Clinical Outcome of Native Valve Infective Endocarditis in Khon Kaen: 1990-1999

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Abstract

Objective: To compare the survival of infective endocarditis (IE) patients following different treatment strategies and to determine the predictors of patient survival.

Background: IE is a life-threatening infectious disease that is often difficult to manage. Studies on long-term outcome are limited.

Method: Data on 152 patients with IE from 1990 to 1999 were collected from two hospitals. The main outcome is death after definite diagnosis of native valve IE.

Results: The overall case fatality rate was 38 per 100 patient-years. Survival curves showed better survival for patients treated with surgery compared with patients treated medically (p <0.0001). Survival rate at year 1 was 72 per cent for surgically treated patients and 33 per cent for medically treated patients. Five-year survival rates were 66 per cent and 27 per cent in the two groups, respectively. Based on Cox proportional hazards regression analysis, surgery to be an independent predictor of survival (relative risk [RR] = 0.23; 95% confidence interval [CI] 0.14 to 0.39, p <0.0001), while the presence of congestive heart failure (RR = 2.55; 95% CI 1.61 to 4.02, p <0.0001), and being male (RR = 1.76; 95% CI 1.04 to 2.82, p <0.05) were independent predictors of mortality.

Conclusion: Patients with native valve endocarditis have a high long-term mortality rate. The most common types of cardiac death are post-operative and sudden death. Surgical treatment was the preventive factor of mortality.

Key word : Infective Endocarditis, Long-Term Study, Long-term Survival

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Infective endocarditis (IE) remains a formidable problem, not only in diagnosis but also clinical management. In developed countries, rheumatic valvulitis is less common than it was 75 years ago. However, it remains an important disorder in developing countries, and in this location. IE that complicated rheumatic heart disease is still a major problem.

The clinical diagnosis of IE may be relatively straight forward in patients whose history and physical findings are evident and blood cultures reveal a characteristic microorganism. However, it may be very difficult when the patient's blood cultures remain sterile, because of either prior antimicrobial therapy or the fastidious nature of the infecting agent. Demonstration of abnormalities in heart valves, particularly by the use of echocardiography technology[1-3], has resulted in new paradigms for the diagnosis of IE. Studies by Durack et al, have resulted in the so-called "Duke criteria"[4], which have been modified slightly[5]. In either original or modified versions, the Duke criteria have been very valuable and their usefullness has been confirmed in a number of studies[6,7].

Effective antibiotic treatment has favorably influenced the natural history of IE and has led to an improvement in survival[8-10]. Yet soon after the introduction of effective medical therapy for IE, it became apparent that a number of patients continued to show poor outcome because of residual valvular damage[11,12]. The successful replacement of an aortic valve in a patient with active IE was first reported in 1965[13]. Thereafter, it became apparent that surgical treatment was a lifesaving option for patients with IE, even if the procedure was carried out before eradication of the active infection could be assured.

Recent information regarding long-term prognosis of IE is limited[10,14]. Survival of IE patients has been reported variably[14,18]. In Thailand, there have been no reports on the long-term survival of IE patients.

A follow-up study of patients was conducted after the first episode of native valve IE. The purpose of the study was to evaluate the long-term outcome of patients with IE and the factors affecting the survival of IE patients.

MATERIAL AND METHOD

Patients were included in the study if they met the Duke criteria for the diagnosis of IE[4] and had been hospitalized for treatment of active native valve IE between January, 1990, and February, 1999 at Srinagarind Hospital, Khon Kaen University, a tertiary referral center and Khon Kaen Regional Hospital.

Follow-up: The end-point during follow-up period was either death or survival. The censor date was on February 28, 1999. For an individual patient, the follow-up time covered the date of diagnosis to the date of event or the date of loss to follow-up. Death from any cause was ascertained from hospital records. Assessment of congestive heart failure severity based on New York Heart Association (NYHA) class I-IV was conducted during hospitalization. Informed letters were sent to the patients presumed or known to be alive.

Statistical Analysis

Case fatality rates for IE patients were calculated according to standard methods[15] as the number of patients who died during the follow-up period divided by total patient-years at risk.

