Predictors of Mortality in Early Surgical Intervention for Active Native Valve Endocarditis and Significance of Antimicrobial Therapy: A Single-Center Experience

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Background and aim of the study: **Cardiac surgery for active infective endocarditis remains a challenging and high-risk procedure. The outcome from early surgical intervention for active native valve endocarditis (ANVE) was studied, the aim being to identify significant predictors of mortality and the relationship between duration of preoperative antibiotics and outcome.**

Methods: **Between January 1996 and February 2002, 61 patients with ANVE underwent surgery within four weeks of diagnosis. Preoperatively, 29 patients received antibiotics for <2 weeks (group A), and 32 received antibiotics for 2-4 weeks (group B). The median follow up period was 37.4 months (range: 21-55 months). Data were collected retrospectively and analyzed. To determine factors related to mortality, Kaplan-Meier survival analysis was employed, utilizing log-rank statistics to identify evidence of significant differences between the groups. The relationship between the duration of preoperative antibiotics and morbidity was determined using chi-square and Fisher's Exact tests, as appropriate.**

Results: **Overall operative mortality was 14.8% (group A, 13.8%; group B, 15.6%). Rates of early and late prosthetic valve endocarditis were 1.8% and 1.9% (only in group B) respectively. The overall survival rate for the follow up period was 81.9%. Predictors of mortality were extensive infection (p = 0.01), poor left ventricular function (p <0.0001), progressive cardiac failure as an indication for surgery (p <0.0001), postoperative sepsis (p <0.0001), renal failure after surgery (p = 0.0002) and use of a bioprosthetic valve (p = 0.045). There were no significant inter-group differences for extensive infection (p = 1.00), postoperative sepsis (p = 1.00), reoperation (p = 1.00) and mortality (p = 1.00).**

Conclusion: **In patients with ANVE, early aggressive surgical intervention before the onset of cardiac failure and spread of infection is warranted. The present data suggest that, in these patient groups, the duration of preoperative antibiotics had no significant influence on postoperative morbidity and mortality.**

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Infective endocarditis is a life-threatening emergency even when promptly diagnosed and treated by a multidisciplinary team. For the majority of patients with infective endocarditis, antibiotic therapy remains the mainstay of treatment. Active infective endocarditis (AIE) usually requires prolonged antibiotic therapy due to the high concentration of organisms within cardiac vegetations (1). In a proportion of patients with complications who do not respond to medical therapy, surgery plays an important role (2-4), and these cases represent a major challenge to the cardiac surgeon. Wallace et al. (5) reported the first case of valve replacement for aortic valve endocarditis in 1965. Since the advent of diagnostic tools such as transesophageal echocardiography (TEE), along with advancements in operative techniques such as native valve repair and the Ross procedure for endocarditis, the surgical outcome for infective endocarditis has shown remarkable improvement (6-8).

Identification of the causative organism, assessment of the antibiotic's sensitivity pattern and careful observation of the response to treatment form the cornerstones of successful medical treatment in infective endocarditis. Among patients who have undergone surgery for infective endocarditis, early intervention has consistently provided better results (2-4). Today, however, few authors advocate delaying surgery preceded by prolonged antibiotic therapy with a view to

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sterilizing the infected valve (9,10). Although many series have combined patients with both native and prosthetic valve endocarditis (2,3,10), surgery for the latter condition is often a more complicated and high-risk procedure than for the former (2,11). As the findings of these combined studies may be misleading, the decision was made to assess the predictors of operative mortality specifically in patients who underwent early surgical intervention for active native valve infective endocarditis, and to explore the relationship between the duration of preoperative antibiotic therapy and surgical outcome.

