Effect of Changes in Diagnosis and Management of Active Infective Endocarditis on the Clinical Outcome at Srinagarind Hospital

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Background: *In recent years, diagnostic methods and treatment of infective endocarditis (IE) have been improved. It is not known whether the clinical outcome is any better.*
Objective: *To assess the effect of changes on the clinical outcomes of IE patients*
Material and Method: *The authors performed a retrospective study comparing IE patients hospitalized at Srinagarind hospital during the period from 1/1/1990 to 31/12/2002. The authors classified the patients according to the period of diagnosed from 1990 to 1993 (n = 57), 1994 to1997 (n = 71), and 1998 to 2002 (n = 72) cohorts.*
Results: *There were two hundred IE patients in the present study. Mean age and degenerative heart disease were increasing. Operative and in-hospital mortality were decreasing. Overall survival rate was 81% at the first year, 60% at 5 years, 55% at 12 years in surgically treated patients, with 30-day mortality in 27.1% mostly from the 1990 to1993 cohort. In medically treated IE, overall the survival rate was 37% in the first year, 32% at 5 years, 20% at 12 years, with 30-day mortality in 72.86% mostly in the 1990 to1993 cohort. Early surgical intervention, improved long-term survival rates (hazard ratio 0.23; 95%CI 0.14-0.37), severe congestive heart failure (hazard ratio 1.87; 95%CI 1.17-2.99) and renal failure (hazard ratio 4.10; 95%CI 2.05-7.84) are the predictors of mortality by multivariate analysis. Survival rate from 1998 to 2002 cohort was 85%, 1994 to 1997 cohort was 54% and 1993 to 1990 cohort was 27% at 1-year ($p < 0.001$).*
Conclusion: *The data indicated that the changing clinical outcome of this disease, reflected improvements in diagnostic method and treatment. Although IE remains a serious condition characterized by significant morbidity and mortality, the overall survival rate has significantly improved over time. The authors therefore, believe that early diagnosis and prompt treatment both medical or surgical interventions will improve the outcome of IE patients.*

Keywords: *Infective endocarditis, Survival and outcome*

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Despite improvements in health care, the incidence of infective endocarditis (IE) has not decreased over the past decades. This apparent paradox is explained by progressive evolution in risk factors; while classic predisposing conditions such as rheumatic heart disease have been eradicated, new risk factors for IE have emerged. These include sclerotic valve disease in elderly patients, prosthetic valves, and nosocromial disease. Newly resistant organisms are challenging conventional antimicrobial

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therapy. Keeping up with these changes, allow understanding of pathogenesis of disease with the development of new drugs for IE. New ideas for antimicrobial agents are being developed.

Infective endocarditis is lethal if not aggressively treated with antibiotics, combined or not with surgery. Developments in antibacterial therapy, clinical microbiology, echocardiography, and cardiac surgery have revolutionised its diagnosis and prognosis. Epidemiologic studies of IE have been hampered in the past by several factors; the rarity of the disease, the fact that it is not officially reportable, and the absence of a precise case definition. Therefore, many studies have been based on autopsy series[1]. An approved assessment of infective endocarditis in patients is now possible, however, because of the introduction of new diagnostic criteria (Duke criteria)[2,3].

The authors hypothesized that improvements in diagnosis and early treatment have occurred. The current study was designed to compare the clinical outcomes of three cohorts of infective endocarditis diagnosed from 1990 to 1993, 1994 to 1997, and 1998 to 2002.

Material and Method

Study groups: All consecutive patients with a diagnosis of active infective endocarditis treated from 1990 to 2002 at Srinagarind Hospital. Both referral and primary care patients populations were included in the present study and reviewed. The diagnosis of IE was made by Duke criteria with database of uniformly defined cases of IE. Three cohorts with IE from 1990 to 1993, 1994 to 1997, and 1998 to 2002 were identified.

In patients with negative blood culture, the diagnosis was established when infection was confirmed by surgery. All patients received antibiotics treatment in accordance with the susceptibility of the causal organism. Surgical treatment was indicated during hospitalization in the following circumstances: moderate to severe heart failure from significant valvular regurgitation; repeated major emboli (two or more); virulent organisms which can not be eradicated by antibiotics treatment alone (such as fungal endocarditis, staphylococcus aureus endocarditis). Early and late surgical treatments were defined as valve replacement during and after the active phase of IE respectively. Medical- surgical treatment and medical treatment refer to the patients undergoing and not undergoing early surgical treatment, respectively. Death within 30 days after admission was defined as in-hospital mortality.

