both the study and control groups received a calcineurin inhibitor and corticosteroids before and after operation. Immunosuppressive regimens for each patient are shown in Table 2. With respect to the 5 study patients, sirolimus was initiated 2 to 10 years prior to retransplantation/VAD implant (median, 933 days). Sirolimus was initiated because of: CAV (3 patients), protracted rejection episode (1 patient), and renal failure (1 patient). Sirolimus was discontinued at the time the donor organ was accepted or VAD was placed. Of the 5 study patients, 1 patient (denoted in Table 2) resumed sirolimus 4 days after the operation, because this was the second transplantation for CAV.

Comorbidities

Wound Healing Complications

All patients (100%) in the sirolimus group had pleural effusions (one requiring chest exploration and another requiring pleurodesis) compared with 1 of 6 patients (17%) in the control group, who did not require operative management ($p=0.013$). No patients in either group had delayed sternal closure. There was one episode of wound dehiscence in the control group, involving a prior abdominal wound, and no such episodes in the study group.

Serious Bacterial Infection

A total of 3 of 5 patients (60%) in the sirolimus group compared with none (0%) in the control group developed serious bacterial infections ($p=0.182$). The causative organisms in the sirolimus group included coagulase-negative *Staphylococcus* bacteremia, *Staphylococcus aureus* bacteremia, and coagulase-negative *Staphylococcus* mediastinitis.

Renal Dysfunction

A total of 4 of 5 patients (80%) in the sirolimus group compared with 4 of 6 patients (67%) in the control group developed renal dysfunction ($p=0.455$). Table 3 delineates the RIFLE classification of each patient. The patient who underwent VAD placement (included in the study group data) did not recover from renal dysfunction, and then underwent kidney transplantation with his eventual heart retransplantation (included in the control group data). The remainder of the patients in both groups who developed renal dysfunction recovered from this complication during the study period.

Rejection

No patient in the study group who underwent retransplantation, including the patient who had a VAD placed as a bridge to transplant, had a rejection score greater than 1R. One patient in the control group had a rejection score of 2R; the remainder had scores of 1R in the follow-up period. Considering scores 2R and higher as clinically significant rejection, 1 of 6 patients (17%) in the control group vs 0 of 4 (0%) in the study group

Table 3. Outcomes

	Length of Stay, days*	Rejection Score	Serious Bacterial Infection	Acute Renal Failure	Recovery From Acute Renal Failure	Pleural Effusion	Intervention for Pleural Effusion
Control 1†	28	1R	–	Kidney transplantation†		–	
Control 2	11	2R	–	+	+	–	
Control 3	9	1R	–	+	+	–	
Control 4	50	1R	–	+	+	+	Chest tube reinsertion
Control 5	16	1R	–	–	–	–	
Control 6	19	1R	–	+	+	–	
Control group	Mean, 22.2 ± 15.2; median, 17.5						
Sirolimus 1‡	112	NA‡	CONS§ bacteremia	+		+	
Sirolimus 2	51	1R	<i>Staphylococcus aureus</i> bacteremia	+	+	+	
Sirolimus 3	14	1R	CONS§ mediastinitis	+	+	+	Chest exploration
Sirolimus 4	6	1R	–	–	–	+	
Sirolimus 5	36	1R	–	+	+	+	Pleurodesis
Sirolimus group	Mean, 43.8 ± 42.1; median, 36.0						

CONS, coagulase-negative *Staphylococcus*

*After operation

†Ventricular assist device (VAD) patient at retransplantation; patient underwent kidney transplantation with cardiac transplantation

‡Placement of VAD (no rejection data)

§Coagulase-negative *Staphylococcus*

had rejection ($p=0.6$).

Length of Stay

Three patients in the study group had been hospitalized prior to retransplantation/VAD implant. Length of stay after operation ranged from 6 days to 112 days (median, 36). Two patients in the control group had been hospitalized prior to retransplantation. Length of stay after operation ranged from 9 days to 50 days (median, 18). There was no statistically significant difference in length of stay between the two groups ($p=0.54$). Outcomes for the control and study groups are shown in Table 3.

Deaths

There were no deaths in the study or control groups during the 90-day postoperation study period.

DISCUSSION

This single-institution, retrospective study is the first to our knowledge to specifically evaluate

the postoperative complications of perioperative sirolimus use in children and young adults undergoing cardiac retransplantation. As has been shown in other studies, there was a statistically significant increase in pleural effusions in those on sirolimus.^{11–13} Although patients in the sirolimus group appeared to have more serious bacterial infections and longer length of stay than the control group, these outcomes did not reach statistical significance in our small study cohort.

As patient survival improves after transplantation, long-term complications, including renal dysfunction and CAV, are becoming increasingly problematic. Therefore, an increasing use of sirolimus is likely. As the waiting time for listed patients increases, cardiac transplant physicians will be forced to decide whether the benefits of continued sirolimus use outweigh the risks of discontinuing it at an arbitrary time point before retransplantation to avoid its postoperative complications.

This series is limited by its small sample size, retrospective nature, and nonuniform use of immunosuppressives before and after retrans-

plantation. Although the series has replicated an increase in effusions as seen in prior adult studies, there was no increase in mortality, suggesting that continuing sirolimus up to the time of retransplantation is an acceptable option in these high-risk patients. At this time, however, a larger study to assess outcomes is necessary before definitive recommendations can be made.

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Abbreviations BMI, body mass index; CAV, coronary allograft vasculopathy; RIFLE, risk, injury, failure, loss, end-stage; VAD, ventricular assist device

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