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Impact of the Cardioplegia Interval on Myocardial Protection Using the Modified St. Thomas Solution in Minimally Invasive Mitral Valve Surgery: A Double-Center Study

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Abstract: It has been reported that a single-dose cardioplegia interval is useful, but the safe interval doses are not clear. We aimed to investigate the impact of the cardioplegia interval on myocardial protection using the modified St. Thomas solution. We included consecutive isolated minimally invasive mitral valvuloplasty procedures (n = 229) performed at a hospital and medical center from January 2014 to December 2020. We compared postoperative peak creatine kinase MB and creatine kinase levels and other indicators between the short (Group S, n = 135; maximum myocardial protection interval <60 minutes) and long (Group L, n = 94; maximum myocardial protection interval ≥60 minutes) interval groups. Propensity score matching was used to adjust for confounders between the two groups. After propensity score matching, Groups S and L contained 47 patients each. Groups S and L did not differ significantly in peak creatine kinase MB (45.8 ± 26.3 IU/L and 41.5 ± 27.9 IU/L, respectively; p = .441) and creatine kinase levels (1,133 ± 567 IU/L and 1,100 ± 916 IU/L, respectively; p = .837) after admission to the intensive care unit on the day of surgery based on propensity score matching. In multivariate analysis, a cardioplegia dosing interval ≥60 minutes was not significantly associated with the maximum creatine kinase MB level after admission to the intensive care unit on the day of surgery (p = .354; 95% confidence interval: −1.67 to 4.65). Using the antegrade modified St. Thomas solution, the long interval dose method is useful and safe in minimally invasive mitral valvuloplasty. **Keywords:** cardioplegia, cardiopulmonary bypass, mitral valve surgery, myocardial protection, modified St. Thomas solution. *J Extra Corpor Technol. 2022;54:135–41*

Cardioplegia is an essential procedure in cardiac surgery and has evolved along with cardiac surgery. Current myocardial protective solutions can be classified into two main types: intracellular fluid type and extracellular fluid type; crystalloid myocardial protection solutions of Glucose-insulin-potassium (GIK) solutions and blood myocardial protection (including Microplegia and del Nido) in which these crystalline solutions are mixed with blood (1–4). Cardioplegia is generally initiated at 20–30 minutes after the initial cardiac arrest with additional doses (i.e., multidose) administered in an antegrade and retrograde manner (5).

Several studies have recently reported that a single dose of cardioprotection, which can be administered less frequently by extending the interval between the doses of cardioprotection provides equivalent cardioprotection and shortens the operative time compared to using multiple doses (6–9). Since Plasma-Lyte A (Baxter) is not sold in Japan, del Nido solution could not be prepared and used in this study (Figure 1). In contrast, some investigators have reported that the longer the interval between administration of a single dose of del Nido solution, the lower the postoperative cardiac contractility (10,11).

Minimally invasive cardiac surgery (MICS) tends to require a longer cardiopulmonary bypass (CPB) time and aortic cross-clamp (ACC) time than median sternotomy (12). Therefore, safer and more reliable myocardial

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Plasmalyte A	
Component	Concentration
Na^+ (mEq/L)	140
K^+ (mEq/L)	5
Mg^+ (mEq/L)	3
Cl^- (mEq/L)	98
Acetate (mEq/L)	27
Gluconate (mEq/L)	23
del Nido Additives	
Component	Concentration
K^+ (mEq/L)	26
Mg^+ (mEq/L)	2
$NaHCO_3$ (mEq/L)	13
Mannitol (g/L)	3.26
Lidocain (mg)	130

Figure 1. Components of the del Nido solution. Na, sodium; K, potassium; Mg, magnesium; Cl, chloride; $NaHCO_3$-, sodium bicarbonate.

protection is required. The only crystalloid myocardial protection solution sold by pharmaceutical companies in Japan is the intracellular fluid type, i.e., the St. Thomas solution. Some studies have reported the benefits of long interval doses using the St. Thomas solution; thus, we modified the St. Thomas solution based on these studies (13,14). We investigated the impact of the cardioplegia interval on myocardial protection using the modified St. Thomas solution (Figure 2).

