Long-term clinical outcomes and risk factors for the occurrence of post-operative complications after cardiovascular surgery in patients with Behçet's disease

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ABSTRACT

Objective. *Cardiovascular surgery in patients with Behçet's disease (BD) frequently leads to post-operative complications such as anastomotic leakage, occlusion or pseudoaneurysm. We evaluated the clinical outcomes and related risk factors of post-operative complications in BD patients undergoing cardiovascular surgeries, as well as the long-term efficiency of post-operative immunosuppressive treatment.*

Methods. *Forty-one patients with BD who had undergone cardiovascular surgery between 1990 and 2009 were studied. We evaluated the patients' clinical data, post-operative complications, and survival rate. Risk factors related to the occurrence of post-operative complications were identified by univariate analysis using the Kaplan-Meier method with the log-rank test and multivariate analysis using the Cox proportional hazards regression model.*

Results. *Fifty-nine operations were performed in 41 patients. During the mean follow-up period of 65.3±48.1 months, complications such as paravalvular leakage, dehiscence, fistula, graft occlusion, or pseudoaneurysm occurred in 29 operations (49.2%). The cumulative occurrence rate of post-operative complication was 10.2% at three months, 32.8% at 12 months, and 43.8% at 24 months. Upon univariate analysis, young age, high C-reactive protein levels, lack of post-operative immunosuppression, and short disease duration were identified as significant factors responsible for the occurrence of post-operative complications. In multivariate analysis, post-operative immunosuppression was found to independently lower the risk of complications. The 5-year survival rate was significantly higher in patients with post-operative immunosuppression than in those without (84.5% vs. 45.0%, p=0.011).*

Conclusion. *The present study suggests that post-operative immunosuppressive therapy after cardiovascular surgeries in BD patients is important for reducing the development of serious post-operative complications.*

Introduction

Behçet's disease (BD) is a chronic relapsing multisystemic vasculitis, which was first defined as a distinct clinical syndrome by Dr Hulusi Behçet (1). He described the classic triad of signs: 1) recurrent oral ulcers, 2) genital ulcers, and 3) iridocyclitis with hypopyon. Further studies have shown that manifestations of BD are not confined to these three organs; BD can cause diverse manifestations in almost every organ of the body (2).

Cardiovascular involvement is found in 7% to 46% of patients with BD and accounts for the majority of mortalities (3, 4). Clinical manifestations of cardiovascular involvement are diverse, and venous thrombosis is the most frequent vascular complication. Arterial lesions such as arterial aneurysm or arterial occlusion can occur and, although rare, cardiac involvement such as acute myocardial infarction, valvular dysfunction, and ventricular thrombosis can also occur (3, 5). Surgery has been performed to treat these lesions of cardiovascular BD, but the results thereof have been unsatisfactory due to high treatment failure and high mortality rates after surgery (6-9). The failures of surgical treatments have been attributed to valve detachment, suture dehiscence, or a thrombosis at the site of the surgical repair.

Several studies have reported on the clinical outcomes and related prognostic factors in surgical patients with car-

diovascular BD. In terms of reducing post-operative complications, post-operative immunosuppressive treatment was reported to be helpful for controlling inflammation in surgical patients with BD (7, 10).

In this study, we evaluated clinical outcomes and related risk factors for the occurrence of post-operative complications in BD patients undergoing cardiovascular surgeries, and the long-term efficiency of post-operative immunosuppressive treatment aimed at reducing post-operative complications and mortality rate.

Patients and methods

Study subjects

We reviewed the medical records of 41 consecutive patients with cardiovascular BD who underwent cardiovascular surgery between January 1990 and December 2009 at Severance Hospital, Yonsei University Health System in Seoul, Korea. Diagnosis of BD was based on the revised diagnostic criteria for complete and incomplete types of the Behçet's Disease Research Committee of Japan (Japanese criteria) (11). Also, we reviewed whether patients met the International Study Group (ISG) criteria (12). Since 1996, we have been using postoperative immunosuppressive treatment to reduce fatal post-operative complications. However, patients who underwent cardiovascular surgery before the typical symptoms of BD appeared were not treated with post-operative immunosuppression. As an immunosuppressive regimen, high-dose prednisolone (1mg/kg/day) and azathioprine (2mg/kg/day) were most commonly used and were started from post-operative day 1 or 2. Prednisolone was gradually tapered to a maintenance dosage of <10mg/day within 3-6 months, whereas the azathioprine was continued unless complications were encountered. This study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System in Seoul, Korea.

