In-Hospital Prognosis of Prosthetic Valve Endocarditis After Urgent Surgery

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Introduction and objectives. Prosthetic valve endocarditis is associated with high morbidity and mortality, particularly when urgent surgery is needed. The identification of factors that predict a poor prognosis is the first step in improving outcomes. The study objectives were to characterize patients with prosthetic valve endocarditis who need urgent surgery and to identify factors that predict in-hospital mortality in this high-risk group.

Methods. From a database of 648 consecutive patients with infective endocarditis diagnosed between 1996 and 2006 at 4 tertiary-care centers with cardiac surgery facilities, 46 patients with left-sided prosthetic valve endocarditis who needed urgent surgery were identified. A retrospective study was carried out to determine these patients' main characteristics and to identify predictors of in-hospital mortality.

Results. The main indications for urgent surgery were heart failure (57%) and persistent infection (33%). In-hospital mortality was 41%. Factors significantly associated with a poor prognosis were fever at admission, persistent infection, positive blood cultures, persistently positive cultures, and echocardiographic evidence of vegetations (*P*<.05). No specific microorganism was associated with a poor prognosis.

Conclusions. Prosthetic valve endocarditis was associated with high mortality when urgent surgery was needed. Although heart failure was the principle reason for urgent surgery, it did not lead to a worse in-hospital prognosis. The presence of vegetations and uncontrolled infection were the main factors associated with higher in-hospital mortality in patients with left-sided infective endocarditis who needed urgent surgery.

Pronóstico hospitalario de la endocarditis protésica tras cirugía urgente

Introducción y objetivos. La endocarditis protésica conlleva una alta morbimortalidad, más aún si precisa cirugía urgente. Determinar los factores predictores de mal pronóstico es el primer paso para disminuirla. Nuestro objetivo es definir el perfil de los pacientes con endocarditis protésica que precisan cirugía urgente e identificar los factores predictores de mortalidad hospitalaria en este grupo de alto riesgo.

Métodos. De una base de datos que incluye un total de 648 casos de endocarditis infecciosa diagnosticados consecutivamente en cuatro centros terciarios con cirugía cardiaca entre 1996 y 2006, 46 fueron endocarditis protésicas izquierdas y precisaron cirugía urgente. Hemos realizado un estudio retrospectivo de las principales características de estos pacientes y un análisis para determinar los factores asociados a una mayor mortalidad hospitalaria.

Resultados. Las principales indicaciones de cirugía urgente fueron la insuficiencia cardiaca (57%) y la infección persistente (33%). La mortalidad hospitalaria fue del 41%. Los factores asociados a un peor pronóstico (p < 0,05) fueron: fiebre al ingreso, infección persistente, hemocultivos positivos y persistentemente positivos y vegetaciones en el ecocardiograma. Ningún microorganismo se asoció a peor pronóstico.

Conclusiones. La endocarditis protésica es una enfermedad con una alta mortalidad cuando precisa cirugía urgente. Aunque la insuficiencia cardiaca es la principal causa de cirugía urgente, no empeora el pronóstico hospitalario. Las vegetaciones y la falta de control de la infección son los factores asociados a mortalidad hospitalaria en los pacientes con endocarditis infecciosa izquierda intervenidos urgentemente.

INTRODUCTION

Despite progress in heart surgery and the systematic use of antimicrobial prophylaxis, prosthetic valve endocarditis (PVE) continues to appear in a small percentage of patients with prosthetic heart valves. It has a bad prognosis and high morbidity and mortality due to cardiac or extracardiac complications.[1-3] It is often managed by heart surgery[2,4,5] and numerous studies indicate that the prognosis of patients with PVE is better using a combined medical-surgical approach than when antibiotic treatment alone is used.[2,6-8] Nevertheless, surgery for PVE is complex and involves high mortality, between 15% and 64% according to different series.[5,8-10] Furthermore, it has been demonstrated that urgent surgery for infective endocarditis (IE) is an important predictor of in-hospital mortality due to complications and severe clinical deterioration of the patient.[5,11,12] A previous study showed that the predictors of in-hospital mortality in patients with left-sided IE needing urgent surgery are persistent infection and kidney failure.[13] However, it remains unknown which factors determine the prognosis of patients with PVE undergoing urgent surgery. Once the factors that worsen prognosis among these patients are identified, the following step would be to assess the usefulness of early heart surgery in high-risk patients before clinical deterioration has occurred.