Comparison was made between IE patients who received only medical treatment and the patients who underwent surgery. Differences in patient and clinical characteristics as well as disease severity were tested for statistical significance using Student's *t*-test for continuous variables and Chi-square test for categorical variables.

The primary end point was death from all causes. Survival curves were estimated using Kaplan–Meier method. Multivariate Cox proportional hazards regression was used to determine the significant predictors of survival when controlled for demographics and disease severity. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Although 203 patients were diagnosed with infective endocarditis (IE), only 152 patients met the criteria and were included in the analyses. The median follow-up time after definite diagnosis was 16 months (range 0-9.7 years). Crude case fatality rate in the study patients was 38 per 100 patient-years. Cumulative survivals are shown in Fig. 1. The survival rates were 52 per cent, 47 per cent, and 43 per cent at 1, 2, and 3 years, respectively.

Baseline characteristics

Of the 152 study patients, 70 patients (group A) underwent surgery during the active stage

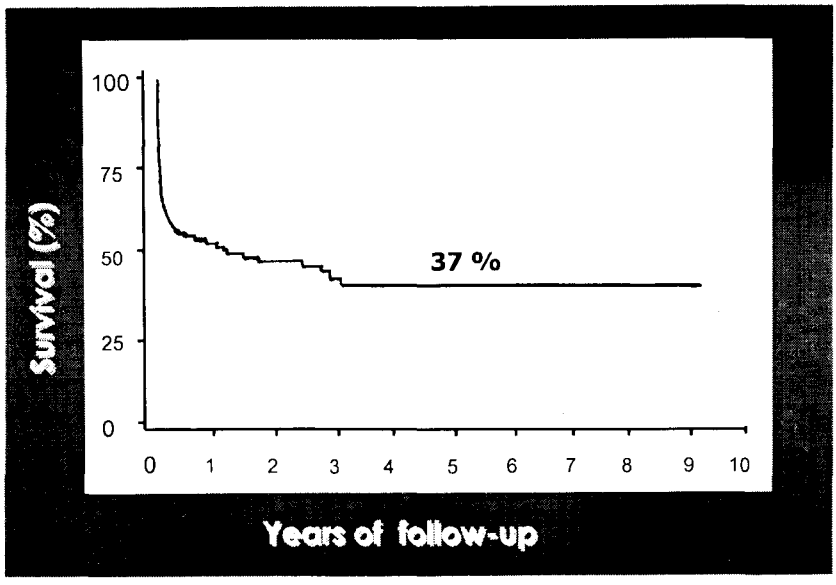

Fig. 1. Long-term survival of native valve endocarditis.

Table 1. Baseline characteristics of IE patients receiving surgical (Group A) and medical (group B) treatment.

	Group A (n=70)	%	Group B (n=82)	%
Male *	55	79	46	56
Age (years, mean ± S.D.) *	34±13		42±16	
Duration of symptoms (day, mean ± S.D.)	37±52		44±40	
Streptococcus viridans	14	20	23	28
Staphylococcus aureus	8	11	10	12
Culture negative	30	43	31	38
AV endocarditis	35	50	31	38
MV endocarditis	28	40	40	49
AV ring abscesses *	12	17	5	6
Cerebral embolism *	4	6	16	20
NYHA Class I-III	48	69	56	68
Class IV	22	31	26	32

* Indicates statistically significant difference between the two groups ($P < 0.05$)

MV= mitral valve, AV= aortic valve, NYHA= New York Heart Association

Embolic event was defined as the acute onset of organ system dysfunction consistent with ischemia, based on objective changes found during physical examination or radiologic studies.

of IE, often with multiple indications. All patients were receiving intravenous antibiotics at the time of surgery for clinically apparent ongoing infection. The other 82 patients (group B) with active native valve IE were treated conservatively with antibiotics. Eight patients in group B were lost to follow-up.

