Korean J Thorac Cardiovasc Surg 2013;46:256-264 □ Clinical Research □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) http://dx.doi.org/10.5090/kjtcs.2013.46.4.256

Single and Multiple Valve Surgery in Native Valve Infective Endocarditis

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Background: Surgical treatment of infective endocarditis (IE) remains a challenge, especially in cases of multiple valve surgery. We evaluated the clinical outcomes of native valve IE and compared the outcomes of single valve surgery with those of multiple valve surgery. ***Materials and Methods:*** From 1997 to 2011, 90 patients underwent surgery for native valve IE; 67 patients with single valve surgery (single valve group) and 23 patients with multiple valve surgery (multiple valve group). The mean follow-up duration was 73.1±47.4 months. ***Results:*** The surgical mortality in the total cohort was 4.4%. The overall survival (p=0.913) and valve-related event-free survival (p=0.204) did not differ between the two groups. The independent predictor of postoperative complications was New York Heart Association class (p=0.001). Multiple valve surgery was not a significant predictor of surgical mortality (p=0.225) or late mortality (p=0.936). Uncontrolled infection, urgent or emergency surgery, and postoperative complications were identified as independent predictors of valve-related morbidity, excluding multiple valve surgery (p=0.072). ***Conclusion:*** In native valve IE, multiple valve surgery as a factor was not an independent predictor of mortality and morbidity. The number of surgically corrected valves in native IE seems to be unrelated to perioperative and long-term outcomes.

Key words: 1. Endocarditis
2. Heart valves
3. Thoracic surgery
4. Mortality
5. Morbidity

INTRODUCTION

The incidence of surgical treatment of infective endocarditis (IE) has markedly increased, and the rate of surgical treatment for multiple valve involvement is approximately 70% [1]. Multiple valve IE often has more severe hemodynamic deterioration and extensive tissue destruction, and may need more complex surgical therapy [2].

Many authors have reported on the surgical outcomes of multiple valve IE [3-11]. In their studies, however, prosthetic valve endocarditis was included with native valve endocarditis. Prosthetic valve endocarditis differs from native valve endocarditis in that it has a more difficult diagnosis and surgical strategy, and worse prognosis [12]. Only a few studies have

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†This manuscript was presented at the 44th Annual meeting of Korean Society for Thoracic and Cardiovascular Surgery, and was awarded the research grant of Woochon Park Young Gwan Academic Awards in 2012.
Received: November 16, 2012, Revised: February 5, 2013, Accepted: March 7, 2013
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specifically focused on surgical therapy for multiple native valve IE [4,10,11]. We reviewed the surgical outcomes of native valve IE, and compared single valve surgery with multiple valve surgery during the past 15 years in Sejong General Hospital.

MATERIALS AND METHODS

1) Preoperative patient characteristics

Our study included patients who were operated on from 1997 to 2011 in Sejong General Hospital. Ninety patients underwent valve surgery due to native valve IE with concomitant procedures. The preoperative variables are depicted in Table 1, comparing the single valve IE group (the single valve group, n=67) with the multiple valve IE group (the multiple valve group, n=23). Seventeen patients had underlying congenital heart disease (CHD), including ventricular septal defect (VSD), atrial septal defect (ASD), patent foramen ovale (PFO), and patent ductus arteriosus (PDA), excluding congenital biscupid aortic valve. Blood culture results were available in 77 patients (85.6%; 55 in the single valve group, 22 in the multiple valve group) due to the loss of several old laboratory results during the setup of electronic medical records in our center. Forty-nine patients were determined to be culture-positive, and 28 culture-negative. The most common microorganism was *Streptococcus viridans*. In this study, 13 patients (14.4%) of a total of 90 patients had no report of culture results, but they met the clinical or pathologic criteria of the modified Duke criteria [13]. Three patients (3.3%) of the total of 90 patients had multiple microorganisms. Preoperative complete atrioventricular block was found in 2 patients, both in the multiple valve group. There were no statistically significant differences in preoperative patient characteristics between the single valve group and multiple valve group. The study was reviewed and approved by the institutional review board of Sejong General Hospital. Individual patient consent was waived.