Various studies have analyzed surgery for PVE,[2,10,11,13-16] but they included heterogeneous groups of patients (right-sided IE and left-sided IE, urgent surgery, elective surgery, and unoperated patients), which may have distorted the results. We describe for the first time the clinical profile and factors related to poor prognosis in a very specific and homogeneous subgroup of high-risk patients: those with PVE who needed urgent surgery.

The aim was to describe the clinical characteristics, microbiological profile, echocardiographic findings, and clinical course of patients with left-sided PVE who need urgent surgery and to determine the factors associated with greater in-hospital mortality in this group of patients.

METHODS

This was a multicenter and retrospective study conducted at 4 tertiary-care centers with cardiac surgery facilities which included a total of 648 patients with IE consecutively diagnosed between 1996 and 2006. The Duke criteria were used until 2002[17] and the modified Duke criteria from then on.[18] There were a total of 495 patients with left-sided IE (76%) and 91 with PVE (39%). Urgent surgery was needed in 46 patients with left-sided PVE (24%) and these formed the study group. All the patients included in this analysis fulfilled the criteria for definite IE according to the modified Duke criteria. The contribution of each participating hospital was as follows: total IE patients (n=648): 30%, 30%, 27%, and 13%; PVE patients (n=191): 41%, 24%, 22%, and 13%. A single protocol was followed in all patients that included 90 variables per patient, as described in previous work.[19]

Definition of Terms

The only event considered was all-cause in-hospital mortality. Early-onset PVE was defined as that occurring less than 1 year after surgery.[19] Heart failure was diagnosed according to established criteria[20] and its severity classified according to the NYHA guidelines. Periannular complications were defined as in previous studies.[21-23]

Urgent surgery was defined as that performed during the active phase of the infection and within 48 hours of its indication.[21] Indications for urgent surgery were agreed by prior consensus among the researchers: heart failure uncontrolled by maximum medical treatment according to the guidelines on heart failure, septic shock, persistent infection (persistent fever or positive blood cultures after 7 days of correct antibiotic treatment, once other possible sources of infection are ruled out)[21] and recurrent embolism despite appropriate antibiotic treatment with persistent echocardiographic evidence of vegetations. A single periannular complication in patients with a favorable clinical course was not considered as an indication for urgent surgery; however, this was indicated when there was an increase in the size of pseudoaneurysms and abscesses or when progressing to fistula.

Statistical Analysis

Discrete variables are expressed as an absolute value (percentage) and continuous variables as mean (standard deviation) and median [interquartile range]. The assumption of normality of the quantitative variables was verified using the Shapiro-Wilk test. The χ^2 test was used to compare the qualitative variables and Fisher's exact test was used when necessary. Continuous variables were compared using the Student t test or its

nonparametric equivalent, the Mann-Whitney *U* test, if the hypothesis of normality was not upheld. Due to the low number of events, multivariate analysis could not be performed to determine the independent predictors of in-hospital mortality. A P value less than .05 was used as a cutoff for statistical significance.

RESULTS

Epidemiological and Clinical Characteristics at Admission

The mean age was 60 (12) (26-74) years; 60% were men. A total of 50% of the patients with a diagnosis of PVE was referred from other hospital centers. A total of 52% of the cases was community acquired and 9 patients had presented a previous episode of IE (20%); this involved the native valve in 7 patients, and a prosthetic valve in 2. The clinical picture was of acute onset in 27 episodes (59%). A total of 18 patients presented some type of predisposing disease (39%); the most frequent was diabetes mellitus (22%). In 56% of the patients in which the portal of entry of the infection was identified, antibiotic prophylaxis had been administered prior to the invasive procedure. Outpatient antibiotic therapy had been administered to 16 patients (35%) before their admission for febrile syndrome. Table 1 shows predisposing disease and portal of entry of the infection.

At admission, the majority of patients presented fever (72%) and 21 presented symptoms and signs of heart failure (46%); 13 were in NYHA functional class III or IV. One patient was admitted in a state of septic shock. The main clinical, radiographic, and electrocardiographic characteristics at admission are shown in Table 2.