Demographic and clinical characteristics of the two groups are shown in Table 1. The mean (standard deviation) age of group B patients was 42 ± 17 years, and was significantly older than those in group A (34 ± 14 years). There was significant difference between the groups with regard to gender, cerebral embolism prior to admission, and aortic root

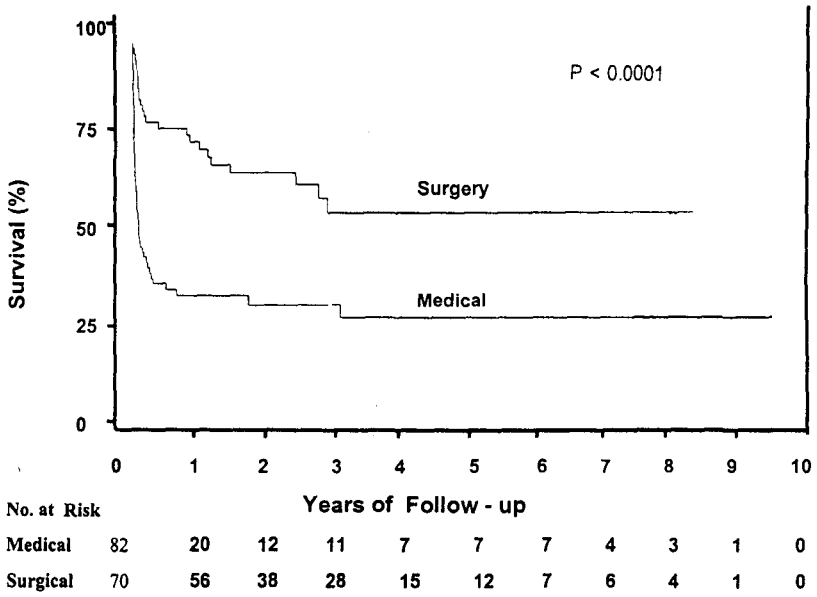

Fig. 2. Long-term survival of patients with infective endocarditis according to treatment strategies.

abscesses. No significant differences in relation to the site of involvement of IE, infective organisms and mean duration of symptoms before admission were found.

Outcome in surgically and medically treated groups

Surgery was performed on 70 patients during the active stage of IE. Indications for surgery included; severe congestive heart failure (NYHA class III or IV) in 27 patients, persistent infection (one patient), recurrent emboli (2 patients), large and mobile vegetations > 15 mm (20 patients), aortic valve ring abscesses (12 patients). In eight patients the indications could not be determined. Aortic valves were replaced in 35 patients, mitral valve in 28 patients, tricuspid valve in 7 patients and pulmonic valve in 2 patients. The operative mortality was 19 per cent (13 deaths among 70 patients). Among the patients who underwent surgery, the median follow-up period was 23 months (range: 0-9 years). Patient survival rates were 72 per cent and 66 per cent at years 1 and 3, respectively (Fig. 2). Among those who survived through the third year (45 patients), no patients died thereafter.

Mortality rate during medical treatment is shown in Table 2. Of the 82 patients, 56 (68%) patients died during the observation period. Causes of death were identified as cardiovascular-related in 26 patients (intractable heart failure in 14 patients, cerebral embolism in 4 patients, sudden death in 4 patients and miscellaneous factor in 4 patients). Noncardiac causes were found in 2 patients and 17 patients had unknown causes. The median follow-up period was 11 months (range: 0-9 years), survival rates were 33 per cent and 27 per cent at 1 and 3 years, respectively (Fig. 2). Among those who survived through the third year (27 patients), 1 patient died thereafter.

Overall survival rate for patients in group A was significantly higher than in group B ($p< 0.0001$, log-rank statistics).

Predictors of survivals

On the basis of univariate analyses, the following factors were not associated with patient survival: age, gender, congestive heart failure, cerebral embolism, sites of involvement, and aortic root abscess. Clinical factors that were significant predictors of survival included duration of symptoms before admission ($p< 0.05$) and surgical treatment ($p<0.0001$).

Results from multivariate analyses are shown in Table 3. Three factors were found to be independent predictors of survival. These included male ($p<0.05$), congestive heart failure (NYHA IV)

Table 2. Mortality of patients with medical treatment for infective endocarditis.

