Combined Medical and Surgical Treatment for Active Native Valve Infective Endocarditis: Ten-Year Experience

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AKTİF DOĞAL KAPAK ENDOKARDİTİNDE KOMBİNE MEDİKAL VE CERRAHİ TEDAVİ: ON YILLIK DENEYİM

ÖZET

Bu çalışmanın amacı, doğal kapak enfektif endokarditinin kombine medikal ve cerrahi tedavisinin yararlarını ve sonuçlarını irdelemektir.

1985 ile Haziran 1999 tarihleri arasında aktif doğal kapak endokardit tanısı ile ameliyat edilen 66 hasta ile bu çalışma retrospektif olarak yapılmıştır. Hastalar ameliyat öncesi ve sonrası antibiyoterapiye tabi tutulmuşlardır. Aort ve mitral kapaklar izole olarak 18'er hastada (%27.2) tutulmuşken iki kapağın beraber tutulumuna 30 hastada (%45.6) rastlanmıştır.

Hastalar ortalama 4 ± 3.4 yıl (2 ay ile 12 yıl), toplam 274.1 hasta-yılı izlendiler. Hastane mortalitesi sekiz hasta ile %12 civarında idi. Erken ölüm riskini artıran anlamlı faktörler acil ameliyat, annuler abse, preoperatif şok tablosu olarak belirlendi. Geç mortalite 6 hasta ile %10.3 olarak bulundu. 2 hasta (%4) en kısa sürede reoperasyon gereksinimi gösterdi. Beş ve 10 yıllık sağ kalım oranları ilk 5 yıl için %80.5 ± 5.5 ve10 yıl için %64.7 ± 9.5 olarak bulundu. Tekrarlayan enfeksiyonsuz yaşam ilk 5 yıl için %94 ± 4.25 ve 10 yıl için %80.44 ± 9.79 idi.

Doğal kapak endokarditinin cerrahi tedavisi halen mortalitesi yüksek olsa da yaşayan hastaların uzun dönem sonuçları yüz güldürücüdür. Aktif endokarditte komplikasyon gelişmemişse, optimal cerrahi tedavi zamanı antibiyotik tedavisinin tamamlanmasından sonradır. Kombine medikal ve cerrahi tedavi uygulaması yaşam süresini olumlu etkiler.

Anahtar kelimeler: *Doğal kapak endokarditi, kombine tedavi, kalb cerrahisi*

In the last quarter of this century, cardiac surgery has become increasingly important in the treatment of active native valve endocarditis (NVE) (1-6). If patients with NVE receive medical therapy, 15% to 25% eventually require operation (7). Antibiotics have contributed to an improvement in survival, but also have changed the major cause of death from infection to congestive heart failure. Although antibiotic therapy remains the first-line treatment of bacterial endocarditis, it becomes insufficient when complications develop. Although the majority of patients who develop infective endocarditis are successfully treated with antibiotics, those who require surgical intervention provide the surgeon with great challenges.

The aim of this study was to investigate early and late results after the combined therapy that was preferred for the treatment of the active native valve infective endocarditis in 66 patients. All patients with an active native valve infective endocarditis treated with only medical therapy or active prosthetic valve infective endocarditis was excluded from this study.

MATERIAL and METHODS

From January 1985 to June 1999, single or double valve replacement was applied to 3650 patients, and only 66 of them (0.018%) were operated on for active NVE. There were 45 male and 21 female patients with mean age 33.5 ± 11.4 years (range, 16 to 65 years). Endocarditis was labeled active if patient had serious hemodynamic deterioration because of increasing of native valve damage during completion of a standard course of antibiotic treatment, or if the patient required an operation before completion of a standard course of antibiotic treatment, or if there were ongoing signs sepsis (2). Preexisting rheumatic valvular disease was present in 26 patients (40%), nearly one third of the aortic infections were on bicuspid valves (17 patients; 28%), and the rest had no preexisting valvular lesion (23 patients; 32%). Associated diseases were diabetes mellitus (9.1%), hypertension (4.5%), coronary artery disease (3%), ventricular septal defect (1.5%). Seven patients (10.6%) were treated for native valve endocarditis previously and they recovered without any complication. The

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Presented in World Symposium on Heart Valve Disease 11- 14 June 1999, London

interval between first and second infection was1.3 ± 0.3 years (range, 0.7 to 1.6 years). There was no drug addict and no fungal endocarditis.