Data collection

We investigated demographic factors, BD symptoms, cause, time and name of operation, and post-operative medication (immunosuppressive drugs such as prednisolone, azathioprine, or cyclosporine). Laboratory findings such as white blood cell count, haemoglobin level, platelet count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were collected just before the operation. Results of HLA-B51 genotyping and pathergy test were also gathered. Disease duration was defined as the time from diagnosis of BD to operation.

Post-operative complication was defined as any confirmation of anastomotic leakage, recurrence of valvular insufficiency, fistula, recurred aneurysm, aneurysmal rupture or occlusion of bypass graft confirmed by echocardiography, computed tomography (CT) angiography, or conventional angiography.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD), and qualitative variables were expressed as a percentage. The significance of differences in the parameters between patients (or operations) with and without complication was determined using a chi-square test or Fisher's exact test for categorical variables and a Student's t-test for continuous variables.

For survival analysis, some clinical variables were categorised using clinically applicable cutoff levels and percentiles. Survival and cumulative probabilities of complication after surgical treatment were calculated using the Kaplan-Meier method. A log-rank test was performed to determine risk factors for the development of complications. Cox proportional hazard regression models, including significant univariate factors, were applied to analyse the risk factors independently associated with the occurrence of complications. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 13.0; SPSS Inc., Chicago, IL).

Results

Clinical features of the patients

A total of 41 BD patients underwent cardiovascular surgical treatment. Their clinical features are summarised in Table 1. Thirty patients were male. The age of the patients at the time of the first operation was 40.6±12.4 years (range: 22 to 70). The mean disease duration was 42.1±67.2 months (range: -81 to 217). They all received the usual medical care for BD except for nine patients who had not been diagnosed with BD at the time of the first operation, as typical BD symptoms appeared after operations. Patients presented recurrent oral ulcers (100%), genital ulcers (73.2%), skin lesions (80.5%), arthritis (46.3%) and uveitis (24%).

A total of 59 operations were performed in 41 patients. At the time of operation, ESR and CRP levels were 35±30 mm/hour and 2.3±3.2 mg/dL, respectively. Valvular surgery was performed in 21 patients, vascular surgery in 13 patients, and both vascular and valvular surgery in seven. Twenty-two (53.7%) patients did not experience complications, while 19 (46.3%) patients did. The mean follow-up duration was 65.3±48.1 months. Among a total of 59 operations, post-operative complications such as anastomotic leakage, fistula, graft occlusion, or pseudoaneurysm developed in 29 operations (49.2%). The median elapsed time from surgery to the occurrence of complications was 10 months (range: 0.1–89). Thirty-six operations (61.0%) were followed by post-operative immunosuppressive treatment, while the remaining 23 operations were not.

Surgical modalities, medical treatments, and outcomes of 59 surgeries

The causes and names of cardiovascular surgeries, combined medical treatments, and outcomes are depicted in Table II (patients with complication) and Table III (patients without complication). The indications for operation were valvular dysfunction (26 patients), arterial aneurysm (12 patients), arterial or graft occlusion (4 patients), fistula (2 patients) and cardiac anomaly (2 Ebstein's anomaly). Nine patients had more than two cardiovascular problems. Among the 19 cardiovascular BD patients who developed post-operative complications, 12 patients underwent reoperations, some of them as many as three reoperations (Table II).

Table I. Clinical characteristics of patients with Behçet's disease who underwent cardiovascular surgery.

Characteristics		
Number of subjects		41
Sex (M:F)		30:11
Age at diagnosis of Behçet's disease, years		37.1 ± 11.7
Age at first operation, years		40.6 ± 12.4
Disease duration, months (range)		42.1 ± 67.2 (-81-217)
Follow-up duration from first operation, months (range)		65.3 ± 48.1 (1-204)
Clinical manifestations, n (%)		
Major	Oral ulcer	41 (100)
	Genital ulcer	30 (73.2)
	Eye lesion	10 (24.4)
	Skin lesion	33 (80.5)
Minor	Arthritis	19 (46.3)
	G-I lesion	5 (12.2)
	Epididymitis	0 (0)
	Vascular lesion	41 (100)
	CNS lesion	3 (7.3)
Positive pathergy test		6 (14.6)
HLA-B51 positivity		3/6
Diagnostic criteria of BD, n (%)		
Japanese criteria	complete	5 (12.2)
	incomplete	36 (87.8)
International Study Group criteria		31 (75.6)
Laboratory parameters at operation		
ESR, mm/hr		35 ± 30
CRP, mg/dL		2.3 ± 3.2
Surgical modality, n (%)		
Valvular surgery		21 (51.2)
Vascular surgery		13 (31.7)
Combined		7 (17.1)
Disease associated complications, n (%)		
Patients	never	22 (53.7)
	more than once	19 (46.3)
Operation	no complications	30 (50.8)
	complications	29 (49.2)
Median elapsed time to complication, months (range)		10 (0.1 ~89)
Post-operative immunosuppression, n (%)		
Operation	no	23 (39.0)
	yes	36 (61.0)