Clinical data: All cases identified as IE were reviewed for clinical history, signs and symptoms on admission, treatment, clinical course, complications and follow-up. In heart failure patients, functional class was determined according to the criteria of New York Heart Association (NYHA)[4]. The site of infection was determined by either transthoracic or transesophageal echocardiography[5-7], at surgery or autopsy.

Follow-up

Data on outcome after discharge and the clinical status at the end of follow-up were obtained from the out-patient clinical records. The end of the follow-up period was December 31, 2002. Complete follow up was defined as availability of information up to the end of the study or death. The mean follow-up time was 1.25 years (range 0 to 9.06 years).

Statistical analysis

All qualitative variables are expressed as percentage and quantitative variables as mean ($\pm$ SD). The differences between patient groups were evaluated by chi-square test. The Kaplan-Meier method was used for cumulative survival. Comparison of the survival curves of the different subgroups was made using the Mantel log rank test. The following indicator variables were tested: gender, age, duration of symptoms prior to admission, microorganisms, site of infection, heart failure, renal failure and major emboli. Values of $p < 0.05$ were considered significant.

Results

During the observation period, there were 220 patients with a discharge diagnosis of infective endocarditis. Of these, 20 patients were excluded from the present study, because of rejection by Duke criteria. Fifty-seven patients were first identified from 1990 to 1993; 71 patients were identified from 1993 to 1997; 72 patients were identified from 1998 to 2002.

Patients characteristics

The clinical characteristics of the three cohorts are represented in Table 1. Condition of the patients in the 1990 to 1993 cohort was more serious in that they had more severe congestive heart failure, (40 vs 28 vs 14%), had a shorter duration of symptoms prior to diagnosis (40 ± 54 vs 43 ± 39 vs 57 ± 60 days), more double valves (aortic and mitral) involvement and renal failure when first identified than the patients in the other two cohorts and were more congenital heart disease and mitral valve prolapse but the 1998

Table 1. Clinical characteristics of the patients

Characteristics	1990-1993 (n = 57)	1994-1997 (n = 71)	1998-2002 (n = 72)
Variables			
Sex (% male)	61.4	67.6	69.0
Age (years, mean ± SD)	36±16	39±16	42±16
Duration of symptoms (days, median)	40±54	43±39	57±60
Severe heart failure (%)	40.3	28.4	14.2
Underlying heart conditions			
No underlying (%)	28.1	21.1	25.4
Rheumatic Heart Disease (%)	56.1	69.0	69.0
Congenital Heart Disease (%)	17.5	2.8	9.8
Degenerative Heart Disease (%)	1.0	5.6	9.9
Prolapsed Mitral Valve (%)	14.1	4.2	4.2
Infective organisms			
Staph. aureus (%)	8.8	9.9	11.3
Strept. viridans (%)	19.3	26.8	35.2
Culture negative (%)	38.6	38.0	32.2
Site of infection			
Aortic valve (%)	42.2	42.3	46.5
Mitral valve (%)	49.1	45.1	35.2
Aortic & Mitral (%)	4.5	2.0	1.0
Tricuspid valve (%)	5.3	9.9	7.0
Concomitant disease			
Renal impairment (Cr >2) (%)	9.2	4.7	1.5
Treatment			
Early surgical intervention (%)	28.0	54.0	58.0
Mortality			
Operative mortality (%)	33.3	7.6	5.3
30 days mortality (%)	49.2	16.3	7.5

NYHA class IV = NewYork Heart Association

to 2002 cohort had more degenerative heart disease.

The mean age of the patients in the three cohorts had increased (36 vs 39 vs 42 years), and surgical replacement of native valve during active IE occurred more frequently from 1998 to 2002 and 1997 to 1994 than 1990 to 1993 (58 vs 54 vs 28%).

The three cohorts were similar overall with respect to valves involved, underlying heart condition (rheumatic heart disease), and infective organisms.