Staphylococci was the cause in 27% of cases and streptococci in 25%, while only three patients (4.5%) had Brucella-endocarditis. We did not exclude any negative culture from the study, because the majority of patients (44%) had negative blood cultures in the first two weeks after NVE had developed. The half of all patients were transported to our clinic in the first two weeks after their NVE was diagnosed and antibiotic therapy was started. Except urgent surgical therapy, all of the patients were treated with our standard antibiotic therapy protocol: *preoperative* IV penicillin G (24-40 million U / day / 4-6 weeks) *plus* IV gentamicin (1 mg/kg / 12 hours / 2-4 weeks) or IV vancomycin (30 mg/kg / day / 4 weeks). Antibiotic therapy was extended more two weeks after surgery to avoid from early recurrence. We completed antibiotic therapy to minimum total four weeks (preoparetive + postoperative) in urgent surgical interventions.

Indications for operation

Sixty-one (92.4%) patients underwent elective surgical intervention after the completion of preoperative antibiotic therapy, where 5 (7.6%) patients underwent urgent surgery. Surgical intervention in the first two weeks after beginning of the antibiotic therapy because of serial complication of endocarditis defined as urgent surgery. The most important indications for operation were congestive heart failure, severe leaflet degeneration, and large vegetation (Table 1).

When leaflet rupture or perforation occurred we defined them as severe leaflet degeneration. Thirty-one patients had severe leaflet degeneration, where 8 patients had middle leaflet degeneration. These 8 patients had annular dilatation and/or valve prolapsus. We separated vegetations in four groups according to their sizes: severe big vegetation (> 12 mm), large vegetation (> 10 mm), middle-sized vegetation (5-10 mm), and small vegetation (< 5 mm). Ten patients had a large vegetation, whereas 14 had a middle-sized vegetation. Two patients with a big vegetation underwent urgent surgery after the detection of vegetation echocardiographically.

The reasons for the urgent surgery were a severe big (> 1.2 cm) and mobile vegetation on the aortic valve in 2 patients, acute leaflet rupture with cardiac decompensation in 2 patients, periannular extensive abscess with intracardiac fistula in 1 patient [8].

There were 6 embolic events (femoral artery in 4 patients, brachial artery in 2 patients). Surgical treatment was performed minimum three days after embolectomy.

Echocardiograpic data

Echocardiographic data were available in all patients preoperatively with mean left ventricular diastolic diameter 62.9 ± 10 mm (range, 48 to 87 mm), and mean left ventricular systolic diameter 41.1 ± 9.3 mm (range, 28 to 60 mm). The native valve lesions are listed in Table 2. Aortic annulus abscesses were detected preoperatively in three patients and mitral annulus abscess was detected in one patient. The other three patients with aortic annular abscess were detected operatively.

Table 1. Native valve lesions of the patients

	n		%
Valve involved			
aortic	18		27.2
mitral	18		27.2
aortic+mitral	30		45.6
Vegetation			
large (>10mm)	16		24.2
medium (5-10mm)	14		21.3
non	36		54.5
Extravalvular extension	7		10.6
aortic root abscess		(6)	(12.5% of aortic NVE)
mitral root abscess		(1)	(2.1% of mitral NVE)
Leaflet rupture	16		24.2
aortic		(10)	
mitral		(6)	
Leaflet perforation	15		22.8
aortic		(9)	
mitral		(6)	

Table 2. Indications for operation

Congestive heart failure	26	39.4 %
+ middle leaflet degeneration	11	
+ middle-sized vegetation	7	
+ arrhythmia	4	
+ severe leaflet degeneration	4	
Severe leaflet degeneration	19	28.8 %
+ congestive heart failure	13	
+ middle-sized vegetation	6	
Large vegetation	10	15.1 %
+ peripheral emboli	6	
+ severe leaflet degeneration + congestive heart failure	4	
Paravalvular abscess	6	9.1 %
+ congestive heart failure + sepsis	4	
+ severe leaflet degeneration + sepsis	1	
+ severe leaflet degeneration + middle-sized vegetation	1	
Urgent surgery	5	7.6 %
+ severe big vegetation	2	
+ severe leaflet degeneration + shock	2	
+ paravalvular abscess + intracardiac fistula + shock	1	