Microbiological Findings

The causal organism was identified in 78% of the patients. The microorganisms most frequently isolated were coagulase-negative staphylococci (28%), followed by *Staphylococcus aureus* (20%). In 10 patients, all blood cultures and serological tests were negative and the causal agent could not be identified (22%). *Staphylococcus epidermidis* was the most common causative agent (55%) in the patients with early-onset PVE, most of whom (90%) were methicillin-resistant, whereas in late-onset PVE the causative agent was *Staphylococcus aureus* (29%), most of whom (75%) were methicillin-sensitive. *Streptococcus viridans* was significantly absent in our group of patients. The microbioligical profile is shown in Table 3.

TABLE 1. Predisposing Disease and Portal of Entry of Infection

	Patients, No. (%)
Predisposing disease	
Diabetes mellitus	10 (22)
Chronic anemia	4 (9)
Chronic kidney failure	4 (9)
Cancer	3 (7)
Alcoholism	1 (2)
COPD	1 (2)
Chronic skin disease	1 (2)
Portal of entry of infection	
Unknown	21 (45)
Previous surgery	12 (26)
Dental procedures	4 (9)
Intravascular catheter	3 (7)
Local infection	3 (7)
Gastrointestinal procedures	2 (4)
Genitourinary procedures	1 (2)

COPD indicates chronic obstructive pulmonary disease.

TABLE 2. Clinical, Radiological, and Electrocardiographic Characteristics at Admission

	Patients, No. (%)
Clinical characteristics	
Fever	33 (72)
Heart failure	21 (46)
Stroke	7 (15)
Ischemic	6
Hemorrhagic	1
Systemic emboli	5 (11)
Kidney failure	4 (9)
Splenomegaly	4 (9)
Cutaneous manifestations	3 (7)
Septic shock	1 (2)
Radiological characteristics	
Cardiomegaly	31 (67)
Left-sided heart failure	19 (41)
Pleural effusion	11 (24)
Electrocardiographic characteristics	
AVB	10 (22)
Atrial fibrillation	3 (7)

AVB indicates atrioventricular block.

Echocardiographic Findings

At least one transthoracic echocardiogram and one transesophageal echocardiogram (TEE) were performed in all patients. The main findings are shown in Table 4.

The disease affected mechanical prosthetic valves in 42 episodes (86%) and biological prosthetic valves in 7 (14%). Multivalvular disease was present in 8 patients (17%) and early-onset PVE in 18 (39%). The presence of vegetations was frequent (80%) and 20 patients presented some type of periannular

TABLE 3. Causative Microorganisms

Microorganism	Patients, No. (%)
Coagulase-negative staphylococci	13 (28)
Negative cultures	10 (22)
Staphylococcus aureus	9 (20)
Gram-negative bacilli	6 (13)
Polymicrobial	3 (7)
S epidermidis + Enterococcus avium	1
MRSA+Candida albicans	1
S epidermidis + Propionibacterium acnes	1
Corynebacterium	2 (4)
Streptococcus viridans	1 (2)
Enterococcus spp	1 (2)
Fungi	1 (2)

MRSA indicates methicillin-resistant *Staphylococcus aureus*.

TABLE 4. Echocardiographic Characteristics

	Patients, No. (%)
Location of the infection	
Mechanical prosthetic valve	42 (86)
Mitral	24
Aortic	18
Biological prosthetic valve	7 (14)
Mitral	0
Aortic	7
Total number of prostheses affected	49
Other echocardiographic findings	
Vegetations by TEE	37 (80)
Periannular complication in any TEE	26 (57)
Abscess	16
Pseudoaneurysm	12
Fistula	1
Perforation	2 (4)
Stenosis	6 (13)
Moderate or severe regurgitation in any TEE	25 (54)

TEE indicates transesophageal echocardiography.