Table 1. Preoperative patient's characteristics

Characteristic	Single valve group (n=67)	Multiple valve group (n=23)	p-value
Age	47.58±16.61	47.52±13.52	0.987
Female	21 (31.3)	3 (13.0)	0.106
NYHA class	2.58±0.91	2.65±1.07	0.761
Hypertension	11 (16.4)	2 (8.7)	0.502
Diabetes mellitus	10 (14.9)	4 (17.4)	0.748
Cerebrovascular accident	10 (14.9)	5 (21.7)	0.520
Atrial fibrillation	9 (13.4)	2 (8.7)	0.722
Coronary artery lesion	5 (7.5)	3 (13.0)	0.416
Renal insufficiency	6 (9.0)	1 (4.3)	0.673
Congenital heart disease	10 (14.9)	7 (30.4)	0.126
LVEF	61.35±11.53	61.13±10.72	0.937
EF less than 50%	9 (13.6)	4 (18.2)	0.729
Recurred IE	3 (4.5)	1 (4.3)	1.000
Active phase	40 (59.7)	15 (65.2)	0.805
Microorganism[a)]	32 (58.2)	17 (77.3)	0.189
Streptococcus viridians	16 (50.0)	12 (70.6)	0.229
Gram-negative bacilli	2 (6.3)	3 (17.6)	0.326
Enterococci	3 (9.4)	1 (5.9)	1.000
Staphylococcus aureus	4 (12.5)	0 (0.0)	0.284
Culture-negative[b)]	23 (41.8)	5 (22.7)	0.189

Values are presented as mean±standard deviation or number (%). NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; IE, infective endocarditis.
[a)]Of 32 in the single valve group, of 17 in the multiple valve group.
[b)]Of 55 in the single valve group, of 22 in the multiple valve group.

2) Definition

The diagnosis of IE was made according to the modified Duke criteria [13]. We excluded suspected IE evidence such as vegetation-like materials, perforation, or other intraoperative findings without any medical evidence. Intracardiac device-related IE such as with a transvenous permanent pacemaker was also ruled out in all of the cases.

Endocarditis was diagnosed as active when one or more of the following was confirmed: (1) surgery necessary prior to the completion of the standard course of antibiotic therapy. The duration of therapy was variable and dependent on the causative microorganism, averaging 4 to 6 weeks; (2) uncontrolled infection signs even after completion of antibiotic therapy; (3) microorganism confirmed by surgical tissue culture; (4) evidence of microscopically severe acute inflammation in surgical tissue biopsy. Endocarditis was defined as healed if the surgery was performed after the completion of antibiotic treatment.

Uncontrolled infection encompassed persistent fever over a 7-day period of antibiotic therapy or growing vegetation dur-

ing appropriate antibiotic therapy. Perivalvular extension was defined as infection extended to the aortic sinus, aortomitral intervalvular fibrosa, or intracardiac chamber. Large vegetation was defined as vegetation with a largest diameter of 10 mm and more in the echocardiographic or operative findings.

Culture-negative endocarditis was defined as endocarditis in which no microorganism could be identified either on serial blood culture or in cultures made from the explanted valvular tissue of patients presenting with the clinical picture of endocarditis.

We included patients undergoing multiple valve surgery with two or more infected valves. For example, when double valve replacement was performed in one infected valve and another non-infected valve, the patient was classified into the single valve group with a concomitant valve procedure. Root replacement was classified into the single valve group. A procedure was defined as emergency if the operation was performed within 24 hours after the decision to operate; urgent when it was performed within several days after the decision to operate but outside the elective surgical schedule due to any worsening situation such as enlarged vegetation on follow-up echocardiography during antibiotic therapy; and elective when the scheduled operation was performed after complete antibiotic therapy. We defined the replacement group as having at least one replacement in multiple valve surgery, and the repair group as only repair procedures in the valve surgery regardless of the number of operated valves. Valve repair included vegetation removal in the infected valvular structure. Aortic root replacement, abscess cavity exclusion with bovine pericardium, sinus repair due to pseudoaneurysm or rupture, and reconstruction of the aortomitral intervalvular fibrous body were defined as perivalvular reconstruction.

3) Indication of surgery

The surgical indications were one or more of the following factors as described in Table 2: heart failure in 40 patients (44.4%), severe valve regurgitation in 27 patients (30%), uncontrolled infection in 23 patients (25.6%), abscess in 10 patients (11.1%), embolism in 23 patients (25.6%), large vegetation in 38 patients (42.2%), and mobile vegetation in 40 patients (44.4%). The multiple valve group had a higher incidence of mobile vegetation than the single valve group (p=0.028). Although without statistical significance, severe valve regurgitation was found much more in the single valve group than the multiple valve group (p=0.063).