Surgical intervention

The operative procedures are listed in Table 3. All operations were performed using cardiopulmonary bypass with either crystalloid or blood cardioplegia at moderate (28° to 32°C) hypothermia before 1993, after that we used retrograde continue blood cardioplegia. Intraoperative findings included vegetation, leaflet perforation or rupture, and annular abscess. A single-valve procedure was performed in 36 patients (54.5%) and double-valve procedure in 30 patients (45.5%). The majority of abscesses (57%) were dealt with obliteration of the cavity at the sinus of Valsalva by incorporation of it into the suture line during valve replacement. Homograft aortic root replacement was applied in 2 patients.

Statistical Analysis

Results were presented as mean ± standard deviation. Univariate (Pearson χ^2 test) analyses was used to show significant improvement of the functional class after operation, the relation between vegetation-size and mortality or thromboembolic events. Multivariate (stepwise logistic regression) analysis was used to identify significant predictors of operative and late mortality, and recurrent endocarditis. Analysis of survival and freedom from complications was performed using Kaplan-Meier survival test, and the results were presented as mean ± standard error. A p value less than or equal to 0.05 was considered statistically significant for all comparisons.

Table 3. Operations and valve types for infective endocarditis

AVR	**18**	
AVR		12
AVR (Homograft)		2
AVR + repair of SVA		4
AVR +MVR	**30**	
AVR + MVR		22
AVR + MVR + TDVA		2
AVR + MVR + PFO		1
AVR + MVR + VSD		1
AVR + MA + TDVA		1
AVR + MA + repair RCSVA		1
AVR + MVR + ARE (Monongian)		1
AA + MA		1
MVR	**18**	
MVR		15
MVR + TDVA		2
MVR + PFO		1
Mechanical	**90**	
Monoleaflet		45
Bileaflet		45
Tissue valve	**6**	
Bioprosthesis		4
Homograft		2

AVR = aortic valve replacement; MVR = mitral valve replacement; TDVA = tricuspid DeVega annuloplasy; SVA = sinus of Valsalva aneurysm; PFO = patent foramen ovale; AA = aortic annuloplasty; MA = mitral annuloplasty; VSD = ventricular septal defect; ARE = aortic root enlargement; RCSVA = right coronary sinus of Valsalva aneurysm

RESULTS

Hospital and late mortality

The hospital mortality was 12% and late mortality 10.3%. The causes of early and late mortality are listed in Table 4. Multivariate analyses showed that urgent operation, annular abscess, and preoperative shock were the predominant risk factors for operative mortality, and congestive heart failure was only significant predictor for late mortality (Table 5).

Follow-up

Follow-up averaged 4 ± 3.4 years (range, 2 month to 12 years) and totaled 274.1 patients-years. Actuarial survival was 80.5% ± 5.5 at 5 years and 64.7% ± 9.5 at 10 years.

Preoperative vegetation size and embolic events

The relation between vegetation size and embolic events was significantly higher at patients with the vegetation size > 10 mm than at the patients with the vegetation size < 10 mm (5/16 versus 1/14; p = 0.01).

Late complications

Late complications are divided into two groups: valve-related and other events. The 6 valve-related complications (10.3%) included 4 recurrent endocarditis (6.9%), and 2 periprosthetic leaks (3.4%). Two patients required a subsequent reoperation and the reason was perivalvular regurgitation without obvious infection.

Table 4. Mortality causes

	patients	death	%
Early Mortality	**66**	**8**	**12**
preoperative shock	(3)	3	(100)
annular abscess (sepsis)	(7)	3	(42.8)
urgent operation	(5)	2	(40)
Late Mortality	**58**	**6**	**10.3**
noncardiac		3	5.15
heart failure		3	5.15

The number in the first brackets means how many patient had these risk factors, and those in the second brackets means how percent of them died.