The cumulative complication rate was 10.2% at three months after surgical treatment, 20.6% at six months, 32.8% at 12 months, and 43.8% at 24 months. After the initial operation, the five-year survival rate was 78.9%. Nine patients died during follow-up. Five deaths were related to cardiovascular BD: two cardiac arrests, one anastomosis site rupture, one aneurysmal rupture, and one heart failure.

Post-operative immunosuppression

Thirty-six operations were followed by post-operative immunosuppressive treatments. Among them, complications occurred in 11 operations (30.5%). In contrast, among 23 operations without post-operative immunosuppression, complications occurred in 18 operations (78.3%). The cumulative complication rate after surgical treatment was significantly higher in operations without post-operative immunosuppressive treatment (34.8%, 60.9%, 69.6% *vs*. 8.4%, 14.2%, 26.5% at 3, 12, and 24 months, respectively, $p<0.001$, Fig. 1A). After the initial operation, the overall survival rate was higher in patients with post-operative immunosuppression (5-year survival rate; 84.5% *vs*. 45.0%, $p=0.011$, Fig. 1B).

As a post-operative immunosuppressive regimen, prednisolone plus azathioprine were used in 28 operations (78%), prednisolone only in 5(14%), prednisolone plus cyclosporine in 2(5%), and prednisolone plus mesalazine in 1(3%). Six of the patients treated with the combination therapy of glucocorticoid and azathioprine experienced drug-related complications (two leukopenia, two hepatitis, and two infections). Among them, five patients discontinued azathioprine, whereas one patient with mild liver enzyme elevation recovered after stopping azathioprine and then restarted on azathioprine without further complication.

Subgroup analysis for patients undergoing valvular surgeries

In total, 40 valvular surgeries were performed in 28 patients. The indication of operation was aortic regurgitation (AR) in 22 patients, mitral regurgitation (MR) in 3, mitral stenosis (MS) in 3, tricuspid regurgitation (TR) in 3, and Ebstein's anomaly in 2. Patients who underwent operations of the aortic valve were analysed separately. Among the patients undergoing aortic valve replacement (AVR), mechanical valves were used in 19 and tissue valves in 9. There was no difference in post-operative complication rate according to the type of valve (mechanical valve 42.1% *vs*. tissue valve 77.8%, $p=0.085$). Among 18 patients receiving AVR, ten patients (56%) experienced post-operative complications. Five patients who developed complications following AVR underwent Bentall operation in the last surgery. Three of them demonstrated good results without post-operative complication (patient 1, 14, and 19 in Table II). The microscopic features of the 18 available aortic valves after surgery showed myxoid degenerative change in 16 cases (89%), fibrosis in 9(50%), neutrophil infiltration in 5(28%), fibrin deposition in 3(17%), microabscess with granuloma formation in 2(11%), and neovascularisation in 1(6%). The microscopic findings of the 18 available aortic walls revealed myxoid degeneration in 10 cases (56%), fibrosis in 5(28%), lymphocytic infiltration in 4(22%), fragmentation of elastic lamina in 2(11%), mucopolysaccharide deposition in 2(11%), fibrin deposition in 1(6%), and vava vasoritis with endothelial thickening in 1(6%).

Table II. Clinical data of BD patients with post-operative complications after cardiovascular surgery.