MATERIALS AND METHODS

Study Design and Ethical Approval

This retrospective observational study was conducted with the approval of the Ethics Committees of Toranomon Hospital and Tokyo Bay Urayasu Ichikawa Medical Center (IRB approval numbers: 2044 at Toranomon Hospital and 569 at Tokyo Bay Urayasu Ichikawa Medical Center). The ethics committees waived the need for patient approval because of the retrospective nature of the study.

Component	Concentration
Na^+ (mEq/L)	120
K^+ (mEq/L)	24
Mg^+ (mEq/L)	32
Ca^+ (mEq/L)	2.4
HCO_3^- (mEq/L)	10
Cl^- (mEq/L)	160.4
Mannitol (g/L)	4

Figure 2. Components of the modified St. Thomas solution. Na, sodium; K, potassium; Mg, magnesium; Ca, calcium, HCO_3-, bicarbonate; Cl, chloride.

Study Population

This study included 338 consecutive MICS mitral valvuloplasty (MICS-MVP) procedures performed at our hospital and medical center from January 2014 to December 2020 (Figure 3). We compared the following two groups: a short interval group (n = 136), wherein the maximum interval of cardioplegia administration was <60 minutes, and a long interval group (n = 93), wherein the maximum interval of cardioplegia administration was ≥60 minutes.

CPB and Cardioplegia Management

The CPB flow rate was 2.2–2.5 L/min/m^2. The CPB priming volume was 600–700 mL with a centrifugal pump and vacuum-assisted venous drainage. An arterial cannula was inserted into the common femoral artery or subclavian artery, and a venous cannula was inserted into the right internal jugular vein and femoral veins. The lowest central temperature (based on the bladder or rectal temperature) during CPB was maintained at approximately 34°C. St. Thomas solution with added potassium and mannitol was used as the cardioplegia solution. The first dose was 30 mL/kg (maximum, 2,000 mL) after ACC, and an additional 10 mL/kg of the cardioplegia solution was administered when it did not interfere with surgery (e.g., while passing sutures on the prosthetic ring outside the chest) or when the electrical activity of the myocardium was observed. Our standard dose interval was <60 minutes. We allowed an interval of up to 90 minutes in the absence of myocardial electrical activity to avoid interfering with the ongoing surgical procedure. The cardioplegia solution temperature was 2–4°C. The flow rate was 400–500 mL/min, and the intracircuit pressure was controlled at approximately 200 mmHg. Cardioplegia was administered using an antegrade approach with a root cannula and without the insertion of a

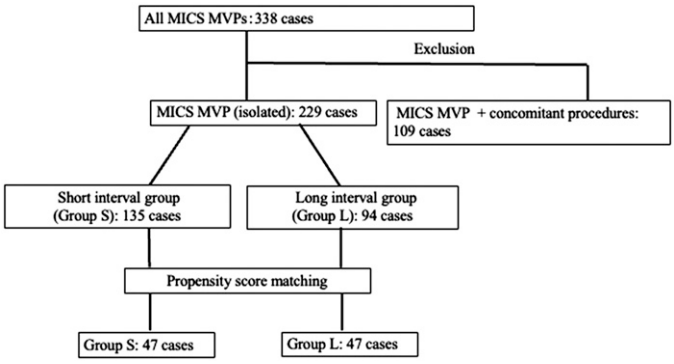

Figure 3. Case inclusion. MICS, minimally invasive cardiac surgery; MVP, mitral valvuloplasty.

retrograde cardioplegia cannula. Terminal warm blood cardioplegia was not used. After aortic declamping, deairing was performed using the left atrial or left ventricular (LV) vent and the aortic root vent as in the case of the median sternotomy. The CO_2 gas flushing was performed in the pericardial sac at a rate of approximately 2 L/min.

