KJTCVS
The Korean Journal of Thoracic and Cardiovascular Surgery
https://doi.org/10.5090/kjtcs.19.091
pISSN: 2233-601X eISSN: 2093-6516
Korean J Thorac Cardiovasc Surg. 2020;53(6):375-380

Clinical Research

The Effect of Supplemental Cardioplegia Infusion before Anastomosis in Patients Undergoing Heart Transplantation with Long Ischemic Times

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ARTICLE INFO
Received December 5, 2019
Revised August 18, 2020
Accepted August 18, 2020

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[†]This paper was presented at the 50th Fall Conference of the Korean Society for Thoracic and Cardiovascular Surgery.

Background: Prolonged ischemic time is a risk factor for primary graft dysfunction in patients who undergo heart transplantation. We investigated the effect of a supplemental cardioplegia infusion before anastomosis in patients with long ischemic times.
Methods: We identified 236 consecutive patients who underwent orthotopic heart transplantation between February 2010 and December 2014. Among them, the patients with total ischemic times of longer than 3 hours (n=59) were categorized based on whether they were administered a complementary cardioplegia solution (CPS) immediately before implantation (CPS+, n=30; CPS–, n=29).
Results: The mean total ischemic times in the CPS+ and CPS– groups were 238.1±30.1 minutes and 230.1±28.2 minutes, respectively (p=0.3). The incidence of left ventricular primary graft dysfunction (CPS+, n=6 [20.0%]; CPS–, n=5 [17.2%]; p=0.79) was comparable between the groups. In the Kaplan-Meier survival analysis, no significant difference in overall survival at 5 years was observed between the CPS+ and CPS– groups (83.1%±6.9% vs. 89.7%±5.7%, respectively; log-rank p=0.7). No inter-group differences in early mortality (CPS+, n=0; CPS–, n=1 [3.4%]; p=0.98) or complications were observed.
Conclusion: The additional infusion of a cardioplegia solution immediately before implantation in patients with longer ischemic times is a simple, reproducible, and safe procedure. However, we did not observe benefits of this strategy in the present study.

Keywords: Heart transplantation, Induced heart arrest, Primary graft dysfunction, Cold ischemia

Introduction

As a result of improvements in survival rates after cardiac transplantation, orthotopic heart transplantation has become the treatment of choice for end-stage heart failure. In situations of donor shortage, increasing numbers of organs are retrieved from relatively old, distantly located, and marginal donors with long ischemic times. In particular, an allograft ischemic time that exceeds 3 hours is a known risk factor for mortality [1]. As donor organ preservation methods have improved, there is a recent dramatic increase in cases where ischemic times of 4 to 6 hours are accepted [2]. However, even though the survival rate has increased over time, a prolonged ischemic time is still regarded as a risk factor for primary graft dysfunction [3]. Therefore, we have sought effective organ preservation methods to decrease the incidence of primary graft dysfunction. One method that we used was the administration of a complementary cardioplegia solution (CPS) immediately before implantation. A few articles have addressed this strategy as a simple, easily reproducible method. However, whether supplemental cardioplegia infusion has any

potential benefit remains to be determined [4-6]. We therefore sought to evaluate the safety and possible benefits of this strategy.

Methods

Patients

Using a prospective registration database at our institution, we identified 236 consecutive patients who underwent orthotopic heart transplantation at Asan Medical Center in Seoul, South Korea between February 2010 and December 2014. Patients who underwent multi-organ transplantation (n=11; 10 heart-lung transplantation, 1 heart-kidney transplantation) or pediatric heart transplantation (n=25) were excluded. Among the 236 patients, only those with total ischemic times of longer than 3 hours were included in this study (n=59). The patients were categorized based on whether they were administered a CPS immediately before implantation (CPS+, n=30) or did not receive this solution (CPS–, n=29). The surgeon's preference determined supplemental infusion of cardioplegia solution. Only 1 surgeon adopted the administration of a CPS immediately before implantation in patients with long ischemic time (more than 3 hours).