Patient	No. of operation	Cardiovascular lesion	Surgical procedure	Post-operative immunosuppression	Complication	Complication time (month)*
1	First	AR, MR	AVR, MV repair	none	Paravalvular leakage	5
	Redo	AR d/t paravalvular leakage	Redo AVR	high-dose PL + AZT	AR d/t incomplete coaptation	89
	Trido	AR, MR	Redo Bentall operation	low-dose PL + AZT	MR d/t dehiscence of MR repair ring	
2	First	AAA, AR, MS	Graft interposition, re-implantation of IMA, DVR	none	Aorto-duodenal fistula	24
	Redo	Aorto-duodenal fistula	Interposition of aortic graft	none	Ruptured aneurysm d/t anastomosis site leakage	0.5
	Trido	Ruptured aneurysm d/t anastomosis site leakage	Graft interposition, Rt. Renal artery reimplantation	none	Death (anastomosis site rupture)	0.1
3	First	Rt. CCA aneurysm	Aneurysmectomy, graft interposition of Rt. CCA	none	Rt. CCA obstruction	56
	Redo	Graft occlusion in CCA, Rt.	Anastomosis between proximal Rt. CCA and ICA	none	Stenosis of vascular graft	2
	Second	Lt. femoral artery aneurysm	Aneurysmectomy, graft interposition of Lt. CIA, SFA, DFA	low-dose PL + cyclosporine		
4	First	Sinus Valsalva rupture with acute AR	AVR, PVR with Ross procedure	none	Death (sudden cardiac arrest)	3
5	First	AR	AVR	none	AR d/t dehiscence of prosthetic AV	8
	Redo	AR d/t dehiscence of prosthetic valve	Redo AVR	none	AR d/t dehiscence of prosthetic AV	3
	Trido	AR d/t dehiscence of prosthetic	Trido AVR, CABG	none	Death (heart failure)	0.1
6	First	Dissecting aneurysm of ascending arch of aorta	Graft replacement of ascending arch of aorta & innominate artery	none	Graft dehiscence, death d/t aneurysmal rupture	10
7	First	AR, MR, TR	Cusp replacement of left coronary cusp (AV), mitral / tricuspid annuloplasty	high-dose PL + AZT	AR d/t incomplete coaptation, death (drowning)	11
8	First	Acute AR	AVR	none	AR d/t dehiscence of prosthetic AV	3
	Redo	AR d/t dehiscence of prosthetic valve	Ross operation	high-dose PL + AZT		
9	First	Both CIA occlusion	Aorto-bifemoral bypass graft	none	Total occlusion of bypass graft, death (GI Behcet, pneumonia)	7
10	First	AR, sinus valsalva aneurysm	Aortic valvuloplasty	high-dose PL + AZT (discontinue after 24 months)	AR, flap at aortic arch	50
	Redo	AR	Redo AVR	high-dose PL + AZT	AR d/t dehiscence of prosthetic AV	19
11	First	Popliteal artery aneurysm, Rt.	Aneurysmectomy, saphenous vein interposition of popliteal artery	high-dose PL + AZT	Aneurysm recur	17
12	First	AR	AV repair	none	AR d/t incomplete coaptation	13
	Redo	AR	Redo AVR	high-dose PL + AZT		
13	First	Femoral artery aneurysm, Lt.	Aneurysmectomy and graft interposition of CFA	none	Femoral artery pseudoaneurysm, lt.	49
	Redo	Femoral artery pseudoaneurysm, Lt.	Aneurysmectomy and graft replacement of CFA, SFA	none		
14	First	SMA aneurysm	Endoaneurysmal repair & aorto-SMA bypass	none		
	Second	AR	AVR	high-dose PL + AZT	Paravalvular leakage	10
	Redo	AR d/t paravalvular leakage	Bentall operation	high-dose PL + AZT		
15	First	AR	AVR	none	Paravalvular leakage	12
	Redo	AR d/t paravalvular leakage, MR	Redo AVR, mitral ring annuloplasty	high-dose PL + AZT	Paravalvular leakage	3
	Trido	AR d/t paravalvular leakage	Redo Bentall operation	high-dose PL + cyclosporine	Paravalvular leakage, death (sudden cardiac arrest)	13
16	First	Congestive heart failure, MR, TR	MVR	high-dose PL + AZT	Annulus dissection & mechanical valve deviation to left atrium, death (pneumonia, septic shock)	15
17	First	AR, sinus Valsalva aneurysm	AVR	none	Paravalvular leakage	11
	Redo	AR d/t paravalvular leakage	Redo AVR	high-dose PL + AZT		
18	First	AR, endocarditis on AV, VSD	Bentall operation, patch repair of VSD	none	Paravalvular leakage	3
19	First	AR d/t perforated AV, endocarditis on AV	AVR	high-dose PL	Paravalvular leakage	0.5
	Redo	AR d/t paravalvular leakage	Redo-Bentall procedure, pseudo-aneurysmectomy, graft replacement of ascending aorta	high-dose PL		

*Duration between operation and development of complication.
AR: aortic regurgitation; MR: mitral regurgitation; AVR: aortic valve replacement; MV: mitral valve, PL: prednisolone; AZT: azathioprine; AAA: abdominal artery aneurysm; MS: mitral stenosis; IMA: inferior mesenteric artery; DVR: double-valve replacement; CCA: common carotid artery; ICA: internal carotid artery; CIA: common iliac artery; SFA: superficial femoral artery; DFA: deep femoral artery; AV: aortic valve; CABG: coronary artery bypass graft; TR: tricuspid regurgitation; CFA: common femoral artery; SMA: superior mesenteric artery; MVR: mitral valve replacement; VSD: ventricular septal defect.