TABLE 5. Type of Heart Surgery

Mechanical prosthetic valve 36 (78%)	
Mitral	16
Aortic	5
Mitro-aortic	8
Mitral + aortic valved tube	1
Mitral + thrombectomy	1
Mitral + mitro-aortic junction resection	1
Aortic + repaired pseudoaneurysm	1
Aortic + pacemaker	1
Aortic + mitral valve plasty	1
Aortic valved tube	1
Biological prosthetic valve	4 (9%)
Aortic	3
Aortic + vegetectomy of the mitral valve	1
Homograft	4 (9%)
Aortic	3
Aortic + debridement and mitral valve plasty	1
Mitral valve leak repair	1 (2%)
Bentall-De Bono Procedure	1 (2%)
Total	46

complication during the first transesophageal study (43%): 13 abscesses and 8 pseudoaneurysms (1 patient presented both complications during the same study). Subsequent studies objectified de novo periannular abscesses in 3 patients, and pseudoaneurysms in 4 (1 patient presented both complications in the same study). The initial study objectified an abscess in 1 patient which progressed to fistula. In total, 26 patients presented some type of periannular complication (57%). Moderate or severe valvular regurgitation was detected in 25 patients (54%), which was generally due to prosthetic dehiscence (88%).

Clinical Course

During the clinical course, the patients presented various complications that required surgery: heart failure uncontrolled by medical treatment in 23 patients (50%), persistent infection despite appropriate antibiotic treatment in 12 (26%), both causes in 3 (7%), periannular complications in 6 (13%) septic shock in 1 (2%), and recurrent embolism in 1 (2%). Other complications during the clinical course were kidney failure in 15 patients (33%), splenic emboli in 2 (4%), and cerebral hemorrhage in 1 (2%).

In most cases, surgery consisted in replacement with a mechanical prosthetic valve (78%). Only 3 patients needed reintervention as follows: 2 patients for prosthetic dehiscence with acute pulmonary edema and 1 for early-onset PVE. Table 5 shows the type of heart surgery used in the study group.

A total of 19 patients died during admission (41%): 5 due to intraoperative cardiogenic shock, 5 due to septic shock, 3 due to heart failure, 3 due to multiorgan failure, 2 due to septic shock and heart failure, and 1 due to ventricular fibrillation. Among the patients who underwent surgery for heart failure, mortality was 22% (5/23), whereas in those who underwent surgery due to persistent infection, mortality was 83% (10/12). Of the 3 patients in whom the cause of surgery was heart failure and concomitant persistent infection, 1 patient died. There were no significant differences in mortality between early-onset and late-onset PVE (44% vs 39%).

Predictors of In-Hospital Mortality

Table 6 shows the factors associated with greater in-hospital mortality in the univariate analysis. The variables associated with uncontrolled infection (positive blood cultures, persistently positive

TABLE 6. **Univariate Analysis of In-Hospital Mortality**

	Death	Survival	*P*
Patients	19 (41%)	27 (59%)	
Fever at admission	18 (95%)	15 (56%)	.004
Positive blood cultures	16 (84%)	10 (39%)	.002
Positive blood cultures after 48 h of appropriate antibiotic treatment	8 (50%)	2 (11%)	.022
Vegetation by TEE	18 (95%)	18 (67%)	.031
Local infection	15 (79%)	7 (26%)	<.001
Heart failure	8 (42%)	21 (78%)	.014

TEE indicates transesophageal echocardiography.

cultures 48 h after beginning antibiotic treatment, fever, and persistent infection) and evidence of vegetations by TEE were associated with greater in-hospital mortality. Heart failure was not associated with greater mortality in our group of patients.

DISCUSSION

According to our analysis, the factors associated with worse in-hospital prognosis in PVE were signs of uncontrolled infection. A study previously published by our group determined that the predictors of poor prognosis in IE were the need for urgent surgery due to persistent infection and kidney failure.[13] However, heart failure did not negatively influence prognosis among these patients. The present work indicates that this is also observed in patients with PVE requiring urgent surgery. Heart failure is a serious complication in IE in general, and is associated with greater mortality and the need for urgent surgery in most series.[15,24-27] However, in the context of urgent surgery, heart failure does not seem to worsen the prognosis. This may be due to the fact that heart failure in IE is usually secondary to valvular dysfunction (severe periprosthetic regurgitation, prosthetic disk immobilization, perforated or torn leaflets in biological prosthetic valves, etc) and surgery is an effective solution in these situations. Thus, it is a local problem that is solved with local treatment (valve replacement). Nevertheless, series that include greater numbers of patients are needed to confirm our finding.

Persistent infection is an indication for antibiotic treatment[28] and is associated with high mortality.[28-30] Surgery is recommended in these patients and the attempt to complete the antibiotic treatment cycle should never delay its execution.[21] In our series, mortality among the group of patients with persistent infection was 3 times higher than that of the other patients. This is probably due not only to greater damage to the valvular and perivalvular tissue (which requires a more complex surgical procedure), but also to increased involvement at the time of surgery, caused by the infection spreading. Thus, a systemic problem due to an uncontrolled infection process is almost impossible to control by heart surgery.