Table 2. Surgical indication

Variable	Single valve group (n=67)	Multiple valve group (n=23)	p-value
Heart failure	29 (43.3)	11 (47.8)	0.809
Severe valve regurgitation	24 (35.8)	3 (13.0)	0.063
Uncontrolled infection	17 (25.3)	6 (26.1)	1.000
Abscess	7 (10.4)	3 (13.0)	0.712
Embolism	18 (26.9)	5 (21.7)	0.784
Large vegetation	29 (43.3)	7 (30.4)	0.330
Mobile vegetation	25 (37.3)	15 (65.2)	0.028

Values are presented as number (%).

4) Surgery

The most common procedure was mitral valve replacement (21 patients, 31.3%) in the single valve group, and aortic valve and mitral valve replacement (11 patients, 47.8%) in the multiple valve group. Valve replacement was performed more in the multiple valve group (91.3%) than the single valve group (73.1%) (p=0.086), but the difference was not statistically significant. On the other hand, the valve repair procedure was done more in the single valve group (26.9%) than the multiple valve group (8.7%) (p=0.086). Perivalvular reconstruction included aortic root replacement (n=8; 7 patients [6 homograft, 1 mechanical composite graft] in the single valve group, 1 patient [1 homograft] in the multiple valve group), aortomitral intervalvular fibrous body reconstruction (n=3; all in the multivalve group), sinus repair due to pseudoaneurysm or rupture (n=3; 2 in the single valve group, 1 in the multiple valve group), and abscess exclusion with bovine pericardium (n=4; 2 in the single valve group, 2 in the multiple valve group).

Concomitant valve procedures were performed in 19 patients (21.1%; 16 in the single valve group, 3 in the multiple valve group; p=0.379). Other concomitant cardiac procedures were performed in 28 patients (31.1%; 21 in the single valve group, 7 in the multiple valve group; p=1.000) including the following: ascending aorta replacement, reduction aortoplasty, VSD or ASD or PFO closure, repair of Valsalva sinus rupture, coronary artery bypass graft, maze procedure, PDA divi-

Table 3. Operative data

Variable	Single valve group (n=67)	Multiple valve group (n=23)	p-value
Procedures			
AVR, MVR	-	11 (47.8)	
AVR, MVP	-	3 (13.0)	
AVP, MVR	-	1 (4.3)	
AVP, MVP	-	2 (8.7)	
AVR, MVP, TVP	-	1 (4.3)	
AVR	19 (28.4)	-	
AVP	1 (1.5)	-	
MVR	21 (31.3)	-	
MVP	15 (22.4)	-	
Others[a)]	4 (6.0)	4 (17.4)	
Root replacement	7 (10.4)	1 (4.3)	0.674
Perivalvular reconstruction	11 (16.4)	7 (30.4)	0.225
Valve replacement	49 (73.1)	21 (91.3)	0.086
Mechanical valve	24 (35.8)	12 (52.2)	0.219
Tissue valve	25 (37.3)	9 (39.1)	1.000
Valve repair	18 (26.9)	2 (8.7)	0.086
Perivalvular extension	19 (28.4)	9 (39.1)	0.434
Right side involvement	4 (6.0)	5 (21.7)	0.044
Concomitant valve procedure	16 (23.9)	3 (13.0)	0.379
Concomitant other procedure	21 (31.3)	7 (30.4)	1.000
CPB time	153.87±63.20	196.00±61.18	0.007
ACC time	111.25±39.60	153.96±49.62	<0.000
2nd CPB	5 (7.5)	2 (8.7)	1.000
Urgency or emergency	26 (38.8)	9 (39.1)	1.000
Urgency	21 (31.3)	4 (17.4)	0.282
Emergency	5 (7.5)	5 (21.7)	0.073
Operative death	4 (6.0)	0 (0.0)	0.569

Values are presented as number (%) or mean±standard deviation.

AVR, aortic valve replacement; MVR, mitral valve replacement; MVP, mitral valvuloplasty; AVP, aortic valvuloplasty; CPB, cardiopulmonary bypass; ACC, aortic cross-clamping.