Table III. Clinical data of BD patients without complication after cardiovascular surgery.

Patient	Cardiovascular lesion	Surgical procedure	Post-operative immunosuppression	Outcome
1	MR	MVR	high-dose PL + AZT	
2	AR, MR	AVR	high-dose PL + AZT	
3	Rt. ilio-femoral artery occlusion	Rt. ilio-femoral bypass	high-dose PL + AZT	
4	AR, MR, annuloaortic ectasia	Bentall operation	none	
5	AR, MS	DVR	high-dose PL + AZT	
6	AR, MR	AVR, MV repair	high-dose PL + AZT	
7	AR, MR	AVR, MV annuloplasty	low-dose PL + mesalazine	
8	AR, dilated ascending aorta	AVR, Graft replacement of ascending aorta	high-dose PL + AZT	
9	Popliteal artery aneurysm, Lt.	Aneurysmectomy, graft interposition of popliteal artery, Lt	high-dose PL + AZT	
10	Ebstein's anomaly	Modified Fontan operation	high-dose PL + AZT	
11	AAA	Graft replacement of AA	high-dose PL + AZT	
12	AR	AVR	high-dose PL	
13	Ebstein's anomaly	Extracardiac modified Fontan operation, closure of MPA	none	
14	MR, TR	MVR, TVR	high-dose PL	
15	MS, TR	MVR, tricuspid annuloplasty	high-dose PL + AZT	
16	Lt. iliac artery occlusion	Graft replacement	none	
17	Rt. femoral artery aneurysm	Graft interposition of femoral artery	high-dose PL + AZT	
18	AR, sinus Valsalva aneurysm	AVR	high-dose PL + AZT	
19	Thoracoabdominal aortic aneurysm with separated saccular aneurysm	Graft replacement of DTA, AA	high-dose PL	Death (pneumonia, cerebral haemorrhage)
20	Aortobronchial fistula, lt. subclavian artery aneurysm	Graft interposition of innominate artery & aortic arch	high-dose PL + AZT	
21	AR	AVR	high-dose PL + AZT	
22	Lt. femoral artery aneurysm	Aneurysmectomy and graft interposition of lt. CFA	high-dose PL + AZT	

MR: mitral regurgitation; MVR: mitral valve replacement; PL: prednisolone; AZT: azathioprine; AR: aortic regurgitation; AVR: aortic valve replacement; MS: mitral stenosis; DVR: double-valve replacement; MV: mitral valve; TR: tricuspid regurgitation; AAA: abdominal aorta aneurysm; AA: abdominal aorta; TS: tricuspid stenosis; MPA: main pulmonary artery; TVR: tricuspid valve replacement; DTA: descending thoracic artery; CAOD: coronary artery occlusive disease; CABG: coronary artery bypass graft; CFA: common femoral artery.

Long-term clinical outcomes and risk factors for the occurrence of postoperative complications

Table IV demonstrates the univariate comparisons of demographic, clinical, and surgical characteristics between patients (or operations) with and without postoperative complications. The differences in demographics, clinical features, and surgical modalities between the two groups were insignificant except for shorter disease duration and younger age in the patients with postoperative complications. When compared to complicated operations, non-complicated operations showed lower acute phase reactants (ESR and CRP) and greater use of postoperative immunosuppression at the time of surgery. The mean follow-up period after surgery was 37.7 months, ranging from 0.1 to 198 months.

Univariate analysis using the Kaplan-Meier method and the log-rank test revealed that age <40 years (p=0.03), CRP level ≥0.8 mg/dL(p=0.04), lack of postoperative immunosuppression (p<0.001), and disease duration of ≤3 years (p=0.011) were associated with higher complication rates. Subsequently, multivariate analysis identified that postoperative immunosuppression was an independent risk factor for lower complication rate (Table V).

Discussion

This study revealed the long-term clinical outcomes of BD patients who underwent cardiovascular surgery and identified the risk factors for the occurrence of postoperative complication. Our results showed that postoperative complications frequently occurred after cardiovascular surgery in patients with BD, and that postoperative use of immunosuppressive drugs was helpful in reducing the rate of complications. Although there have been a few studies conducted on the clinical outcomes in cardiovascular surgical patients with BD, these were either case-series or small series (10, 13-16).