The primary outcome of interest was primary graft dysfunction, which was defined according to the International Society of Heart and Lung Transplant (ISHLT) consensus [3]. The secondary outcomes were death and clinical complications, the latter of which included bleeding, graft failure, rejection, cardiac allograft vasculopathy, and cardiac enzyme elevation. Early cardiac enzyme elevation after transplantation may predict post-reperfusion myocardial damage and death [7]. Graft failure was defined as the need for mechanical circulatory support or re-transplantation. Grading of the endomyocardial biopsies followed the 2004 ISHLT guidelines, with rejection defined as moderate grade or higher. Transplant coronary artery disease was defined as mild or greater vasculopathy on coronary angiography.

Data on mortality and cause of death were obtained from the Korean National Registry of Vital Statistics. The requirement for informed consent was waived because of the retrospective nature of the study. The study was approved by the institutional review board of Asan Medical Center (IRB approval no., 2020-1100).

Operation

Graft procurement was performed using cardioplegia with 2,000 mL of cold (4°C–8°C) histidine-tryptophan-ketoglutarate (Custodiol histidine-tryptophan-ketoglutarate [HTK]; Essential Pharmaceuticals, Newtown, PA, USA) administered through the aortic root cannula. If additional cardioplegia infusion is determined following allograft arrival, an additional 1,000 mL of cold HTK solution (4°C–8°C) was infused in an antegrade fashion. The cardioplegia bag was placed at a height of 1 m above the patient to provide infusion pressure. While the cardioplegia solution was infused, the procurement heart was inspected and trimmed (a process which took 5 to 10 minutes). All transplants were performed using the bicaval anastomosis technique.

Postoperative management and immunosuppression

In the intensive care unit (ICU), postoperative care was similar to that provided in other cases of open-heart surgery. Serial cardiac enzyme level testing and arterial blood gas analysis were performed. After confirming the absence of mediastinal bleeding or neurologic dysfunction, we weaned the patients off of mechanical ventilation and extubated them. The details of the postoperative management process have been described previously [8].

The preoperative immunosuppressive protocol consisted of anti-interleukin-2 (IL-2) receptor monoclonal antibody (anti-IL-2 R mAb) with 1.5–2.0 g of mycophenolate mofetil administered orally. Intraoperatively, intravenous methylprednisolone (500 mg) was administered before reperfusion. Immediately after surgery, 1–2 g/day of mycophenolate mofetil and anti-IL-2 R mAb were administered. On postoperative day 2, once the creatinine level had stabilized, FK506 treatment was initiated. The initial postoperative prednisone dose was 1 mg/kg/day, which was reduced to 0.25 mg/kg/day after 1 month and to 0.1 mg/kg/day after 1 year. When possible, prednisone was discontinued at 1 year after transplantation.

Endomyocardial biopsies were performed at 1, 3, 6, and 12 months and then regularly for a 2-year period after surgery. After the patients were discharged, they were followed up with at our outpatient clinic. The mean duration of follow-up was 63.0±22.7 months.

Statistical analysis

The categorical variables are presented as percentages or frequencies, and the continuous variables are expressed as means±standard deviations. The variables for the 2 groups

were compared using the Student t-test or the chi-square test. Survival curves were created using the Kaplan-Meier method, and differences in survival rates between the groups were assessed using the log-rank test. Relationships between clinical outcomes and the surgical strategy were identified using logistic regression analysis. A p-value <0.05 was considered to indicate statistical significance. Statistical analysis was conducted with R statistical software ver. 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the patients. The baseline demographic and clinical characteristics were similar between the 2 groups. In both groups, the most common cause of heart failure was dilated cardiomyopathy, followed by ischemic cardiomyopathy. The mean total ischemic times (CPS+, 238.1±30.1 minutes; CPS–, 230.1±28.2 minutes; p=0.3) and cold ischemic times (CPS+, 179.1±25.1 minutes; CPS–, 177.7±31.0 minutes; p=0.84) were comparable between groups.