Primary Endpoint

In this study, the primary endpoint was the maximum creatine kinase MB (CK-MB) and maximum CK levels after admission to the intensive care unit (ICU) on the day of surgery and postoperative day 1 (POD 1) to compare the cardioprotective effect between the two groups.

Secondary Endpoints

Secondary endpoints included intraoperative electrical defibrillation use, inotropic drug use after ICU admission (i.e., dobutamine, noradrenaline, adrenaline, or milrinone), intubation time, postoperative echocardiographic LV ejection fraction (LVEF), electrocardiography (ECG) findings at discharge (i.e., percentage of sinus rhythm), incidence of acute kidney injury (Kidney Disease Improving Global Outcomes stage I or higher), postoperative 30-day mortality, postoperative myocardial infarction, postoperative ICU stay, and postoperative hospital stay.

Preoperative Factors

Preoperative factors included age, sex (i.e., percentage of female individuals), body surface area (BSA), body mass index (BMI), EuroSCORE II, the presence of coronary artery disease, preoperative ECG findings (i.e., percentage of sinus rhythm), serum creatinine level, hemoglobin level, hypertension, diabetes, chronic obstructive pulmonary disease, and New York Heart Association functional classification.

Perioperative Factors

Perioperative factors included left atrial diameter, effective regurgitant orifice area, LVEF, LV end-diastolic diameter, LV end-systolic diameter, degree of aortic regurgitation, etiologies of mitral valve regurgitation (degenerative, functional, active endocarditis, previous endocarditis, or dilatation of the annulus), and procedure (annuloplasty, neochordae implantation, or resection).

Intraoperative Factors

We compared the following intraoperative factors between the two groups: operative time, CPB time, ACC time, presence or absence of re-ACC, re-ACC time, amount of cardioplegia solution administered during re-ACC, rate of femoral artery cannulation, red blood cell transfusion, fresh frozen plasma transfusion, and platelet transfusion.

Cardioplegia Data

We collected the following data as cardioplegia data and compared them between the groups: maximum cardioplegic interval, cardioplegic interval between the first and second doses, average number of cardioplegia doses, total amount of cardioplegia solution, and timing of the additional dose.

Statistical Analysis

JMP Pro 15 (SAS Inc., Cary, NC) was used to perform the statistical analyses. Continuous variables are expressed as the mean ± standard deviation, and nominal variables are expressed as the percentage of cases. Continuous variables were compared using the t test, and nominal variables were compared using the chi-squared test or Fisher's exact test. A value of $p < .05$ was considered statistically significant. Propensity score matching (PSM) was used to

Table 1. Preoperative factors.

		Unmatched			Matched		
Variable	All Cases (n = 229)	Group S (n = 135)	Group L (n = 94)	P Value	Group S (n = 47)	Group L (n = 47)	P Value
Age (years)	54.9 ± 13.7	54.6 ± 13.3	55.1 ± 14.2	.829	54.5 ± 12.7	53.2 ± 14.3	.643
Sex (female) (%)	83 (36.0)	49 (36.3)	34 (36.2)	>.99	19 (40.4)	15 (31.9)	.519
BSA (m^2)	1.71 ± .19	1.69 ± .19	1.74 ± .20	.078	1.71 ± .19	1.73 ± .19	.692
BMI	22.9 ± 3.5	22.4 ± 3.2	23.6 ± 3.8	.<01	22.6 ± 3.1	22.1 ± 3.2	.497
EuroSCORE II (%)	.89 ± .52	.90 ± .56	.87 ± .46	.574	.84 ± .3	.80 ± .4	.559
CAD (>75% stenosis) (%)	0 (0)	0 (0)	0 (0)	>.99	0 (0)	0 (0)	>1.0
ECG finding (sinus rhythm) (%)	227 (98.6)	134 (99.3)	92 (98.7)	.569	46 (97.89)	45 (95.7)	>1.0
Serum creatinine level (mg/dL)	.81 ± .20	.82 ± .21	.81 ± 20	.481	.81 ± .23	.82 ± .22	.881
Hemoglobin level (g/dL)	13.7 ± .1	13.7 ± 1.6	13.9 ± 1.4	.494	13.7 ± 1.4	14.1 ± 1.2	.119
Hypertension (%)	49 (21.4)	29 (21.3)	20 (21.5)	.970	11 (23.4)	10 (21.3)	>1.0
Diabetes (%)	7 (3.0)	3 (2.2)	4 (4.3)	.449	1 (2.1)	3 (6.4)	.617
Chronic obstructive pulmonary disease (%)	13 (5.7)	6 (4.4)	7 (7.5)	.390	3 (6.4)	3 (6.4)	>1.0
NYHA III, IV (%)	7 (3.1)	4 (3.0)	3 (3.2)	>.99	0 (0)	1 (2.1)	>1.0

BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; ECG, electrocardiography; NYHA, New York Heart Association.

Table 2. Perioperative variables.

Variable	All Cases (n = 229)	Unmatched			Matched		
		Group S (n = 135)	Group L (n = 94)	P Value	Group S (n = 47)	Group L (n = 47)	P Value
LVEF (%)	63.8 ± 4.6	63.8 ± 4.5	63.8 ± 4.9	.953	63.6 ± 4.5	64.1 ± 5.2	.635
LAD (mm)	41.7 ± 6.3	41.3 ± 6.2	42.1 ± 6.5	.318	40.8 ± 5.7	40.9 ± 6.6	.905
ERO area (cm^2)	.49 ± .17	.50 ± .15	.47 ± .17	.296	.48 ± .15	.48 ± .17	.932
LVEDD (mm)	52.4 ± 5.9	52.1 ± 5.8	52.9 ± 6.1	.356	52.0 ± 6.7	52.4 ± 6.1	.717
LVESD (mm)	31.5 ± 4.9	31.4 ± 4.7	31.7 ± 5.3	.664	31.6 ± 5.4	31.5 ± 5.3	.954
AR (more than mild) (%)	17 (7.4)	9 (6.7)	8 (8.5)	.617	4 (8.5)	4 (8.5)	1.0
Etiologies of MR							
Degenerative (%)	229 (100.0)	135 (100.0)	94 (100.0)	1.0	47 (100.0)	47 (100.0)	1.0
Functional (%)	0 (.0)	0 (.0)	0 (.0)	1.0	0 (.0)	0 (.0)	1.0
Active endocarditis (%)	1 (.4)	1 (.7)	0 (0)	1.0	0 (.0)	0 (.0)	1.0
Previous endocarditis (%)	10 (4.4)	7 (5.2)	3 (3.2)	.531	2 (4.3)	1 (2.1)	1.0
Dilatation of annulus (%)	2 (.9)	0 (.0)	2 (2.1)	.167	0 (.0)	2 (4.3)	.495
Procedure							
Annuloplasty (%)	227 (99.1)	134 (99.3)	92 (97.9)	.569	47 (100.0)	46 (97.9)	1.0
Neochordae implantation (%)	226 (98.7)	134 (99.3)	92 (97.9)	.569	47 (100.0)	45 (95.7)	.496
Resection (%)	44 (19.2)	10 (7.4)	21 (22.3)	.394	9 (19.1)	11 (23.4)	.801

AR, aortic valve regurgitation; ERO, effective regurgitant orifice; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral valve regurgitation.

adjust for confounding factors, such as age, sex, BSA, LVEF, CPB time, and ACC time between the two groups. After PSM, Groups S and L contained 47 patients each (Figure 1). In addition, linear multivariate analysis was conducted with CPB time, ACC time, and Group L as the adjustment factors to investigate the relationship between the interval between cardioplegia administration and the postoperative CK-MB level.