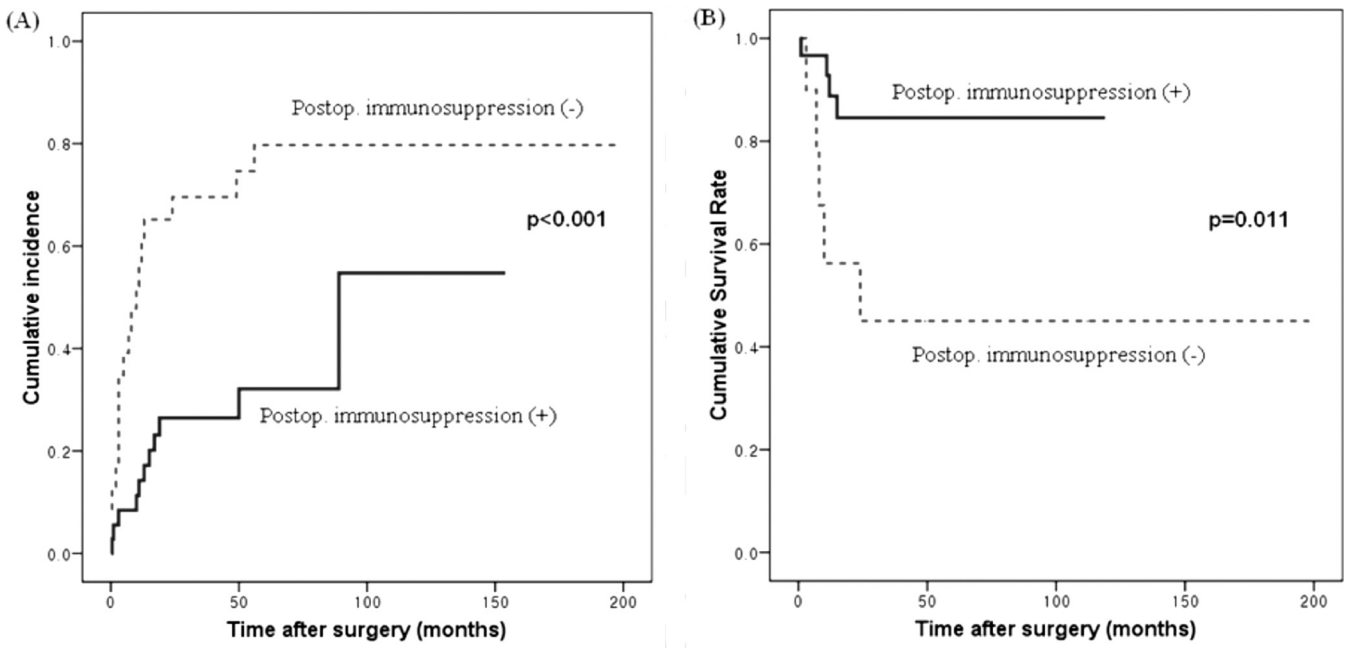

Fig. 1. Cumulative complication and survival rate. (**A**) Cumulative incidences of post-operative complications were significantly higher in operations without post-operative immunosuppression (p<0.001), (**B**) and cumulative survival rate was higher in patients with post-operative immunosuppression (p=0.011).

Table IV. Comparison of characteristics between BD patients with and without post-operative complications.

Total 41 patients	Complicated n=19	Not complicated n=22	p-value
Age at diagnosis of Behçet's disease, years	36.8 ± 9.6	37.5 ± 13.4	0.860
Age at first operation, years	36.8 ± 8.6	43.9 ± 14.3	0.057
Male	16 (84.2)	14 (63.6)	0.138
Disease duration, months	0.7 ± 25.7	77.7 ± 71.8	<0.001
Clinical parameters			
Oral ulcer	19 (100)	22 (100)	
Genital ulcer	14 (73.7)	16 (72.7)	0.945
Skin lesion	15 (78.9)	18 (81.8)	0.562
Uveitis	3 (15.8)	7 (31.8)	0.205
Arthritis	9 (47.4)	10 (45.5)	0.902
G-I involvement	2 (10.5)	3 (13.6)	0.572
CNS involvement	0 (0)	3 (13.6)	0.144
Positive pathergy test	2 (10.5)	4 (18.2)	0.406
Surgical modality			
Valve surgery	14 (73.7)	14 (63.6)	0.491
Vascular surgery	9 (47.4)	11 (50.0)	0.867
Total 59 operations	n=29	n=30	
Laboratory parameters at the time of operation			
ESR, mm/hr	50.0 ± 35.6	20.4 ± 15.9	0.002
CRP, mg/dL	36.2 ± 39.3	7.2 ± 8.1	0.006
Immunosuppressive treatment	11 (37.9)	25 (83.3)	<0.001