Operative and in-hospital mortality was significantly lower in the 1998 to 2002 cohort, compared to the earlier cohort (5.3 vs 33.5%, $p < 0.001$).

Stratified and multivariable analysis

Several clinical variables were examined as possible predictors of mortality. Using multivariate analysis of the selected variables, independent predictors of mortality were defined and are listed in Table 2. Congestive heart failure (NYHA class IV), early surgery and renal failure were independent predictors of mortality. Importantly age, sex, liver failure, neurological complications, valve ring abscess and infective organisms were not independent predictors of mortality. In addition, when analysed the impact of surgery on the long-term outcome of patients, the mortality was still high in the medical cohort. The 1-year survival rate for patients who had combined medical and surgical treatment was 81%; for patients who received only medical treatment was 37% ($p < 0.001$) (Fig.1).

Fig. 2 shows the survival of overall patients in the three cohorts described in the current study.

Table 2. Predictors of mortality in infective endocarditis (based on Cox proportional hazards regression)

Variables	Hazard Ratio	95%CI
NYHA class IV	1.87	1.17-2.99
Renal failure	4.01	2.05-7.84
Early surgery	0.23	0.14-0.37

Adjusted for age, sex, liver failure, stroke, organisms, and perivalvular abscesses

The 1 year survival rate (85%) from 1998 to 2002 cohort was significantly better than that of 1994 to 1997 (54%) and 1990 to 1993 (27%) cohorts.

Fig. 3 predicts the survival rate of combined medical and surgical treated patients, as this figure shows, the improved survival was in the more recent cohort 1998 to 2002 (1 year survival was 80%) when compared to 1994 to 1997 (76%) and 1990 to 1993 (43%) cohorts, from the first year of initial evaluation.

Fig. 4 predicts the survival of medical treatment alone, the improved survival in the more recent cohort, 1998 to 2002, (1-year survival rate was 87%) when compared to the 1994 to 1997(26%) and 1990 to 1993 cohorts (21%).

Discussion

Infective endocarditis is still a life-treatening disease; to initiate early diagnosis and appropriate treatment is essential.

The current study reports the authors' experience with both medically and surgically treated patients with active IE in a tertiary referral center during a 12-year period (1990 to 2002). The three cohorts were identified in 1990 to 1993, 1994 to 1997, and 1998 to 2002 cohorts. When comparing the first and last 4-year periods of treatment, there was a shift toward a higher underlying degenerative heart disease, increasing age and increase in emergency surgery, similar shifts have been observed in other Western populations[8-12].

Overall mortality of IE in the present study was high, there was a significantly improved survival rate among the patients from 1998 to 2002 cohort better than that observed in the earlier periods (1990 to 1993, and 1994 to 1997). This is probably due to early approach in diagnosis with echocardiograhy that is recognized as the method of choice for detection of valvular vegetations associated with endocarditis[13-15] and early treatment before wide-spread tissue destruction and complications have occurred for both medical and surgical intervention.

Mortality in medically treated patients with severe congestive heart failure was high, even with low virulent organisms, which was in agreement