RESULTS

Preoperative, Perioperative, and Intraoperative Factors

Among the preoperative factors, BMI was significantly higher in Group L (Group S [n = 135] vs. Group L [n = 94]: BMI: 22.4 ± 3.2 vs. 23.6 ± 3.8, $p < .006$). There was no significant difference after PSM (Group S [n = 47] vs. Group L [n = 47]: 22.6 ± 3.1 vs. 22.1 ± 3.2, $p = .497$). There were no significant differences in other preoperative factors or any of the perioperative factors before or after PSM (Tables 1 and 2). CPB and ACC times were significantly longer in Group L than in Group S (CPB time: 123 ± 27 minutes vs. 161 ± 42 minutes, $p < .0001$; ACC time: 89 ± 22 minutes vs. 122 ± 33 minutes, $p < .0001$). After PSM, CPB time (136 ± 29 minutes vs. 136 ± 33 minutes, $p = .902$) and ACC time (103 ± 24 minutes vs. 103 ± 25 minutes, $p = .956$) were not significantly different between the two groups (Table 3).

Primary and Secondary Endpoints

Compared to Group S, the following levels were significantly higher in Group L: the CK-MB level on ICU admission (37.0 ± 20.7 IU/L vs. 53.2 ± 34.2 IU/L, $p < .0001$),

Table 3. Intraoperative factors.

Variable	All Cases (n = 229)	Unmatched			Matched		
		Group S (n = 135)	Group L (n = 94)	P Value	Group S (n = 47)	Group L (n = 47)	P Value
CPB time (min)	138 ± 39	123 ± 27	161 ± 42	<.001	136 ± 29	136 ± 33	.902
ACC time (min)	103 ± 32	89 ± 22	123 ± 33	<.001	103 ± 24	103 ± 25	.956
Femoral artery cannulation (%)	226 (98.2)	134 (98.5)	91 (97.9)	>.99	47 (100)	46 (97.9)	>1.0
Re-ACC (%)	21 (9.1)	9 (6.7)	12 (12.8)	.161	4 (8.5)	4 (8.5)	>1.0
Re-ACC time (min)	33 ± 15	26.8 ± 14.5	37.1 ± 14.6	.122	38 ± 14	31 ± 12	.460
Amount of cardioplegia solution at re-ACC (mL)	1552 ± 635	1289 ± 270	1750 ± 762	.101	1312 ± 409	1625 ± 394	.313
RBC transfusion (%)	13 (5.6)	7 (5.2)	5 (5.3)	>.99	1 (2.1)	2 (4.3)	>1.0
FFP transfusion (%)	9 (3.9)	5 (3.7)	3 (3.2)	>.99	1 (2.1)	1 (2.1)	>1.0
Plt transfusion (%)	2 (.9)	1 (.7)	0 (0)	>.99	0 (0)	0 (0)	>1.0

ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Plt, platelet; RBC, red blood cell.

Table 4. Cardioplegia dosing interval and number of doses.

Variable	All Cases (n = 229)	Unmatched			Matched		
		Group S (n = 135)	Group L (n = 94)	P Value	Group S (n = 47)	Group L (n = 47)	P Value
Maximum interval (min)	56 ± 13	47 ± 8	69 ± 7	<.001	49 ± 8	67 ± 6	<.001
Time from the first dose to second dose (min)	41 ± 12	37 ± 9	47 ± 13	<.001	38 ± 11	47 ± 13	<.01
Average number of cardioplegia doses	2.2 ± .6	2.1 ± .5	2.3 ± .8	.057	2.3 ± .5	1.9 ± .6	<.001
Number of cardioplegia doses							
1 (%)	22 (9.6)	10 (7.4)	12 (12.8)	.254	0 (0)	11 (23.4)	<.001
2 (%)	153 (66.8)	102 (75.6)	51 (54.2)	<.001	34 (72.3)	32 (68.1)	.652
3 (%)	48 (21.0)	22 (16.3)	26 (27.7)	.037	12 (25.5)	3 (6.4)	.021
4 (%)	5 (2.2)	1 (.7)	4 (4.3)	.161	1 (2.1)	1 (2.1)	>1.0
5 (%)	1 (.4)	0 (.0)	1 (1.1)	.410	0 (0)	0 (0)	>1.0
Amount of cardioplegia solution (mL)	2754 ± 744	2708 ± 673	2826 ± 827	.237	2923 ± 708	2474 ± 491	<.001
Timing of the second additional dose							
Threaded prosthetic valve leaflets	194 (93.7)	123 (98.4)	71 (86.6)	<.001	47 (100)	31 (86.1)	.013
Electrical activity in the myocardium	3 (1.5)	2 (1.6)	1 (1.2)	>.99	0 (0)	0 (0)	>1.0