[a)]Tricuspid valve replacement (TVR), tricuspid valvuloplasty (TVP), pulmonary valve replacement (PVR), pulmonary valvuloplasty (PVP) each in the single valve group, MVR and TVP, AVP and PVR, AVR and PVP, AVR and TVR each in the multiple valve group.

sion, and removal of intracoronary vegetation after coronary arteriotomy. The rate of right heart involvement of IE was significantly higher in the multiple valve group than in the single valve group (p=0.044). Bilateral infection was found in 5 patients. Cardiopulmonary bypass (CPB) time (p=0.007) and aortic cross-clamping (ACC) time (p<0.000) were longer in the multiple valve group than the single valve group. Deep hypothermic circulatory arrest was used in only one patient for the division and repair of PDA. Further surgical data are outlined in Table 3.

5) Follow-up

Clinical follow-up data were collected from the database and retrospective review of medical records. Follow-up information was also obtained by means of telephone interviews with the patient or the patient's relatives. The date of last inquiry was between July and September 2012. The mean follow-up durations of the 86 hospital survivors were 71.5±46.9 and 77.8±49.3 months in the single valve group and the multiple valve group, respectively (p=0.583), and 96.5% (n=83) of the hospital survivors had complete follow-up. Among all of the 86 hospital survivors, the mean follow-up duration was 73.1±47.4 months (median [interquartile range], 71.0 [35.0, 112.2]).

The definition of complications followed the "Guidelines for reporting morbidity and mortality after cardiac valvular operations" [14]. Operative mortality was defined as death occurring during hospitalization or within 30 days of the operation. Follow-up duration for the overall survival was measured from the date of the surgery to the date of death, or of last contact alive, and for the event-free survival, from the date of the surgery to the date of the first event or last contact alive.

6) Statistical analysis

Descriptive statistics were presented as the mean±standard deviation for continuous variables, and number and percentage for categorical variables. The differences between continuous variables were tested using the Student's t-test. The differences between categorical variables were tested using Fisher's exact test. Results with p values of less than 0.05 were considered statistically significant. In a univariable analysis, variables related to the patient's characteristics, operation, and postoperative morbidities were screened by logistic regression analysis. Variables significant by univariable analysis (p-values of less than 0.05 in mortality and postoperative complications, less than 0.25 in late morbidity) were consid-

Table 4. Predictors of operative mortality in the total population (n=90) and late mortality in the hospital survivors (n=86)

	Operative mortality[a)]		Late mortality[a)]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Diabetes mellitus	-		225.525 (1.341-37,932.955)	0.038
Atrial fibrillation	8.556 (1.071-68.347)	0.043	-	
Renal insufficiency	61.500 (5.172-731.246)	0.001	-	
Left ventricular ejection fraction	1.162 (1.004-1.345)	0.044	0.757 (0.580-0.989)	0.042
Concomitant valve procedure	13.125 (1.280-134.551)	0.030	-	
Cardiopulmonary bypass time	1.011 (1.001-1.022)	0.036	-	
Second cardiopulmonary bypass	16.200 (1.872-140.199)	0.011	-	
Multiple valve surgery	4.167 (0.416-41.699)	0.225	0.909 (0.090-9.207)	0.936

OR, odds ratio; CI, confidence interval.
[a)]Operative mortality in univariable logistic regression analysis ($p < 0.05$), late mortality in multivariable logistic regression analysis ($p < 0.05$), mitral valve surgery in univariablelogistic regression analysis in operative and late mortality.

ered in the multivariable analysis, and the results with p values of less than 0.05 were considered statistically significant in a multivariable analysis. Subsequent stepwise logistic regression analysis (backwards method) was performed to identify the potential risk factors of mortality and morbidity. Long-term survival and event-free survival were analyzed with the Kaplan-Meier method and compared with the log-rank test. The SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

The following variables were analyzed as independent factors affecting the dependent variables: sex, age, New York Heart Association (NYHA) functional class, hypertension, diabetes mellitus (DM), cerebrovascular accident, atrial fibrillation, coronary artery disease (>50% stenotic lesion), renal insufficiency, underlying CHD, left ventricle ejection fraction, culture-negative result, recurred IE, phase, perivalvular involvement of infection, primary surgical indication (heart failure, severe valvular regurgitation, uncontrolled infection, abscess, embolism, large vegetation, mobile vegetation), multiple valve surgery, perivalvular reconstruction, valve replacement, implanted mechanical valve, implanted tissue valve, valve repair, right heart involvement, bilateral heart involvement, concomitant valve procedure, other concomitant cardiac procedure, CPB time, ACC time, second CPB, urgent or emergency operation, postoperative complications, and valve-related morbidity (embolism, valve thrombosis, bleeding event, recurrence of IE, reoperation, structural valve deterioration, or nonstructural valve dysfunction).