Clinical material and methods

Patients

Between January 1996 and February 2002, a total of 94 patients underwent surgical intervention for infective endocarditis at The Royal Infirmary of Edinburgh, Scotland. Among these patients, 61 (40 males, 21 females; median age 61 years; range: 43.5 to 68.5 years) had surgery for active native valve endocarditis. Thirty-one patients (51%) were aged over 60 years. Preoperatively, all patients were assessed using either TEE or transthoracic echocardiography. The diagnosis of infective endocarditis was based on defined criteria, including the combination of positive blood culture, definite echocardiographic findings and clinical signs such as pyrexia, heart murmur, and vascular and immunological phenomena. The diagnosis of infective endocarditis was confirmed intraoperatively in all patients either by macroscopic findings or valve tissue culture/histological confirmation of operative biopsy specimens. All patients in the present study satisfied the definite classification of Dukes' criteria (12), and all underwent surgery within four weeks of diagnosis. Patients with healed endocarditis and those who had received antibiotic therapy for more than four weeks were excluded from the study. Patients were allocated to two groups on the basis of their duration of preoperative antibiotic treatment. Group A (n = 29) patients had received antibiotics for less than two weeks, while group B (n = 32) patients had received antibiotics for between two and four weeks. The preoperative baseline characteristics of the two groups are listed in Tables I and II.

Definitions

Infective endocarditis was labeled 'active' if the patient had received less than four weeks' antibiotic therapy and at least one or more of the following factors was present: clinical signs of ongoing sepsis; posi-

Table I: Patient preoperative clinical data.

Parameter	Duration of preoperative antibiotics	
	<14 days (Group A; (n = 29) (%)	14-28 days (Group B; (n = 32) (%)
Age range (years)	22-80	23-80
Gender		
Male	22 (76)	18 (56)
Female	7 (24)	14 (44)
NYHA class		
I-II	15 (52)	21 (66)
III-IV	14 (48)	11 (34)
Causative organism		
Staphylococcus aureus	8 (28)	8 (25)
Streptococcus viridans	4 (14)	9 (28)
Coagulase-negative *Staphylococcus*	2 (7)	3 (9)
Other organisms*	2 (7)	3 (9)
Site of endocarditis		
Aortic valve	13 (45)	13 (41)
Mitral valve	12 (41)	15 (47)
Aortic and mitral valve	5 (17)	3 (9)

**Enterococcus* sp. (n = 3); *Candida albicans* (n = 1); *Coxiella burnetii* (n = 1).

tive bacteriology within three weeks before surgery; and macroscopic operative findings of valve infection such as vegetations or paravalvular abscess.

The term 'early surgical intervention' indicated that the operative procedure was carried out within four weeks of diagnosis of infective endocarditis.

Poor left ventricular function was defined as an ejection fraction <30%.

Extensive infection meant that the heart valve infection had spread beyond the valve leaflets, or involved more than one heart valve.

Postoperative sepsis was defined as non-valvular infection with positive blood culture during the postoperative period, which required inotropic support to maintain hemodynamic stability. If the endocarditis recurred within 60 days after surgery, it was classified as 'early prosthetic valve endocarditis' (EPVE).

The term 'late prosthetic valve endocarditis' (LPVE) signified the recurrence of endocarditis at two months after the initial surgery.

Microbiology

Serial blood cultures were positive in 39 patients (64%), but in the remaining 22 (36%) the etiological organisms were not identified preoperatively. Among the culture-positive patients (Table I), *Staphylococcus aureus* was the most common causative organism, and was isolated in 16 (26%). *Streptococcus viridans* and coagulase-negative *Staphylococcus* sp. were cultured in 13 (21%) and five (8%) patients, respectively. Three patients (4.9%) were infected with *Enterococcus* sp., while other organism such as *Coxiella burnetii* and *Candida albicans* were each cultured in one patient (2%). Culture-positive patients were treated with appropriate antibiotics according to the sensitivity of the organism, while culture-negative patients were administered empirical treatment with broad-spectrum antibiotics. The antibiotics were continued at least for four weeks during the postoperative period for all patients.

Site of infection

Isolated aortic valve infection was noted in 17 patients (28%), and aortic root abscess in eight (13%). Isolated mitral valve infection was identified in 23 patients (38%). Both aortic and mitral (double valve) infection occurred in eight patients (13%). Two patients had mitral valve infection with ventricular septal defect, and one patient had an aortoatrial fistula. Mitral valve involvement with annular abscess occurred in two patients.