CK level on ICU admission (908 ± 586 IU/L vs. 1479 ± 1067 IU/L, $p < .0001$), CK-MB level on POD 1 (23.7 ± 15.4 IU/L vs. 32.6 ± 22.4 IU/L, $p = .0004$), and CK level on POD 1 (808 ± 368 IU/L vs. 1237 ± 837 IU/L, $p < .0001$). PSM revealed no significant difference between Groups S and L in the CK-MB level after ICU admission (45.8 ± 26.3 IU/L vs. 41.5 ± 27.9 IU/L, $p = .441$) or CK level (1133 ± 567 IU/L vs. 1100 ± 916 IU/L, $p = .837$) (Table 4). Secondary endpoints, including the intubation time (613 ± 344 minutes vs. 722 ± 306 minutes, $p < .0001$) and length of hospital stay (5.1 ± 1.6 days vs. 5.8 ± 2.1 days, $p = .004$), were significantly longer in Group L than in Group S. After PSM, there was no significant difference in any secondary endpoint (Tables 5 and 6).

Cardioplegia Dosing Interval and Number of Doses

The following times were significantly longer in Group L than in Group S: the maximum cardioprotective dosing interval (47 ± 8 minutes vs. 69 ± 7 minutes, $p < .0001$) and time between the first and second doses (37 ± 9 minutes vs. 47 ± 13 minutes, $p < .0001$). After PSM, both times remained longer in Group L than in Group S: the maximum cardioplegia dosing interval (49 ± 8 minutes vs. 67 ± 6 minutes, $p < .0001$) and time between the first and second doses (38 ± 11 minutes vs. 47 ± 13 minutes, $p = .002$). The percentage of patients receiving a single dose was significantly higher in Group L than in Group S (.0% vs. 23.4%, $p = .0004$), and the percentage receiving a third dose was significantly lower in Group L than in Group S (25.5% vs. 6.4%, $p = .021$). The cardioplegia dose was significantly lower in Group L than in Group S (2923 ± 708 mL vs. 2474 ± 491 mL, $p = .0006$). In addition, there was a significant difference in the timing of the second dose (i.e., when the thread was attached to the prosthetic valve leaflet) (Table 4).

Association of Cardioplegia Interval with Postoperative CK-MB

The multivariable analysis showed that a cardioplegia interval of ≥60 minutes was not significantly associated with the maximum CK-MB level after admission to the ICU on the day of surgery ($p = .354$; 95% confidence interval [CI]: −1.67 to 4.65). In addition, there was no significant association with the maximum CK-MB level on POD 1 ($p = .260$; 95% CI: −1.01 to 3.73). However, the CPB time, which was included in the multivariate model as an adjustment factor, was significantly associated with the maximum CK-MB level after admission to the ICU on the day of surgery ($p < .001$; 95% CI: .39–.93) and maximum CK-MB level on POD 1 ($p < .001$; 95% CI: .17–.58) (Table 7).

Table 5. Primary endpoints.