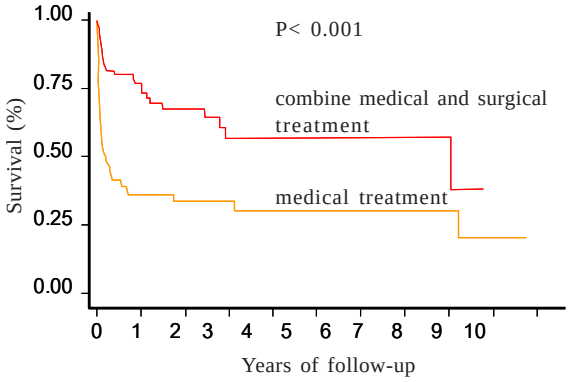

Fig. 1 Long-term survival by treatment strategies

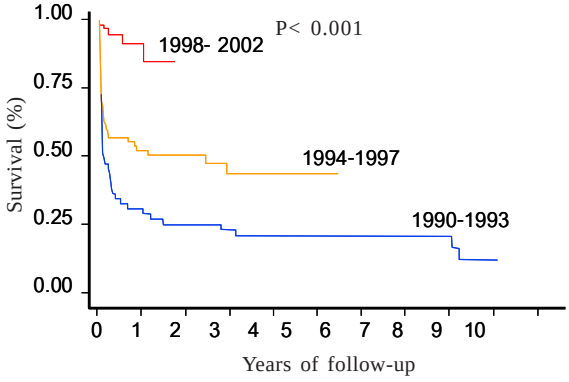

Fig. 2 Survival by year of follow-up

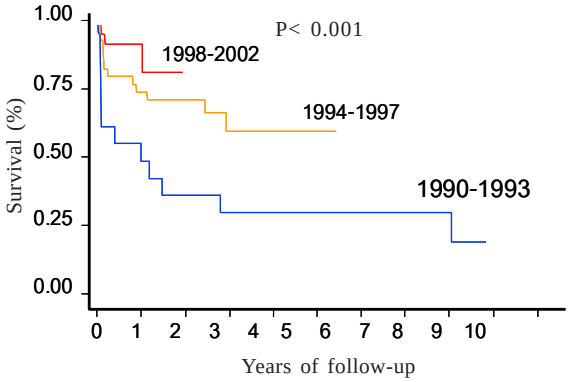

Fig. 3 Survival of combined medical and surgical treated

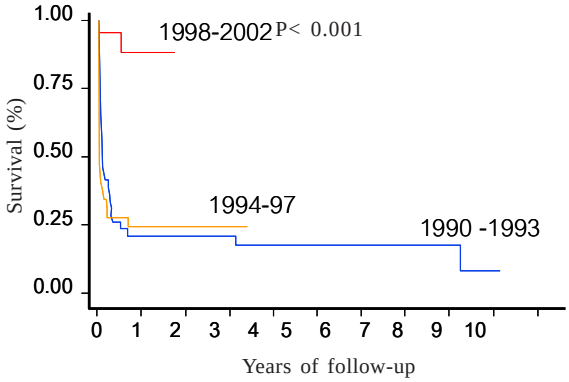

Fig. 4 Survival of medical treated

with the literature[16,17]. Pelletier et al[18] reported that prolonged infection with low virulence organism; streptococcal species was associated with increasing mortality due to valvular destruction and congestive heart failure and increase in risk associated with advanced age.

A trend toward increased risk of death was evident in medically treated patients due to co-morbidities such as renal failure, hepatic failure, elderly and embolic manifestations. In these cases, valve replacement could not be performed early and had a worse prognosis.

Cardiac surgery has become increasingly important in the treatment of IE. In the present series, the percentage of surgically treated patients with active IE increased from 28 to 58% (from 1990 to 2002).

In recent years, earlier diagnosis of disease, echocardiographic, and microbiologic techniques have changed considerably in making the number of blood culture-negative cases and the percentage of negative echocardiographic results much lower than they were at the beginning of our studies. Early surgical intervention had an important effect on the survival. The survival was significantly improved in both medically treated and surgically treated patients.

The independent predictors of mortality were not only indexes of the severity of congestive heart failure, presence of co-morbidity (renal failure), but also included the time period of surgical intervention.

To the authors' knowledge this is the first study comparing the clinical outcome from the past to recent cohorts. The authors found that patients identified in the earlier cohort had a higher mortality which may be due to delay in diagnosis and management especially early surgery. Many patients presented with co-morbidities and severe congestive heart failure, due to progressive and destructive cardiac valves, which may have a potent effect on the survival. The role of surgery in the management of this condition has become increasingly important. Valve replacement appears to contribute to an improved survival rate[19-23] particularly in the patients with severe congestive heart failure from destroyed valves and perivalvular extension of infection. In addition, the differences in mortality for surgical treatment of active IE may result from inability to remove all the 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 and valve dysfunction. 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.

Croft et al[24] reported a significantly better overall survival rate for the patients in the surgical group, compared with the medically treated patients matched for severity of illness. However, they found no significant difference in long-term survival rates between the 2 groups after discharge from the hospital.

Limitations

Limitations in the present study include: 1) The result of the present study may be influenced by some of a retrospective nature. 2) The referral bias resulted in the inclusion of a high proportion of severely compromised patients who might have benefited from urgent surgery. This would have a profound effect on the outcome. 3) Because of the low prevalence of the disease, hence, a small sample size is unavoidable.