Indications for surgery

Indications for surgery included progressive cardiac failure (n = 12), severe valve dysfunction with impending heart failure (n = 25), uncontrolled sepsis not responding to antibiotic therapy (n = 20), and multiple emboli/increasing size of vegetation with a threat to embolism (n = 4).

Table II: Preoperative complications and indications.

Complication/indication	Duration of preoperative antibiotics	
	<14 days (Group A; (n = 29) (%)	14-28 days (Group B; (n = 32) (%)
Complication		
Systemic embolism*	3 (10)	4 (13)
CVA	1 (34)	2 (6)
Renal dysfunction	10 (10)	8 (25)
RRT	2 (7)	3 (9)
Ventilatory support	-	2 (6)
Arrythmias†	4 (14)	5 (16)
Indications for operation		
Progressive cardiac failure	7 (24)	5 (16)
Severe valve dysfunction	13 (45)	12 (38)
Failure to control infection	8 (28)	12 (38)
Other indications‡	-	4 (13)

*Coronary embolism (n = 1); femoral embolism (n = 3); brachial embolism (n = 1); digital infarct (n = 2).
†Complete heart block (n = 2); 2° heart block (n = 3); supraventricular tachycardia (n = 4).
‡Multiple embolism/increasing size of the vegetation.
CVA: Cerebrovascular accident; RRT: Renal replacement therapy.

Operative techniques

All operations were performed using standard hypothermic cardiopulmonary bypass. Myocardial protection was achieved with a combination of antegrade or retrograde, cold blood or crystalloid cardioplegia and topical cooling of the heart. The aim of surgery was complete eradication of all infective foci, repair of the resulting defect, and the restoration of hemodynamic stability with the least possible undesired early and late morbidity. Bioprosthetic valves (n = 15) and mechanical valves (n = 40) were inserted using interrupted sutures dipped in antibiotic solutions. The freehand subcoronary implantation technique was used for homograft insertion (n = 6), with interrupted sutures for the proximal suture line and continuous sutures distally. Aortic root endocarditis with extensive annular and subannular abscess was treated by aortic root replacement using a trimmed homograft conduit. Wherever feasible, a native valve repair (seven mitral valves, one aortic valve) was carried out. Additional procedures such as left ventricular outflow tract reconstruction (n = 4), ventricular septal defect (n = 2) and coronary artery bypass grafting (n = 3) were also performed, depending on the needs of the patients. The operative data are listed in Table III.

Data collection and statistical analysis

Eligible patients for the study were identified from the cardiac surgical database. The patients' perioperative data were collected retrospectively from hospital medical records. Information regarding microbiology was obtained from the authors' hospital microbiology department. The status of discharged patients was acquired by telephone interview in order to ascertain long-term outcome. Each patient or their general practitioner was asked a standard set of questions regarding clinical status, possible recurrence, subsequent cardiac operations and the cause of death. Follow up information was available for all of the discharged patients. As this was a retrospective study, institutional review board permission was not required.

Data were analyzed using SAS V8 (SAS Institute, Cary, NC, USA) statistical software. In order to identify factors related to mortality, a Kaplan-Meier survival analysis was employed, utilizing log-rank statistics to identify any evidence of significant differences between the two patient groups. The relationship between differences in preoperative antibiotics duration and morbidity was determined using chi-square and Fisher's Exact tests, as appropriate. A p-value <0.05 was considered to be statistically significant.

Table III: Operative data.

Surgery	No. performed
AVR	16
Aortic root replacement	4
AVR and LVOT repair	4
AVR and Gerbode defect repair	1
AVR + CABG	1
MVR	18
MV repair	5
MVR + VSD repair	2
Double (AVR + MVR)	5
MVR + AV repair	1
MVR + CABG	2
AVR + MV repair	2

Mean cardiopulmonary bypass time = 105 min; mean cross-clamp time = 70.3 min.
AV: Aortic valve: AVR: Aortic valve replacement; CABG: Coronary artery bypass graft; LVOT: Left ventricular outflow tract; MV: Mitral valve; MVR: Mitral valve replacement; VSD: Ventricular septal defect

Results

The median overall survival rate during the follow up period (median 37.4 months; range: 21 to 55 months) was 81.9%. Of the 61 patients, nine died within 30 days of surgery, and contributed to a total operative mortality of 14.8%. The causes of death in these patients were multiorgan failure (n = 4), septic shock (n = 1), myocardial failure (n = 2), cerebrovascular accident (n = 1) and pulmonary embolism (n = 1).