Variable	All Cases (n = 229)	Unmatched			Matched		
		Group S (n = 135)	Group L (n = 94)	P Value	Group S (n = 47)	Group L (n = 47)	P Value
CK-MB level on ICU admission (IU/L)	43.9 ± 28.2	37.0 ± 20.7	53.2 ± 34.2	<.001	45.8 ± 26.3	41.5 ± 27.9	.441
CK level at on ICU admission (IU/L)	1142 ± 862	908 ± 586	1479 ± 1067	<.001	1133 ± 567	1,100 ± 916	.837
CK-MB level on POD 1 (IU/L)	27.5 ± 19.1	23.7 ± 15.4	32.6 ± 22.4	<.001	28.3 ± 21.3	24.7 ± 16.4	.363
CK level on POD 1 (IU/L)	985 ± 639	808 ± 368	1237 ± 837	<.001	944 ± 399	930 ± 577	.895

CK, creatine kinase; ICU, intensive care unit; POD, postoperative day.

Table 6. Secondary endpoints.

Variable	All Cases (n = 229)	Unmatched			Matched		
		Group S (n = 135)	Group L (n = 94)	P Value	Group S (n = 47)	Group L (n = 47)	P Value
Use of a defibrillator (%)	44 (19.1)	26 (19.3)	18 (19.1)	.983	7 (14.9)	10 (21.2)	.593
Use of an inotropic drug (%)	95 (41.3)	52 (38.5)	43 (45.7)	.279	23 (48.9)	15 (31.9)	.091
Dobutamine (%)	82 (35.6)	46 (34.1)	36 (38.3)	.575	21 (44.7)	12 (25.5)	.051
Noradrenaline (%)	33 (14.3)	14 (10.3)	19 (20.2)	.054	6 (12.7)	4 (8.5)	.740
Adrenaline (%)	1 (.4)	0 (0)	1 (1.1)	.410	0 (0)	1 (2.1)	1.0
Milrinone (%)	0 (0)	0 (0)	0 (0)	>1.0	0 (0)	0 (0)	1.0
LVEF at discharge (%)	53.1 ± 8.7	52.2 ± 9.7	54.3 ± 6.9	.065	50.9 ± 11.0	54.2 ± 6.7	.085
Intubation time (min)	667 ± 356	613 ± 344	722 ± 306	<.001	662 ± 313	618 ± 246	.450
ECG findings at discharge (sinus rhythm) (%)	209 (90.8)	124 (91.9)	84 (89.3)	.523	42 (89.3)	44 (93.6)	.714
Postoperative AKI (%)	19 (8.2)	7 (5.2)	11 (11.7)	.083	3 (6.4)	3 (6.4)	>1.0
30-day mortality (%)	0 (0)	0 (0)	0 (0)	>1.0	0 (0)	0 (0)	>1.0
Myocardial infarction (%)	0 (0)	0 (0)	0 (0)	>1.0	0 (0)	0 (0)	>1.0
ICU stay (day)	1.1 ± .4	1.1 ± .4	1.1 ± .4	.778	1.1 ± .6	1.1 ± .4	.690
Hospital stay (day)	5.4 ± 2.0	5.1 ± 1.6	5.8 ± 2.1	<.01	5.3 ± 2.2	5.5 ± 1.5	.516

AKI, acute kidney injury; ECG, electrocardiogram; ICU, intensive care unit; LVEF, left ventricular ejection fraction.

DISCUSSION

In this study, we evaluated the impact of cardioplegia intervals on myocardial protection in MICS-MVP. We observed no differences in myoprotective markers between the short- and long-interval dose methods using the modified St. Thomas solution. A single-dose method using del Nido, histamine-tryptophan-ketoglutarate, and Bretschneider solutions can prolong the interval between cardioprotective doses and reduce the number of doses (6–9). A meta-analysis comparing single and multiple doses found that a single dose of del Nido particularly reduced the CPB and ACC times by simplifying myocardial protection management and significantly reduced CK-MB and defibrillator use (9). However, animal studies have shown that a single dose increases the myocardial temperature because of the presence of noncoronary collateral blood vessels at longer administration intervals, thereby increasing oxygen consumption and consequently decreasing myocardial protection, and that cardiac contractility after declamping was significantly lower at an ACC time of 120 minutes than at 90 minutes (10,11). To what extent the single-dose cardioplegia administration interval can be safely extended is unclear. In addition, studies showing that a single dose is effective in MICS reported an ACC time as short as 90 minutes (6,8). CPB and ACC times tended to be longer in MICS compared to median sternotomy due to adverse visual field conditions and narrow working space (12). Therefore, to safely perform myocardial protection during long ACC, additional doses should be considered.