Table 5. Multivariate analysis (* logistic regression showed that this factor was significant)

Operative death Risk factors	Odds ratio (± 95% CI)	p
preoperative shock	166.8	0.0075*
annular abscess	38.5	0.0089*
urgent operation	42.2	0.0254*
congestive heart failure	4.5	0.373
age	2.3	0.495
double valve replacement	3.32	0.304
microorganism	0.45	0.65
Late death Risk factors	**Odds ratio (± 95% CI)**	**p**
preoperative shock	0.006	0.96
annular abscess	0.001	0.90
urgent operation	0.009	0.93
congestive heart failure	9.40	0.038*
age	1.78	0.65
double valve replacement	0.55	0.55
Recurrent IE Risk factors	**Odds ratio (± 95% CI)**	**p**
preoperative shock	0.029	0.92
annular abscess	4.02	0.32
urgent operation	0.012	0.84
congestive heart failure	0.98	0.99
age	0.98	0.98
double valve replacement	1.25	0.79
vegetation	1.07	0.94

Valve-related events

Actuarial freedom from valve-related complications was 89.18% ± 5.24 at 5 years and 76.3% ± 9.72 at 10 years.

Recurrent infective endocarditis

Actuarial freedom from recurrent infection was 94% ± 4.25 at 5 years and 80.44% ± 9.79 at 10 years. All patients admitted to our clinic with fever, palpitation, hepatomegaly, and splenomegaly. They underwent transesophageal echocardiographic examination. All of them had negative culture. They were treated with the same medical therapy protocol. We did not see any recurrence in the first year after operation. We did not find any correlation between the recurrence of infective endocarditis and risk factors.

Functional class

Functional results as assessed by the NYHA class at follow-up showed a major improvement ($p = 0.0001$) in nearly all cases (Figure 1).

DISCUSSION

Infective endocarditis (IE) is the condition in which there is microbial infection of the endothelial surface of the heart and at more than 80% of patients with native valve endocarditis develop symptoms within two weeks. Rheumatic valvular disease was the predisposing cardiac lesion for IE in 20 to 25% of cases in the developed countries 20 years ago [9]. In our series this ratio was 40%.

Two major objectives must be addressed to effectively treat of IE. The microorganism must be eradicated, because failure to accomplish this results in relapse of infection. The second objective often exceeds the capacity of infective antimicrobial therapy and requires cardiac or other surgical intervention. Retrospective data suggested that mortality was unacceptably high when patients with the complications were treated with antibiotics alone, whereas mortality was reduced when treatment included antibiotics and surgical intervention [7,10]. Before the antibiotic era, uncontrolled sepsis was responsible for the majority of deaths in infective endocarditis, giving a mortality rate close to 100%. Antimicrobial therapy resulted in survival rates of 75% [1]. Prior antibiotic therapy is a major cause of blood culture-negative IE, particularly when the causative micro-

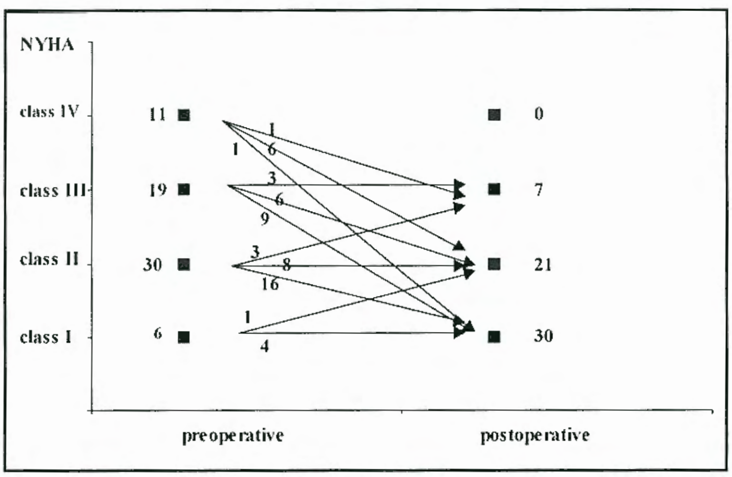

Figure 1. Improvement of the patients' functional capacity. 45.4% of all patients were in NYHA functional class ≥ III before operation. After operation 88% of survivors were in NYHA functional class I or II ($p = 0.0001$)

organism is highly antibiotic susceptible (11). Mortality rate was lower for patients with culture-negative endocarditis who received antibiotics preoperatively to obtain blood cultures and those who became afebrile during the initial week of antimicrobial treatment (10,12). In the other hand, the correlation between higher operative mortality and staphylococci has been well proved (13-15). But in present study, there was no any correlation between early mortality and any microbiologic agent.