During the follow up period only two patients died after being discharged from hospital. One of these had developed late prosthetic valve endocarditis at one year after his initial operation for aortic valve endocarditis. He again underwent emergency surgery due to prosthetic valve dehiscence (aortic valve replacement with left ventricular outflow tract repair), but

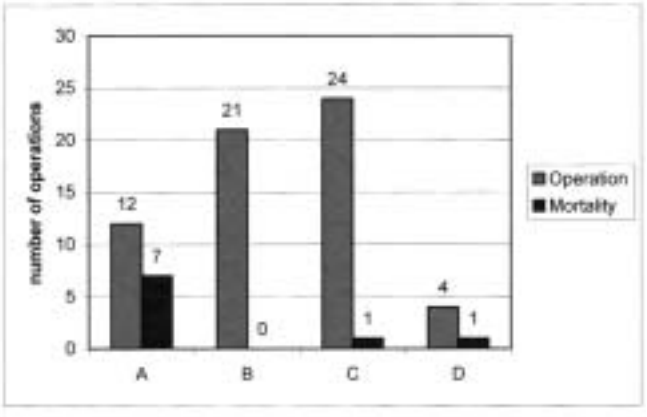

Figure 1: Indications for surgery. A: Progressive cardiac failure; B: Severe valve dysfunction; C: Uncontrolled sepsis; D: Multiple embolism.

Table IV: Statistical analysis of perioperative variables.

Variable	Log-Rank chi-square	PR> chi-square
Gender	0.0101	0.9201
Site of infection	2.0638	0.5593
<14 days preop. antibiotics	0.0277	0.8678
Positive blood culture	0.0564	0.8124
Causative organism	5.6652	0.2256
Presence of extensive infection	6.0976	0.0135
Renal dysfunction before surgery	3.4015	0.0651
Preoperative vasculopathy	0.4618	0.4968
Poor left ventricular function	37.4611	<0.0001
Arrhythmias before surgery	0.5177	0.4718
Cardiac failure as an indication for surgery	29.0091	<0.0001
Postoperative sepsis	52.4855	<0.0001
Renal failure after surgery	13.5830	0.0002
Cerebrovascular accident	0.0191	0.8901
Postoperative arrhythmias	1.5232	0.2171
Paravalvular leak	3.8347	0.0502
Prosthetic valve failure	0.3068	0.5797
Reoperation	2.6104	0.1062
Bioprosthetic valve	6.1692	0.0457

died 46 days after surgery. At autopsy, thrombus was seen to be present in the left ventricle. The other patient died as the result of a road traffic accident.

Univariate analysis of 19 perioperative variables (Table IV) showed the following to be significantly related to hospital mortality: extensive infection ($p = 0.014$); poor left ventricular function ($p < 0.0001$); progressive cardiac failure as an indication for surgery ($p < 0.0001$); postoperative sepsis ($p < 0.0001$); renal failure after surgery ($p = 0.0002$); and use of a bioprosthetic valve ($p = 0.045$).

Preoperatively, group B patients had more embolic and respiratory complications than group A patients (Table II). Four patients (14%) in group A and five (16%) in group B died after surgery. There was one EPVE and one LPVE in group B patients. There was no statistically significant difference between two groups with regard to extensive infection ($p = 1.00$), postoperative sepsis ($p = 1.00$), reoperation ($p = 1.00$) and mortality ($p = 1.00$) (Table V).

Discussion

Based on the results of this retrospective study, which was confined to native valve endocarditis with active infection, it was concluded that the duration of preoperative antibiotics did not appear to have any significant influence on postoperative morbidity and mortality. One case of EPVE and one of LPVE were identified during the postoperative period, with both recurrent conditions occurring only in group B patients. This indicates that surgery during the active infective stage before the completion of standard antibiotic therapy is not a risk factor for recurrent

Table V: Outcome in patient groups A and B.