Events	Group A (N=70)	%	Group B (N=82)	%
Death from any cause	30	43	56	68
Death from cardiac cause	13	19	26	32
Congestive Heart Failure				
NYHA class I-III	20	29	56	68
NYHA class IV	23	31	26	32
Survival rate				
At 1 year		72		33
At 2 year		66		27

Table 3. Predictors of mortality in infective endocarditis (based on Cox proportional hazards regression).

Variables	Relative risk	95% CI	P-value
NYHA class IV •	2.55	1.6-4.0	<0.0001
Male	1.76	1.0-2.9	<0.026
Surgery ••	0.23	0.13-0.39	<0.0001

• NYHA Class I-III = Reference group, •• Medical treatment = Reference group

(p<0.0001), and surgical treatment (p<0.0001). Surgical treatment was found to be the preventive factor of mortality (relative risk=0.23, p< 0.0001, 95% CI=0.138-0.391). This result could be interpreted as patients receiving surgical treatment had less risk of death than those receiving medical treatment only 77 per cent.

DISCUSSION

Infective endocarditis on native heart valves is a disease with a well-defined clinical course in its active phases. The short-term prognosis is well known and, in recent years, mortality rates have dropped as a result of better antibiotics and surgical treatment. IE is considered to be cured when symptoms disappear, a course of antibiotics treatment has been completed and blood culture remains negative. It should be emphasized, however, that even in patients who recover and become asymptomatic, IE leaves important cardiac sequelae: Some patients are left with valvular prostheses and others with valvular lesions secondary to the infective process in most cases. Because data regarding the natural history of IE after the active disease is scarce, the authors evaluated the long-term outcome in infective endocarditis and determined the predictors of patient survival.

Our study consisted of a group of patients who had IE on native heart valves and had been treated in two medical institutions. Steckelberg et al (16) recently showed how referral can distort the clinical spectrum of IE. Our population shared the clinical findings of both community and referral cohorts because the two hospitals are referral center and general hospitals admitting a large proportion of IE patients from the community. Despite a bias in favor of the inclusion of more severe cases, the cohort did not comprise a highly selected group of patients referred for consideration of surgery or unusual causative organisms. The study results, although not representative of the community at large, are probably indicative of current trends of evolution of patients with IE in general, particularly for those in areas where surgical facilities are readily available.

The study population was similar to that described in several studies, having a predominance of male patients(14,17). The follow-up period, up to

10 years after diagnosis is the first and longest follow-up reported in this region. The survival of the patients is comparable to that described in several studies[18,19]. It shows that mortality is high during the first year of follow-up, especially in medically treated patients and remains stable thereafter. Congestive heart failure and sudden cardiac death are the main causes of death in survivors from IE after hospital dismissal. In a quarter of the deaths however, the exact cause of death remained unknown.

The univariate analysis showed that some parameters were associated with mortality. Among the usual clinical factors, a short duration of symptoms before admission and surgical treatment indicated a more favorable prognosis. This finding is concordant with most previous reports following surgical treatment[10,19-22]. The present study used a multivariate analysis model to determine predictors of long-term survival. Using the Cox proportional hazards regression, it was found that three factors were associated with survival. Surgery was the preventive factor of mortality.

Prediction of mortality, staphylococcal infective endocarditis has been found to have a higher mortality and embolization[17]. In the present study, staphylocoocal endocarditis was commonly found in males, who had a higher mortality than female patients.

Since Wallace et al[21] reported the first case of aortic valve replacement in active IE in 1965, the role of surgery in the management of this condition has become increasingly important. Valve replacement appears to contribute to the improved survival rate[10], particularly in patients with congestive heart failure. In the reports on surgical treatment of active IE, there are considerable differences in early mortality ranging from 10-47 per cent [10,11,23,24]. This may be due to the differences in preoperative hemodynamic status, comorbidities, and age of patients. In addition, the differences in mortality for surgical treatment of active IE may be due to the inability to remove all infected tissues and restore valve function.

Surgical treatment of IE unequivocally improves the symptoms and long-term survival, and is indicated primarily for patients with NYHA class IV symptoms. However, a randomized controlled trial in consecutive patients to resolve the issue of early surgery *versus* medical therapy of active IE has not been performed. Therefore, the optimal timing of surgical intervention remains a therapeutic dilemma. If surgery is performed too early, some patients, who would have recovered with medical treatment only and without any complications, will be subject to surgery and to the morbidity associated with a valve prosthesis.