A few studies of single-dose St. Thomas solution exist. Mork et al. (13) compared the myocardial protective effect of single-dose St. Thomas solution and Bretschneider solution in minimally invasive mitral valve surgery and found that the postoperative myocardial protective effect was similar between these; however, the postoperative troponin T level was significantly lower in the St. Thomas group. Hiraoka et al. (14) reported that the postoperative CK-MB level was significantly lower in the St. Thomas group when comparing glucose-insulin-potassium and St. Thomas solutions with an interval of approximately 40 minutes and 60 minutes, respectively, in isolated aortic valve replacement. These findings suggest that a long interval dose can be safely administered using the St. Thomas solution.

In this study, the mean number of doses of myocardial protection was 2.2 ± .6. Among our patients, 9.6% received a single dose, and 93.7% of the patients received the second dose while the annular sutures were passed through the prosthetic ring, while 1.5% received them when electrical activity on the electrocardiogram was observed. These findings indicate that additional cardioplegia was administered without interfering with the ongoing operative procedures in most cases.

Table 7. Results of the linear multivariate analysis.

Variable	Standard error	P Value	95% CI	Standard β	VIF
CK-MB level at ICU admission					
CPB time	.136	<.001	.39–.93	.904	15.3
ACC time	.170	.305	−.51–.16	−.197	16.1
Group L	1.597	.354	−1.67–4.65	.052	1.4
CK-MB level at POD 1					
CPB time	.102	<.001	.17–.58	.759	15.3
ACC time	.127	.551	−.32–.17	−.126	16.1
Group L	1.204	.260	−1.01–3.73	.070	1.4

ACC, aortic cross-clamp; CI, confidence interval; CK, creatine kinase; CPB, cardiopulmonary bypass; POD, postoperative day; VIF, variance inflation factor.

The CPB and ACC times were longer in Group L than in Group S, but there was no significant difference after PSM, the number of cardioplegia doses was smaller in Group L, and the total amount of cardioplegia administered was significantly smaller in Group L than in Group S. These findings may be attributable to the surgeon's decision to avoid additional cardioplegia when the procedure was expected to be completed shortly at 60 minutes after administering the first dose (the mean time from cardioplegia administration to aortic declamping for patients in Group L who received only a single dose after PSM was 67 ± 6 minutes). The largest confounders in the association between the cardioplegia dosing interval and myocardial protection effect were the CPB and ACC times. We adjusted for both factors with PSM. This study yielded no findings suggesting an association between the cardioprotective dosing interval and postoperative CK-MB or CK level upon group comparison or multivariate analysis after PSM. In addition, no significant differences existed in the secondary parameters in the post-PSM comparison.

These results suggested that, in isolated MICS-MVP, the myocardial protection method using the antegrade modified St. Thomas solution, wherein the cardioplegia administration interval is primarily determined based on the progress of surgery, may not reduce the myocardial protection effect, even if the cardioplegia administration interval is ≥60 minutes. However, as mentioned previously, to what extent the myocardial protection administration interval can be safely extended is unclear. In addition, quantitative monitoring of myocardial damage during cardiac arrest is not possible; therefore, the administration interval should be extended with caution.

The study limitations include incomplete bias adjustment because of the retrospective observational nature of the study. In addition, the generalizability of the study findings is limited by the fact that the data analyzed were from only two centers and the study was limited to isolated MVP. Therefore, further large-scale observational studies and randomized trials are needed in the future.

In conclusion, the long interval dose method using the antegrade modified St. Thomas solution is useful and safe in MICS-MVP. In isolated minimally invasive MVP, the long interval dose method can be safely used with a maximum dosing interval of approximately 60 minutes and the modified St. Thomas solution.

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