Complication	Group A (n = 29) (%)	Group B (n = 32) (%)	p-value
Extensive infection	12 (41.3)	19 (59.3)	NS
Postoperative sepsis	4 (13.8)	5 (15.6)	NS
Early PVE	0 (0)	1 (3.4)	NS
Late PVE	0 (0)	1 (3.7)	NS
Reoperation	2 (6.9)	1 (3.2)	NS
Mortality	4 (13.8)	5 (15.6)	NS

Values in parentheses are percentages.
NS: Not significant; PVE: Prosthetic valve endocarditis.

endocarditis, provided that the infected tissue is completely debrided during surgery. The incidence of preoperative complications was also found to be higher in group B patients compared to group A (Table II). Hence, a delay while waiting to sterilize the bloodstream by prolonged antibiotics therapy is not advisable in these high-risk patients. Al Jubair and colleagues (13) also found an increased incidence of preoperative embolic and other complications among patients in whom surgery had been delayed due to prolonged preoperative antibiotics therapy.

Operative mortality in these patients is multifactorial, with preoperative hemodynamics and the type of procedure appearing to be the most important factors (2). Operative mortality in the present study was 14.8%, and compared favorably with that reported in other studies confined to native valve endocarditis (14-16). Nonetheless, it was still higher than values quoted more recently (4,17,18). Almost one-third of the present patients (36%) required an additional procedure with isolated valve replacement, mainly due to extensive infection. This is a well-known situation, as the complicated operative procedures involved cause these patients generally to have a higher mortality rate (8). Moreover, more than half (51%) of the patients operated on for infective endocarditis in the present study were aged over 60 years, and increasing age is an established independent risk factor for late and hospital mortality (11,18). The late death rate of 3.2% (only one death was due to LPVE) in the present series during a follow up period of up to five years was well below the values quoted elsewhere (3,17-19). The overall survival rate for the median follow up period of 37.4 months (range: 21 to 55 months) was 81.9%, and survival of hospital-discharged patients at follow up was 96.2%.

The presence of extensive infection not only indicates progression of the disease but is also a distinctive sign of the failure of antibiotic therapy. Local spread of infection into the annular and surrounding structures often causes periannular abscess, while further advancement of infection results in fistula formation and spread to other valves (20). In the present study 41% of the patients had extensive infection, and this was found to be a significant predictor of operative mortality ($p = 0.014$). The high incidence of extensive infection in the present study might have been related to the fact that many of the patients were infected by *Staphylococcus aureus*. Reinhartz et al. (3) and Miller (15) also found that extravalvular spread of infection is a risk factor for operative mortality; however, Jault et al. (18) reported that operative mortality was not affected by the presence of annular abscess. In multivalve endocarditis, which represents a distinct clinical entity, Mihaljevic et al. (20) reported that the outcome was adversely affected by annular abscess and deep tissue infection.

Left ventricular function in infective endocarditis patients significantly influences preoperative hemodynamic stability and post-cardiotomy recovery after surgical intervention. In the present study, 16% of patients had poor left ventricular function, and this was considered to be one of the significant predictors of operative mortality ($p < 0.0001$). In this regard, the present findings support reports by others of impaired left ventricular function as an adverse predictor of operative mortality in active endocarditis (19,21).

Congestive cardiac failure (CCF) is one of the most common indications for surgery in patients with AIE (15). In the present study, 20% of the patients were operated on for progressive cardiac failure, and all were in NYHA class IV and had a higher mortality compared to patients operated on for other indications (Fig. 1). Statistically, progressive cardiac failure as an indication for surgery was found to be a strong predictor of mortality ($p < 0.0001$). Similarly, many published series (3,6,14,15,19) have also shown cardiac failure to be a predictor of operative mortality. In patients with AIE, the basic pathophysiology of CCF is biventricular dysfunction due to sepsis which, along with acute valvular dysfunction caused by the endocarditis itself, renders the myocardium unable to maintain adequate cardiac output (22). In addition, the condition is aggravated by an increased metabolic demand caused by septicemia. As progressive cardiac failure is a critical factor for operative mortality, it is strongly recommended that any surgical intervention be conducted before the onset of cardiac failure. Based on the results of the present study, it is believed that this might improve operative outcome.