RESULTS

1) Operative outcomes

The operative mortality was 4.4% (4 patients) in the total cohort (n=90). They were all in the single valve group (6.0%, of 67). The causes of early death were heart failure (n=1), renal failure (n=1), intracranial hemorrhage (n=1), and sepsis (n=1).

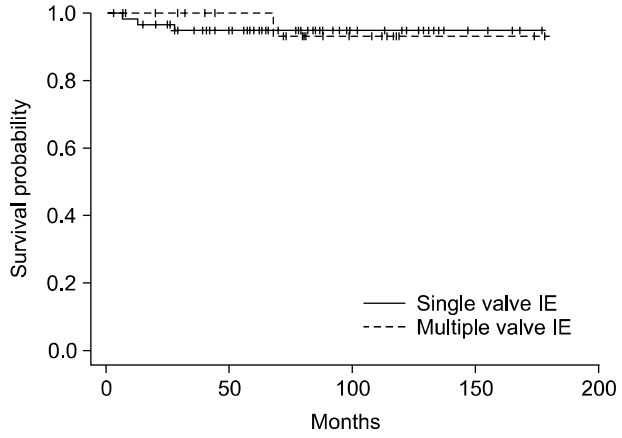
Univariable logistic regression analysis yielded the following risk factors of operative mortality in the total population: hypertension (odds ratio [OR], 6.818; p=0.068), atrial fibrillation (OR, 8.556; p=0.043), renal insufficiency (OR, 61.5000; p=0.001), left ventricular ejection fraction (OR, 1.162; p=0.044), concomitant valve procedure (OR, 13.125; p=0.030), CPB time (OR, 1.011; p=0.036), and second CPB (OR, 16.2000; p=0.011) (Table 4). Multiple valve surgery for multiple infected lesions was not included in predictors of operative mortality in the univariable analysis (OR, 4.167; p=0.225). In multivariable analysis, no predictors could be identified.

The incidence of postoperative early complications did not differ between the single valve group (n=26, 38.8%) and the multiple valve group (n=12, 52.2%) (p=0.330). Early complications included postoperative re-sternotomy for bleeding control (n=4 in the single valve group, n=1 in the multiple valve group), pericardial effusion requiring drainage (n=2, n=4), left ventricular dysfunction (ejection fraction lower than 40%; n=11, n=4), arrhythmia requiring intervention (n=3, n=4),

Table 5. Long-term results of the hospital survivors (n=86)

Variable	Single valve group (n=63)	Multiple valve group (n=23)	p-value[a)]
Late death	3 (4.8)	1 (4.3)	1.000
Valve-related morbidity	14 (22.2)	2 (8.7)	0.216
Embolism	4 (6.3)	1 (4.3)	1.000
Valve thrombosis	2 (3.2)	0 (0.0)	1.000
Bleeding event	6 (9.5)	0 (0.0)	0.186
Recurrence	2 (3.2)	1 (4.3)	1.000
Reoperation	3 (4.8)	2 (8.7)	0.607
Structural deterioration	2 (3.2)	0 (0.0)	1.000
Nonstructural valve dysfunction	1 (1.6)	1 (4.3)	0.466

Values are presented as number (%).
[a)]Fisher's exact test.



Actual numbers of survival patients

	0	50	100	150
Single valve group	63	41	17	4
Multiple valve group	23	23	8	2

Fig. 1. The actuarial rate of the overall survival in the single valve and multiple valve groups (log rank, p=0.913).

pneumonia (n=4, n=1), renal insufficiency (n=6, n=2), wound infection (n=1, n=1), intracranial hemorrhage (n=1, n=2), and other (n=3, n=1, respectively).

The risk factor of postoperative early complications was determined to be NYHA functional class (OR, 2.399; 95% confidence interval [CI], 1.420 to 4.052; p=0.001) after multivariable logistic regression analysis. Multiple valve surgery for multiple infected lesions was not a significant predictor of postoperative complications in univariable logistic regression analysis (OR, 1.720; p=0.236).