Postoperative outcomes

Table 2 shows the odds ratios for the clinical outcomes of the supplemental cardioplegia (CPS+) group compared with those of the control (CPS–) group. No significant difference was observed in the incidence of primary graft dysfunction. The 2 groups had comparable early mortality rates (CPS+, n=0; CPS–, n=1 [3.4%]; p=0.98). Logistic regression analysis of early postoperative clinical outcomes such as early mortality, major postoperative complications, and the need for continuous renal replacement therapy showed no statistically significant difference in odds ratios between the 2 groups. Furthermore, no significant differ-

Table 1. Baseline patient characteristics

Characteristic	CPS+	CPS–	p-value
No. of patients	30	29	
Age of recipient (yr)	47.8±14.4	47.1±13.9	0.86
Age of donor (yr)	31.9±10.7	33.1±11.3	0.68
Male sex (recipient)	19 (63.3)	23 (76.7)	0.17
Male sex (donor)	23 (76.7)	26 (89.7)	0.33
Diabetes mellitus	4 (13.3)	1 (3.4)	0.37
Hypertension	4 (13.3)	4 (13.8)	1
Chronic kidney disease	3 (10.0)	1 (3.4)	0.63
Preoperative creatinine (mg/dL)	1.1±0.6	1.0±0.3	0.59
Total bilirubin (mg/dL)	2.0±4.5	1.6±0.9	0.70
Preoperative extracorporeal membrane oxygenation	2 (6.7)	2 (6.9)	1
Preoperative inotrope administration	19 (63.3)	18 (62.1)	1
Preoperative pulmonary hypertension	16 (53.3)	18 (62.1)	0.68
Right ventricle–right atrium pressure gradient (mm Hg)	36.9±14.7	38.7±19.0	0.68
Etiology			0.73
Dilated cardiomyopathy	19 (63.3)	16 (55.2)	
Ischemic cardiomyopathy	4 (13.3)	6 (20.7)	
Others	7 (23.3)	7 (24.1)	
Korean Network for Organ Sharing grade			0.24
0	4 (13.8)	1 (3.6)	
1	11 (37.9)	7 (25.0)	
2	6 (20.7)	11 (39.3)	
3	8 (27.6)	9 (32.1)	
Total ischemic time (min)	238.1±30.1	230.1±28.2	0.30
Cardiopulmonary bypass time (min)	152.6±45.2	143.4±44.4	0.43
Warm ischemic time (min)	59.0±19.1	52.4±10.8	0.11
Cold ischemic time (min)	179.1±25.1	177.7±31.0	0.84
Anastomosis time (min)	59.5±14.3	55.4±11.6	0.23

Values are presented as number, mean±standard deviation, or number (%).
CPS, complementary cardioplegia solution.

https://doi.org/10.5090/kjtcs.19.091

Table 2. ORs and 95% CI for clinical outcomes in the supplemental cardioplegia group compared with the control group

Variable	CPS+	CPS–	OR (95% CI)	p-value
PGD–right ventricle	1 (3.3)	1 (3.4)	0.52 (0.15–1.85)	0.32
PGD–left ventricle			1.2 (0.32–4.47)	0.79
Mild	0	1 (3.4)		
Moderate	5 (16.7)	2 (6.9)		
Severe	1 (3.3)	2 (6.9)		
Early mortality	0	1 (3.4)		0.98
Major postoperative complications	2 (6.7)	5 (17.2)	0.34 (0.06–1.93)	0.22
Bleeding re-exploration	0	2 (6.9)		0.68
Graft failure	1 (3.3)	3 (10.3)	0.30 (0.03–3.05)	0.30
Requirement for continuous renal replacement therapy	2 (6.7)	3 (10.3)	0.62 (0.1–4.01)	0.61
Right bundle branch block	15 (50.0)	9 (31.0)	2.22 (0.77–6.44)	0.14

Values are presented as number (%), unless otherwise stated.
OR, odds ratio; CI, confidence interval; CPS, complementary cardioplegia solution; PGD, primary graft dysfunction.