Postoperatively, 30% of the present patients developed renal failure (defined as a 50% rise in normal serum creatinine levels), and 17% required renal replacement therapy during the study. Renal failure was identified as a postoperative factor that influenced operative mortality ($p = 0.0002$). Baumgartner et al. (23) reported similar findings in patients with AIE. Postoperative sepsis is another factor which contributes significantly to hospital mortality ($p < 0.0001$), and among the present patients 14.7% were diagnosed with postoperative sepsis. This occurred mainly in patients with multiorgan dysfunction who required prolonged ventilatory support. In all of these patients the causative organism of sepsis was different from that responsible for the infective endocarditis. In these patients, a diagnosis of recurrent endocarditis was excluded by either clinical or autopsy findings. Rather, postoperative pneumonia was the most common cause of postoperative sepsis in these patients.

The use of a bioprosthetic valve was one variable

which adversely affected early outcome in the present study (p = 0.045). Sweeney et al. (24) and Arvay and Legyel (25) showed that bioprosthetic valve use was associated with a higher incidence of reoperation and recurrent infection, but not with increased mortality. The adverse outcome associated with bioprosthetic valve use in the present study could be related to the age of the patients, as these valves are most often used in older subjects.

The incidences of extensive infection (p = 0.95) and postoperative sepsis (p = 1.00) were found not to differ significantly between the patient groups. In total, three patients underwent reoperations during the immediate postoperative period for paravalvular leak (two patients in group A, one patient in group B). None of these patients showed any evidence of prosthetic valve infection, and all of the reoperations involved the repair of a paravalvular leak. There was no statistically significant difference between the two groups with regard to reoperation (p = 1.00). Witchitz et al. (10) reported a high incidence of perivalvular leak as well as mortality if surgery was performed in the active phase before antibiotic therapy was completed, though the present study findings did not support the conclusion of these authors. As all of the patients in the present study were operated on in an active infective state before the completion of standard antibiotic therapy, the number of reoperations for perivalvular leak was less than the rate quoted elsewhere (11,15,18,19).

Among the present patients, no significant difference was found in the incidence of operative mortality between patients who had shorter (group A) and longer (group B) durations of preoperative antibiotic therapy (p = 1.00). Aranki et al. (9) advocated delayed surgery because they found that surgery during active endocarditis was the only predictor for recurrent endocarditis. In contrast, the incidence of recurrent endocarditis in the present study was 3.2% over the median follow up period of 37.4 months (range: 21 to 55 months), and consequently this cannot be used as a justification for delayed surgery. Similar to the present study, Al Jubair et al. (12) also found that there was no increase in the complication rate due to early surgery; rather, they found morbidity to be better in patients operated on within three days of presentation. Whilst Al Jubair et al.'s study was conducted in younger patients (mean age 29 years), the present investigation was confined to older patients (median age 61 years) with native valve infection, and confirmed these findings among the older population. Therefore, it is recommended that if surgery is indicated in this group of patients, early radical surgical excision of the infected heart valve tissue before any hemodynamic deterioration occurs is the best way to improve early and late outcome, rather than applying more importance to infective parameters. Delaying the surgery until the bloodstream is sterilized by prolonged antibiotic therapy is likely to cause more harm than benefit to the patients.

Study limitations

One major limitation to the present study was its retrospective nature. In addition, no tricuspid or pulmonary valve endocarditis was operated on, and consequently the results were applicable only to left-sided heart valve endocarditis. As the number of patients was relatively small and the number of morbidity events limited, a multivariate analysis could not be performed.

In conclusion, extensive infection, poor left ventricular function and progressive cardiac failure as indications for surgery were preoperative predictors of operative mortality in active native valve endocarditis patients. The duration of preoperative antibiotics did not have any influence on surgical outcome. As the patient's hemodynamics appear critically to affect their surgical outcome, early operative intervention is recommended, before cardiac failure and spread of infection occur.

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