When endocarditis is complicated with valvular regurgitation and significant impairment of cardiac function, surgical intervention before the development of severe intractable hemodynamic dysfunction is recommended, regardless of the duration of antimicrobial therapy (16). Except that, early surgical intervention in infective endocarditis is performed only when there is persistence of sepsis or when arterial embolism has occurred, otherwise the completion of the antibiotherapy course is considered necessary (5,15,17). Medical therapy of patients with NVE that is complicated by moderate to severe congestive heart failure due to new or worsening valvular dysfunction results in mortality rates of 50 to 90%. Survival rates for a similar group of patients treated with antibiotics and cardiac surgery are 60 to 80% (7,10). At patients with valvular dysfunction in whom infection is controlled and cardiac function is compensated, surgery may be delayed until antimicrobial therapy has been completed. In our series we undertook five patients into emergency operation because of severe heart failure and persistence of sepsis. We completed the antibiotic therapy to the others before the operation. After valve replacement, we routinely gave antibiotics for 2 or 6 weeks to prevent early recurrence of infective endocarditis.

Hospital mortality for surgical treatment ranges between 3.8 and 20% and statistically significant risk factors for mortality are cardiogenic shock at the time of operation, perivalvular infection, staphylococcal infection, and renal and multiorgan failure (2,5,15,18). In our series, hospital mortality was 12% and significantly predictors were urgent operation, preoperative shock and perivalvular extension. Ring abscesses are usually seen in the aortic position (2,15). It was the same in our study: 12.5% of aortic NVE and 2% of mitral NVE. Congestive heart failure has been shown to be an important prognostic indicator of late mortality (2,6). 50% of all late mortality of our series was due to severe heart failure developed after the fifth years after the valve replacement. Among patients with NVE discharged after medical or medical-surgical therapy, long-term survival was 88% at 5 years and 81% at 10 years (19). Among patients treated surgically for NVE, survival at 5 years ranged from 70 to 80% (18,20-22), at 10 years ranged from 60-75% (2,6,15,18,22). Our results are comparable to these results.

In the other hand, it was established that the presence of an annular abscess was significant predictor of the recurrence of endocarditis and was strongly associated with early recurrence. But in our series, there were four recurrences of endocarditis in the postoperative period and none of them had had anular abscess before the operation. We did not see any early recurrence of endocarditis in the early follow-up period. The long-time antibiotherapy course before and after surgery can be effective to protect the prosthetic valves against the early recurrent endocarditis. Freedom from recurrent endocarditis at 5 years was 87% (18) and 10 years ranged from 64-91% (2,6,15,18). We observed a better freedom from recurrence at 5 years, and no recurrence occurred in the first year after operation.

It was reported that the presence of large vegetation (> 10 mm) has been associated with an increased risk of embolisation (10,23,24). The presence of documented large vegetations, particularly if they are pedunculated, is an indication for surgical intervention even in the absence of symptoms (25). In our series, there was a significantly correlation between thromboembolism and vegetation-size (> 10 mm increased the embolic events).

When there was an extravalvular extension including aortic root, we preferred homograft to replace the aortic valve and ascending aorta. Active bacterial endocarditis remains an ongoing surgical challenge. To optimize surgical results, early diagnosis and aggressive medical therapy need to be combined with surgical referral. Early intervention is essential in those patients known to have poor prognosis for medical cure. The presence of the failure of the medical therapy or the absence of hemodynamic compensation should also precipitate early surgical referral. To continue the antibiotherapy after operation can be useful to prevent early or late recurrent infection. If cultures of the valves or surrounding tissues are positive, antibiotics should be continued after operation. If cultures and histology are negative and there is no perivalvular extension then there is no need for more than completion of the original course of antibiotics.

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