Table 3. Postoperative outcomes

Variable	CPS+	CPS–	p-value
No. of patients	30	29	
Post EF (%)	60.9±3.9	61.2±10.7	0.91
Last EF (%)	61.2±7.2	61.9±4.0	0.64
CK-MB initial (ng/mL)	112.4±79.4	107.8±62.5	0.81
Troponin I initial (ng/mL)	23.2±21.4	21.6±18.0	0.75
CK-MB peak (ng/mL)	126.4±83.4	126.1±98.8	0.99
Troponin I peak (ng/mL)	27.2±28.6	24.3±20.1	0.65
Postoperative peak lactate (mmol/L)	6.6±2.4	8.5±4.2	0.05
Intubation time (hr)	35.0±87.1	30.4±45.3	0.80
Intensive care unit stay (day)	8.3±14.2	7.4±5.1	0.75
Hospital stay (day)	32.4±10.5	35.6±26.7	0.56

Values are presented as number or mean±standard deviation.
CPS, complementary cardioplegia solution; EF, ejection fraction; CK, creatine kinase.

ence was observed in the postoperative left ventricle ejection fraction or cardiac enzyme values between the groups. The postoperative peak lactate level was higher in the CPS– group than in the CPS+ group. The intubation time, length of ICU stay, and length of hospital stay were comparable between groups (Table 3).

The overall survival rates at 1 and 5 years were 96.6%±2.4% (CPS+) and 86.3%±4.5% (CPS–). In the Kaplan-Meier survival analysis, no significant difference in overall survival at 5 years was observed between the CPS+ and CPS– groups (83.1%±6.9% versus 89.7%±5.7%, respectively; log-rank p=0.7) (Fig. 1). No significant difference was seen between the groups with regard to freedom from cardiac allograft vasculopathy (p=0.3) and freedom from rejection (p=0.2) (Fig. 2).

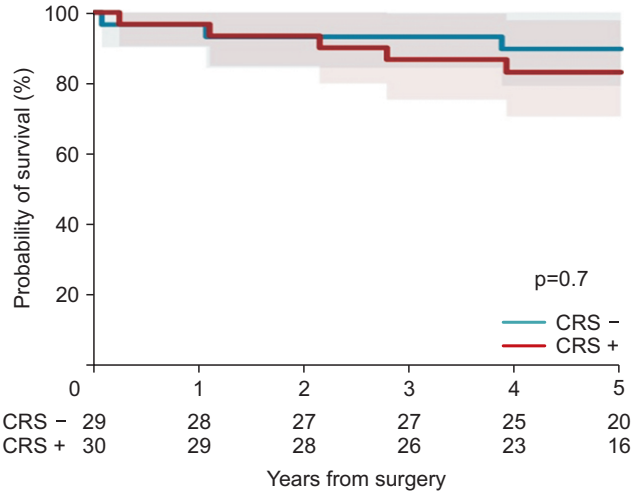

Fig. 1. Kaplan-Meier survival curves for each group. CPS, complementary cardioplegia solution.