Conclusion

In the present day, IE is an acute disease. The appearance of IE has profoundly changed due to the increasing age of the population, new diagnostic criteria, of which echocardiography is an important tool, with early heart valve surgery. Despite a high use of surgery in this cohort, overall mortality remains high. The authors have found initial evidence that early surgery may be critical to improving patient outcomes.

Clinical Implications

The present study documents that the changing clinical course of this disease, reflects in rapid diagnosis and treatment. Although IE remains a serious condition characterized by significant morbidity and early mortality, the overall survival is significantly improving. The authors, therefore, believe that early diagnosis and prompt treatment both medical or surgical intervention will improve the outcome of IE patients

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ผลการเปลี่ยนแปลงการวินิจฉัยและการรักษาในผู้ป่วยลิ้นหัวใจอักเสบติดเชื้อที่โรงพยาบาลศรีนครินทร์

อรทัย พาชีรัตน์, ทรงศักดิ์ เกียรติชูสกุล, เพลินจันทร์ เชษฐโชติศักดิ์, เชิดชัย ตันติศิรินทร์, สุพล ลิมวัฒนานนท์, จุฬาภรณ์ ลิมวัฒนานนท์

วัตถุประสงค์: *เพื่อศึกษาผลการรักษาผู้ป่วยลิ้นหัวใจอักเสบติดเชื้อ เมื่อมีการเปลี่ยนแปลงการวินิจฉัยและการดูแลรักษาที่ดีกว่าเดิม*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลัง ในระหว่างปี พ.ศ. 2532 ถึง พ.ศ. 2544 มีผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นลิ้นหัวใจอักเสบติดเชื้อ และได้รับการรักษาที่ โรงพยาบาลศรีนครินทร์ เป็นจำนวน 200 ราย โดยแบ่งผู้ป่วยออกเป็น 3 กลุ่ม ได้แก่ ผู้ที่รับการวินิจฉัย พ.ศ. 2533-2536 (57 ราย) พ.ศ. 2537-2540 (71 ราย) และ พ.ศ. 2541-2544 (72 ราย)*

ผลการศึกษา: *อายุเฉลี่ยของผู้ป่วยและโรคหัวใจจากความเสื่อมมีจำนวนสูงขึ้น อัตราการเสียชีวิตในห้องผ่าตัดและในโรงพยาบาลมีจำนวนลดลง อัตราการรอดชีวิตโดยรวมสำหรับผู้ป่วยที่ได้รับการรักษาด้วยวิธีการผ่าตัด 81% ที่เวลา 1 ปี, 60% ที่เวลา 5 ปี, 55% ที่เวลา 12 ปี อัตราการเสียชีวิตในโรงพยาบาล 27% ส่วนใหญ่เป็นผู้ที่รับการวินิจฉัย พ.ศ. 2533-2536, ผู้ป่วยที่ได้รับการรักษาด้วยการให้ยาอย่างเดียว อัตราการรอดชีวิตโดยรวม 37% ที่เวลา 1 ปี, 32% ที่เวลา 5 ปี, 20% ที่เวลา 12 ปี อัตราการเสียชีวิตในโรงพยาบาล 73% ส่วนใหญ่เป็นผู้ที่รับการวินิจฉัย พ.ศ. 2533-2536, จากการวิเคราะห์ หาปัจจัยที่มีผลต่อการรอดชีวิต ได้แก่ การรักษาด้วยวิธีผ่าตัด, ส่วนภาวะหัวใจล้มเหลวและไตวาย ทำให้มีความเสี่ยงต่อการเสียชีวิตมากขึ้น อัตราการรอดชีวิตดีที่สุดส่วนใหญ่เป็นผู้ที่รับการวินิจฉัยและรักษา พ.ศ. 2541-2544*

สรุป: *การศึกษานี้แสดงให้เห็นว่ามีการเปลี่ยนแปลงในทางคลีนิคของโรคไปในทางที่ดีขึ้น หลังจากที่มีการเปลี่ยนแปลงการวินิจฉัย การดูแลรักษาที่ดีกว่าเดิม และรวดเร็วขึ้น*