Limitations in this study include: 1) The result of the present study may be influenced by its retrospective nature. 2) Microbiologic and echocardiographic techniques have changed considerably in recent years, making the number of blood culture-negative cases and the percentage of negative echocardiographic results much lower than they were at the beginning of the study 3) There may be a referral bias resulting in the inclusion of a high proportion of severely compromised patients who might benefit from urgent surgery. This would have a profound effect on the outcome. 4) Because of the low prevalence of the disease, the small sample size is unavoidable.

SUMMARY

Survival after infective endocarditis is poor. The most common types of cardiac death are congestive heart failure, postoperative and sudden death. Therefore, surgery should be considered early in IE patients with congestive heart failure.

Clinical Implications: Although advances in antimicrobial therapy and the development of better diagnostic and surgical techniques have reduced the morbidity and mortality of IE, it remains a potentially life-threatening disease. The use of new clinical criteria, emphasizing echocardiography, will certainly guide the practitioner in the correct diagnosis of this disease. Prompt recognition and management of the major complications of IE are also essential to successful patient outcome.

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ผลการติดตามการรักษาในผู้ป่วยลิ้นหัวใจอักเสบติดเชื้อ ชนิด Native Valve

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วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบอัตราการรอดชีวิตของผู้ป่วยลิ้นหัวใจอักเสบติดเชื้อด้วยวิธีการรักษาที่แตกต่างกัน และหาปัจจัยที่มีผลต่อการรอดชีวิต

ผู้ป่วยและวิธีการ: การศึกษานี้เป็นการศึกษาย้อนหลังร่วมกับไปข้างหน้า ในระหว่างปี พ.ศ.2532 ถึงปี พ.ศ.2542 มีผู้ป่วยที่รับการวินิจฉัยว่าเป็นลิ้นหัวใจอักเสบติดเชื้อ เป็นจำนวน 152 ราย

ผล: เมื่อติดตามผู้ป่วยโรคนี้ 100 คน ในเวลา 1 ปี พบว่ามีอัตราตาย 38 คน อัตราการรอดชีวิตของผู้ป่วยที่ได้รับการรักษาด้วยวิธีการผ่าตัดร่วมกับการให้ยาจะดีกว่าผู้ป่วยที่ได้รับการรักษาด้วยยาอย่างเดียว อย่างมีนัยสำคัญทางสถิติ โดยมีอัตราการรอดชีวิตสำหรับผู้ป่วยที่รักษาด้วยวิธีผ่าตัด 72% และ 33% สำหรับผู้ป่วยที่รักษาด้วยยาอย่างเดียวที่เวลา 1 ปี อัตราการรอดชีวิตสำหรับผู้ป่วยที่รักษาด้วยวิธีผ่าตัดที่เวลา 5 ปี = 66%, และ 27% สำหรับผู้ป่วยที่รักษาด้วยยาอย่างเดียว ปัจจัยที่มีผลต่อการรอดชีวิต ได้แก่ การรักษาด้วยวิธีผ่าตัดร่วมกับใช้ยารักษา, ภาวะหัวใจล้มเหลวทำให้มีความเสี่ยงต่อการเสียชีวิตมากขึ้น 2.5 เท่า, เพศชายมีความเสี่ยงที่จะเสียชีวิตมากขึ้น 1.7 เท่า

สรุป: ผู้ป่วยที่มีลิ้นหัวใจอักเสบติดเชื้อ ชนิด native valve ในการติดตามผลการรักษาระยะยาวยังมีอัตราตายสูง การรักษาด้วยวิธีผ่าตัดร่วมกับการให้ยาจะช่วยให้มีการพยากรณ์โรคที่ดีกว่าการรักษาด้วยยาอย่างเดียว

คำสำคัญ : ลิ้นหัวใจอักเสบติดเชื้อ, ชนิด native valve, การติดตามผลการรักษาระยะยาว

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