Table 6. Predictors of valve-related morbidity in hospital survivors (n=86)

Variable	Odds ratio (95% confidence interval)	p-value[a)]
Uncontrolled infection	6.057 (1.458–25.164)	0.013
Urgency or emergency	5.189 (1.149–23.433)	0.032
Postoperative complication	4.249 (1.111–16.248)	0.035
Multiple valve surgery	5.456 (0.861–34.578)	0.072

[a)]In multivariable logistic regression analysis ($p < 0.05$).

2) Long-term mortality

There have been four late deaths (4.7%, of 86 hospital survivors) during the follow-up period; three in the single valve group and one in the multiple valve group (Table 5). There were two valve-related and two non-valve-related deaths. The causes of the valve-related deaths were unknown (n=2, both in the single valve group). There were two non-valve-related deaths, from malignancy (n=1, in the multiple valve group) and pneumonia (n=1, in the single valve group).

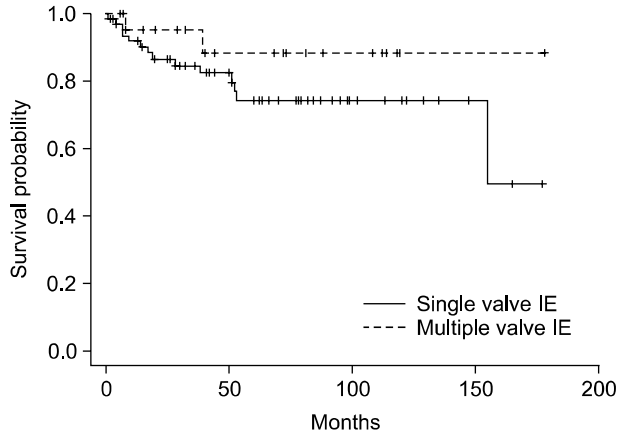
The actuarial rates of the overall survival at 1, 5, and 10 years were 98.4%±1.6%, 95.0%±2.8%, and 95.0%±2.8% in the single valve group, and 100%±0.0%, 100%±0.0%, and 93.3%±6.4% in the multiple valve group, respectively (p=0.913) (Fig. 1). In the total population, the risk factors of late death of hospital survivors were DM (OR, 225.525; p=0.038) and left ventricular ejection fraction (OR, 0.757; p=0.042) from the multivariable logistic regression analysis. Multiple valve surgery for multiple infected lesions was not a significant predictor of late mortality in univariable logistic regression analysis (OR, 0.909; p=0.936).

3) Long-term morbidity

In the total population, multivariable logistic regression analysis identified the following factors to be independent predictors of valve-related morbidity: uncontrolled infection (OR, 6.057; p=0.013), urgent or emergency operation (OR, 5.189; p=0.032), and postoperative complications (OR, 4.249; p=0.035) (Table 6). Multiple valve surgery was not a significant predictor of valve-related morbidity (OR, 5.456; p=0.072).

The actuarial valve-related event-free survival rates at 1, 2, and 5 years were 91.8%±3.5%, 86.4%±4.5%, and 74.2%±6.4% in the single valve group, and 95.2%±4.6%, 95.2%±4.6%, and 88.4%±7.8% in the multiple valve group, respectively (p=0.204) (Fig. 2).

There were no significant differences in the valve-related morbidity between the two groups (Table 5). In the single valve group, multivariable logistic regression analysis identified the following factors to be independent predictors of valve-related morbidity: hypertension (OR, 13.063; p=0.0142), CHD (OR, 22.189; p=0.01136), recurred IE (OR, 36.550; p=0.0324), and mechanical valve (OR, 7.8063; p=0.0363) (Table 7). In the multiple valve group, univariable logistic regression analysis identified atrial fibrillation (OR, 20; p=0.0862) and abscess (OR, 9.5; p=0.1588) as significant risk factors for valve-related morbidity (Table 7). In multivariable analysis, no predictors could be identified.



Actual numbers of survival patients

	0	50	100	150
Single valve group	63	35	14	3
Multiple valve group	23	12	7	2

Fig. 2. The actuarial valve-related event-free survival in the single valve and multiple valve groups (log rank, p=0.204).