As mentioned, various studies have reported that surgical mortality in PVE ranges between 15% and 60%,[2,10,11,13-16] although these studies included heterogeneous groups of patients (right-sided IE, left-sided IE, urgent surgery, elective surgery, and unoperated patients). Mortality in our group was high (41%), and is explained by the severity of the clinical situation at the time of surgery. It is striking that the main factor influencing mortality in our group was the cause of surgery: patients needing surgery for persistent infection presented extremely high mortality (83%), in contrast to those who underwent surgery for heart failure (22%). As mentioned, the explanation for this difference is that surgery in patients with heart failure can solve the problem (replacement of the faulty prosthetic valve), but it is far more difficult for surgery to solve an uncontrolled infection. These results indicate that urgent surgery in PVE can be performed with acceptable risk in patients with heart failure, but in those with persistent infection the risk is very high.

Another explanation for the high mortality in our group may be due to applying the definition of persistent infection indicated in the European guidelines[21] (persistent fever and positive blood cultures after 7 days of appropriate antibiotic treatment, once other possible sources of infection have been ruled out). The cutoff point of 7-10 days is completely arbitrary and is not based on robust scientific data. It is tempting to speculate that the indication for surgery in these patients is very late, and that after 7-10 days of uncontrolled infection a certain degree of multiorgan failure may also occur, which would increase postoperative mortality. In fact, the leading causes of death in patients with persistent infection were septic shock and multiorgan failure.

More studies are needed to determine which factors predict the onset of persistent infection in patients with IE and how a more aggressive

treatment before this situation develops could influence prognosis. In this regard, our group is currently conducting a multicenter randomized study[31] comparing 2 treatment strategies in high-risk patients with IE (NCT00624091): early surgery in the first 48 h after diagnosis of the disease versus the standard management recommended by the guidelines. The results of this study could help clarify this difficult issue in patients with IE.

Various studies have associated staphylococcal infection with a worse prognosis in endocarditis[2,3,6,8,18,32-34]; however, in our series no microorganism was associated with greater mortality. A total of 22% of patients infected by *Staphylococcus aureus* died. Our data indicate that prognosis after urgent surgery mainly depends on whether the infection has been controlled or not, rather than on the causative agent. The fact that *Streptococcus viridans*—one of the main causative agents of late-onset PVE—was significantly absent from our series is explained by its low pathogenicity.[11] This makes the infection easier to manage with antibiotic treatment, which in combination with the low complication rate rarely leads to the need for urgent surgery.[3]

The choice of the type of prosthesis to use in the surgical treatment of IE during the active phase is a controversial subject,[5] due to the risk of the infection recurring on the prosthetic material caused by handling infected tissues. It has not been demonstrated that the duration of antibiotic treatment prior to surgery is associated with greater recurrence of endocarditis on the prosthetic material (mechanical or biological).[16,35,36] Some studies have demonstrated that the early-onset PVE in patients during the active phase of the infection is very rare (1%-3%).[36-38] In our series the main surgical technique used was replacement with a mechanical prosthetic valve. The infrequent use of homografts was due to the great difficulty in obtaining them in sufficient time, given that the patients needed urgent surgery. In our experience, the use of a medical-surgical approach via radical resection of the infected tissue, replacement with mechanical prostheses, and aggressive antibiotic treatment is a safe technique. In our series prosthetic dehiscence only affected 2 patients (4%) and there was 1 relapse (2%), which is in line with other authors.[5]

Limitations

This study was conducted in tertiary centers with heart surgery facilities—those to which IE patients are referred by other hospitals—and therefore our results can only be applied to similar centers. Furthermore, given the low number of patients and events, multivariate analysis could not be performed to determine the independent predictors of in-hospital mortality, and thus larger studies are needed to confirm our results.

CONCLUSIONS

Urgent surgery for PVE is associated with high mortality. Although heart failure was the leading cause of urgent surgery, it did lead to worse prognosis in our group of patients. The presence of vegetations and uncontrolled infection were the main factors associated with higher in-hospital mortality in patients with left-sided IE who needed urgent surgery.

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