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

The diagnosis of BD is mostly based on clinical findings and the ISG classification criteria are the most widely used diagnostic tools (12). Although cardiovascular involvement is not included in the ISG criteria, about one-third of patients experience cardiovascular manifestations during the course of BD (17). The Japanese criteria for BD include cardiovascular involvement as minor symptoms, and the sensitivity, specificity, and accuracy of Japanese criteria are comparable with those of the ISG criteria (80.6%, 95.3%, 88.3% *vs*. 79.4%, 99.4%, 89.8%, respectively) (18). In addition, the Japanese criteria have been applied to considerable studies of BD in East-Asian populations (19, 20). Therefore, our patients were diagnosed with BD using the Japanese criteria, so as not to overlook patients with cardiovascular BD.

In 19 of 41 patients (46.3%) and 29 of 59 surgeries (49.2%), complications such as anastomotic leakage, fistula, graft occlusion, or pseudoaneurysmal formations developed. The cumulative incidences of such complications were 20.6%, 32.8%, and 43.8% at six months, one year, and two years following the operation, respectively. A review of surgical cases in the Japanese literature reported a vascular graft occlusion rate of 35.7% in BD patients (16). Iscan *et al*. reported a 10-year survival rate of 30% and a complication-free survival rate of 13% (21). Re-operation was required in 50% of BD aortitis patients undergoing AVR (22). Ahn *et al*. reported that 5 of 26 operations (19.2%) were complicated with wound dehiscence in BD patients with aortic valvulitis undergoing AVR (10). Thus, BD patients undergoing cardiovascular surgeries have poor clinical outcomes

Table V. Multivariate Cox hazard regression analysis of risk factors for the occurrence of complications following cardiovascular surgery in patients with Behçet's disease.

	Occurrence of post-operative complications		
Variable	HR	95% CI	*p*-value
Age <40	1.157	0.387–3.458	0.794
CRP level ≥ 0.8 mg/dL	1.756	0.524–5.684	0.348
Disease duration < 3 years	2.971	0.955–9.248	0.060
Post-operative immunosuppression	0.243	0.085–0.689	0.008

CRP: C-reactive protein.

due to high complication rates. The pathogenic mechanism of post-operative complications after surgery in BD patients has not yet been proven. However, "arterial wall aphthae" resulting from pathergic phenomenon against injury (needling or suture material) such as mucocutaneous lesions is considered to be a reasonable mechanism (23).

The cumulative incidence of post-operative complications was significantly lower in operations with post-operative immunosuppression than in those without (complication incidence at 1 year; 14.2% *vs*. 60.6%). The overall survival rate was significantly higher in patients with post-operative immunosuppression than in those without (5-year survival rate; 84.5% *vs*. 45.0%). Moreover, among seven patients whose first operation failed without post-operative immunosuppression and subsequently received a second operation with post-operative immunosuppression (patient 1, 3, 8, 12, 13, 15, and 17 in Table II), 5 patients (71.4%) demonstrated good clinical outcome. These results suggest that post-operative immunosuppression is important for reducing the development of serious post-operative complications in BD patients undergoing cardiovascular surgeries.

We separately analysed the patients who received valvular surgery. Although valvular involvement in BD is rare, valvular BD has been relatively widely reported in Middle and Far Eastern regions including Korea and Japan (8, 10, 13, 24). In our series, AR was the most common cause of valvular surgery, concurring with other published studies (10, 13). The suggested mechanisms of AR in BD are valvulitis, functional derangement due to underlying non-specific vasculitis, or annular dilatation and sinus Valsalva aneurysm secondary to aortitis (13, 25, 26). To reduce complications following AVR in BD, some authors support the use of a homograft valve (13, 27). However, there was no difference in complication rate according to type of valve used in our study. Three patients who developed complications following AVR demonstrated good results with different surgical methods (Bentall operation), and these findings are consistent with previous studies (10, 13). In BD patients with aortic valvular disease, surgical modality may be another important prognostic factor.