DISCUSSION

This study demonstrated no difference in late valve-related morbidity between single valve surgery and multiple valve surgery for native valve IE over a long-term period (p=0.216) (Table 5). In addition, significant risk factors of valve-related morbidity in our total cohort did not include multiple valve surgery (p=0.072) after multivariable logistic regression analysis (Table 6). Long-term outcomes in multivalvular surgery for IE were reported to have relatively satisfactory morbidity [3,4]. In these studies, however, meaningful comparison with single valve surgery was not conducted. Recently, Ota et al. [11] reported their experiences with surgical treatment of native valve IE (152 patients; 117 single valve and 35 multivalve). The late valve-related morbidity (reoperation and recurrence) in the multivalve group was not significantly different from that in the single valve group [11]. Their result is in agreement with our statistical analysis.

Next, to assess the risk factors of valve-related morbidity in the multiple valve group, a series of statistical analyses was performed. Because the number of events for statistical analysis in the multiple valve group was only two, univariable logistic regression analysis could be carried out using

Table 7. Predictors of valve-related morbidity in each group

Variable	Single valve group[a)]		Multiple valve group[a)]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Hypertension	13.063 (1.672-102.058)	0.0142		
Atrial fibrillation			20 (0.652-613.182)	0.0862
Congenital heart disease	22.189 (2.0128-244.609)	0.01136		
Recurred infective endocarditis	36.550 (1.35617-988.2708)	0.0324		
Abscess			9.5 (0.4147-217.6129)	0.1588
Mechanical valve	7.8063 (1.1396-53.4704)	0.0363		

OR, odds ratio; CI, confidence interval.
[a)]Single valve group in multivariable logistic regression analysis ($p < 0.05$), multiple valve group in univariable logistic regression analysis ($p < 0.25$).

p-values of less than 0.25. Despite this rough analysis, only two factors were determined to be significant: preoperative atrial fibrillation (OR, 20, p=0.086) and abscess (OR, 9.5; p=0.158). Sheikh and colleagues noted that paravalvular abscess was not associated with valve-related morbidity such as late recurrent endocarditis or reoperation in their experience of double valve surgery [9]. However, that study included a portion of cases of prosthetic valve endocarditis (36%). Other studies were not able to determine any risk factors for valve-related morbidity in native double-valve IE [4]. Difficulty in assessing the predictors of late morbidity in multiple valve surgery for native valve IE seems to be associated with the relatively small population and complex disease entity of multiple valve IE.

There were four operative deaths (4.4%) in our cohort (n=90). By chance, the single valve group contained all of them. The risk factors of operative and late mortality in the total population were estimated using a logistic regression analysis. Similar to the risk factor determination of valve-related morbidity, multiple valve surgery as a variable of statistical analysis was not a significant independent predictor associated with operative mortality after univariable logistic regression analysis in the total population (p=0.225) (Table 4). Multiple valve involvement of IE was not an independent prognostic factor of in-hospital mortality in a large cohort of patients hospitalized for IE [15]. In a surgical experience, multivalve endocarditis was not an independent predictor of early mortality, but postoperative dialysis was the only significant risk factor associated with the in-hospital mortality [11].

In our study, multiple valve surgery for multiple infected lesions was not a significant predictor of late mortality in univariable logistic regression analysis (OR, 0.909; CI, 0.090 to 9.207; p=0.936). Similarly, Ota et al. [11] identified in their recent experience that multivalve endocarditis was not an independent predictor of late mortality.

In our cohort, the preoperative clinical data of patients in the multiple valve group did not significantly differ from those in the single valve group (Table 1). In addition, preoperative heart failure, uncontrolled infection, abscess, and embolic event among the surgical indications in our study did not differ between the two groups, which is similar to the reports of others [1,2,16]. In these other reports, however, patients with multivalvular IE presented a higher frequency of heart failure than those with single valve IE.

Streptococcus viridans was the most common microorganism of the multiple valve group (70.6%) in our population, which was consistent with the previous reports of surgical experience [5,10,11]. Surprisingly, the most common etiologic microorganism was *Staphyloccocus aureus* in the other report of surgical experience of multiple valve IE [9].

The clinical features and therapeutic options of right-sided IE may differ from those of left-sided IE [7]. In this study, however, the right heart involvement and bilateral heart involvement as a risk factor were not significant predictors of mortality and morbidity in univariable logistic regression analysis.