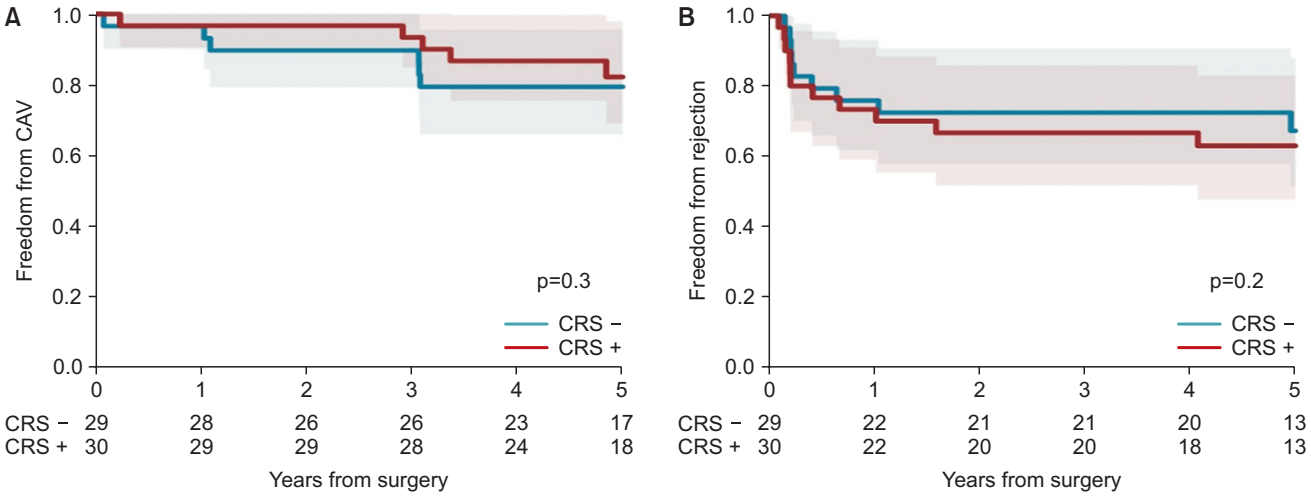

Fig. 2. (A) Kaplan-Meier curves of freedom from CAV and (B) freedom from rejection. CAV, cardiac allograft vasculopathy; CPS, complementary cardioplegia solution.

Discussion

Orthotopic heart transplantation is the treatment of choice for end-stage heart failure. While the number of patients undergoing orthotopic heart transplantation has increased, the limited donor organ pool has forced expansion of the criteria, leading to the acceptance of organs from more distant locations and older donors. According to data from the ISHLT Registry, longer ischemic time is a risk factor for primary graft dysfunction. Therefore, effective donor heart preservation may reduce the incidence of primary graft dysfunction. One such preservation method involves normothermic blood perfusion, such as the Transmedics Organ Care System. However, in South Korea, organ ischemic times longer than 3 hours are rare, and the cost of such techniques restrict their use. Of the many other organ preservation methods, the predominant technique in most centers is static cold storage. In addition to using a static cold storage system, our center utilizes a CPS administered immediately before implantation, which is regarded as simple and cost-effective. A few articles have described similar methods [4-6], but their effects remain uncertain.

Tevaearai et al. [6] demonstrated that dispensing an additional dose of cardioplegia solution at the time of implantation was not independently associated with a better postoperative graft survival outcome; however, they reported that several surrogate markers seemed to indicate an additional protective effect of the strategy, with benefits to factors such as the postoperative creatine kinase (CK)-MB/CK ratio, intubation time, and ICU stay duration. Similarly, in our study, the supplemental infusion strategy did not show a protective effect on early mortality and primary graft failure. However, unlike the results of the previous report, our results showed no difference between the 2 groups in terms of postoperative outcomes such as cardiac enzyme values, intubation time, and ICU stay duration. Furthermore, major factors limiting long-term survival, namely the freedom from cardiac allograft vasculopathy and the freedom from chronic allograft rejection, were not significantly different between the 2 groups. In summary, our strategy did not yield significantly better outcomes.

This finding has some possible explanations. Although HTK solution is widely used for heart transplantation with good results, the optimal strategy for its use has not been clearly defined [9,10]. It is possible that the amount of supplemental HTK solution infused in our study was insufficient to have an effect. It is also possible that the cardioplegia solution was distributed unevenly. This solution was delivered under cold storage conditions, in which coronary artery vasoconstriction may cause uneven distribution of the solution.

An ischemic time that exceeds 4 hours is a known risk factor for long-term survival, and this risk increases with the age of the donor [2]. However, because our study dealt with patients who were relatively young, and the ischemic time for each patient was generally around 4 hours or less, our results may not be sufficient to show the full effect of supplemental cardioplegia across older age groups and in patients who experienced longer ischemic times.

Lactic acidosis is commonly observed after heart transplantation. It is known to be related to low cardiac output, poor peripheral perfusion, and excessive catecholamine

administration [11,12]. The relatively low postoperative peak lactate level in the CPS+ group demonstrates that supplemental cardioplegia infusion may have a positive effect on allograft protection. Therefore, our results do not preclude the possible effectiveness of additional cardioplegia, and further studies involving different cardioplegia infusion strategies or distribution techniques are required for definitive conclusions.

Our study has several limitations. This single-center study had a retrospective observational design. The decision to administer additive cardioplegia was based on the surgeon's judgment, which could have introduced confounders to the results. Also, the number of patients was insufficient to generalize the results. To clarify these issues, further study involving a greater number of patients will be needed.

In conclusion, additional infusion of a cardioplegia solution immediately before implantation in patients with longer ischemic times is a simple and safe procedure. However, we did not identify benefits of this strategy in this study. Further study in a larger patient population is necessary.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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