We investigated the pathologic features of aortic valvular diseases in BD. The histopathology of valvular disease in BD has not been characterised clearly because of the rarity of the disease. A wide variety of histologic findings were observed in our patients, which included myxoid degeneration, fibrosis, inflammatory cell infiltration, fibrin or mucopolysaccharide deposition, and microabscess formation, representing non-specific vasculitis and inflammatory change of the aortic valve and aortic wall. Lee *et al*. reported that acute endothelialitis, neutrophil infiltration, lymphoplasma cells infiltration, granulation with neovascularisation, and fibrosis are commonly observed pathologic changes in cardiovascular BD, similar with our findings (24). In some patients, microabscess formation and neutrophil infiltration were observed as infective endocarditis, but blood culture revealed no growth of bacteria. The presence of microabscess and neutrophil infiltration on valvular pathology with negative blood culture should consider the possibility of cardiac BD.

Some investigators have reported that cardiovascular manifestations were presented before the typical symptoms of BD appeared (28-31). In the present study, nine patients were diagnosed with BD after their initial operation. None of them were treated with immunosuppressive drugs, and eight of them required re-operation. The other one patient with popliteal artery aneurysm underwent endovascular intervention for a recurred aneurysm. These results caused the disease duration of the complicated group to be shorter than that of the uncomplicated group, although it was insignificant in multivariate analysis. Therefore, early detection of BD before cardiovascular surgery is important and might improve the prognosis for BD patients requiring cardiovascular surgery. In relatively young patients with unexplained aneurysm or valvular disease, physicians should be aware of this and conduct detailed medical examinations for BD.

In the current study, inflammatory markers such as ESR and CRP were higher in the group with complications, but not significantly upon multivariate analysis. ESR and CRP are routinely used to check the clinical activity of BD, but these markers are known to not correlate well with disease activity (32). High post-operative levels of acute phase reactants (ESR or CRP) were associated with poor post-operative outcomes in a few reports on cardiovascular BD patients (13). In our study, we used preoperative ESR/CRP levels in the analysis instead of post-operative levels of ESR and CRP, which might be affected by operation. Cardiovascular lesions of BD often require urgent surgical treatment due to the critical nature of cardiovascular complications. It is ideal to delay surgery in the active inflammatory phase of BD until the disease activity is controlled with medical treatment (33); however, circumstances may occasionally not allow the surgery to be delayed in some patients. In our study, post-operative immunosuppressive therapy in these patients proved effective in reducing post-operative complications.

In the present study, the post-operative use of immunosuppressive drugs independently lowered the risk for the

occurrence of post-operative complications. There is some concern for the use of immunosuppression in the surgical treatment of BD lesions because of the contrary features of glucocorticoid, which controls inflammation and increases the risk of delayed wound healing or infection. Surgeons usually dislike the use of the high-dose glucocorticoid before surgery for the latter reason. Several studies have shown results in favour of the use of post-operative immunosuppressive drugs in cardiovascular BD (10, 13, 14). Some studies reported that glucocorticoid alone was unable to significantly reduce the frequency of post-operative complications, while additional immunosuppressive agents in conjunction with glucocorticoids demonstrated more favourable outcomes (14, 23). However, there was insufficient evidence for which immunosuppressive regimen is more effective after cardiovascular surgery. Azathioprine has been proven to be effective in the treatment of systemic involvement of BD such as Behçet uveitis, gastrointestinal Behçet, or neuro-Behçet (34). Also, corticosteroid plus azathioprine or methotrexate is usually recommended in non-life threatening forms of other systemic vasculitis (35). For this reason, our center prefers to use corticosteroid plus azathioprine for post-operative immunosuppression. In our study, most patients were administered prednisolone plus azathioprine as a post-operative immunosuppressive regimen, while a small number of patients (n=5) were administered prednisolone alone. It was therefore difficult to evaluate the effects of the two different regimens. Nevertheless, post-operative immunosuppressive regimen with high-dose prednisolone plus azathioprine was effective in reducing the rate of complications and was tolerable.

The limitation of our study is the heterogeneity of the surgical procedures and treatment modalities, which may have led to biased assessment of the surgical outcomes. Also, advances in surgical procedures over time might affect surgical outcomes, for instance, Bentall operations for aortic valvular disease. As we focused on post-operative immunosuppression, we could not make suggestions for timing the initiation of immunosuppressive therapy before surgery (preoperative immunosuppression) or after surgery (post-operative immunosuppression) for better post-operative outcome. A prospective study with a larger number of patients is needed to address this issue.

In summary, post-operative complications frequently occur following cardiovascular surgeries in patients with BD. Surgeries with post-operative immunosuppression showed better clinical outcome. This study suggests that post-operative immunosuppressive ther-apy after cardiovascular surgeries in BD patients is important for reducing the development of serious post-operative complications.

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