In general, surgical valve procedures depend on the extent of tissue destruction in patients with multivalvular pathology. Where infection is limited to the valve leaflets, a repair technique can be performed. Where infection extends to or beyond the annulus, radical debridement of all infected tissue and any reconstruction with valve replacement forms the cornerstone of surgical management [9]. There was a tendency toward a higher rate of valve replacement in the multiple valve group than that of the single valve group (p=0.086). However, perivalvular extension of IE did not differ between the two groups (28.4% in the single valve group, 39.1% in the multiple valve group; p=0.434). Because the exact conditions of the valve leaflets could not be examined in our study, we did not find any reason for this tendency.

Our study has some limitations that are inherent to a retrospective review. Observational data do not provide causal evidence. The valve-related morbidity cannot be accurately estimated in this series because three patients (3.5%) of 86 hospital survivors were lost to follow-up as of the date of last inquiry. The estimation of the odds ratio, with regard to valve-related morbidity (n=2) in the multiple valve group, could not be possible in multivariable logistic regression analysis due to the low number of events.

Among the most noticeable points, we noted that multiple valve surgery of native valve IE was not an independent predictor of operative mortality or death from all causes or from late valve-related morbidity. After the perioperative period,

the long-term clinical outcomes of multiple valve surgery for native valve IE seem to be similar to those of routine valve surgery.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

We thank Hyonggin Ann, PhD, who is our consultant statistician, for biostatistical advice on the study.

REFERENCES

1. Hoen B, Alla F, Selton-Suty C, et al. *Changing profile of infective endocarditis: results of a 1-year survey in France.* JAMA 2002;288:75-81.
2. Selton-Suty C, Doco-Lecompte T, Bernard Y, et al. *Clinical and microbiologic features of multivalvular endocarditis.* Curr Infect Dis Rep 2010;12:237-43.
3. Mueller XM, Tevaearai HT, Stumpe F, et al. *Multivalvular surgery for infective endocarditis*. Cardiovasc Surg 1999;7: 402-8.
4. Gillinov AM, Diaz R, Blackstone EH, et al. *Double valve endocarditis*. Ann Thorac Surg 2001;71:1874-9.
5. Mihaljevic T, Byrne JG, Cohn LH, Aranki SF. *Long-term results of multivalve surgery for infective multivalve endocarditis.* Eur J Cardiothorac Surg 2001;20:842-6.
6. Siniawski H, Grauhan O, Hofmann M, et al. *Aortic root abscess and secondary infective mitral valve disease: results of surgical endocarditis treatment*. Eur J Cardiothorac Surg 2005; 27:434-40.
7. Musci M, Siniawski H, Pasic M, et al. *Surgical treatment of right-sided active infective endocarditis with or without involvement of the left heart: 20-year single center experience.* Eur J Cardiothorac Surg 2007;32:118-25.
8. Musci M, Siniawski H, Pasic M, et al. *Surgical therapy in patients with active infective endocarditis: seven-year single centre experience in a subgroup of 255 patients treated with the Shelhigh stentless bioprosthesis*. Eur J Cardiothorac Surg 2008;34:410-7.
9. Sheikh AM, Elhenawy AM, Maganti M, Armstrong S, David TE, Feindel CM. *Outcomes of double valve surgery for active infective endocarditis.* J Thorac Cardiovasc Surg 2009; 138:69-75.
10. Yao F, Han L, Xu ZY, et al. *Surgical treatment of multivalvular endocarditis: twenty-one-year single center experience*. J Thorac Cardiovasc Surg 2009;137:1475-80.
11. Ota T, Gleason TG, Salizzoni S, Wei LM, Toyoda Y, Bermudez C. *Midterm surgical outcomes of noncomplicated active native multivalve endocarditis: single-center experience*. Ann Thorac Surg 2011;91:1414-9.
12. Habib G, Thuny F, Avierinos JF. Prosthetic valve endocarditis: current approach and therapeutic options. Prog Cardiovasc Dis 2008;50:274-81.
13. Li JS, Sexton DJ, Mick N, et al. *Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis.* Clin Infect Dis 2000;30:633-8.
14. Akins CW, Miller DC, Turina MI, et al. *Guidelines for reporting mortality and morbidity after cardiac valve interventions.* Eur J Cardiothorac Surg 2008;33:523-8.
15. Delahaye F, Alla F, Beguinot I, et al. *In-hospital mortality of infective endocarditis: prognostic factors and evolution over an 8-year period.* Scand J Infect Dis 2007;39:849-57.
16. Kim N, Lazar JM, Cunha BA, Liao W, Minnaganti V. *Multi-valvular endocarditis*. Clin Microbiol Infect 2000;6: 207-12.