Impact of Early Surgery on Embolic Events in Patients With Infective Endocarditis

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Background—Surgical indications to prevent systemic embolism in infective endocarditis (IE) remain controversial. We sought to compare clinical outcomes of early surgery with conventional treatment in IE patients with embolic indications only.

Methods and Results—From 1998 to 2006, we prospectively enrolled 132 consecutive patients (86 men; age, 49±17 years) with definite IE. Patients were included if they had a left-sided native valve endocarditis with vegetation. The choice of early surgery or conventional treatment was at the discretion of attending physician. Early surgery was performed on 64 patients (OP group) within 7 days of diagnosis, and conventional management was chosen for 68 patients (CONV group). The OP group had larger vegetations and a higher percentage of patients with severe valvular disease (88% versus 62%, \(P=0.001\)). During initial hospitalization, there were no embolic events and 2 in-hospital deaths in the OP group and 14 embolic events and 2 in-hospital deaths in the CONV group. During a median follow-up of 1402 days, there were 2 cardiovascular deaths, 2 embolic events, and 1 recurrence of IE in the CONV group, and 1 cardiovascular death and 2 embolic events in the OP group. The 5-year event-free survival rate was significantly higher in the OP group (93±3%) than in the CONV group (73±5%, \(P=0.0016\)). For 44 propensity score–matched pairs, the OP group had a lower event rate (hazard ratio, 0.18; \(P=0.007\)).

Conclusions—Compared with conventional treatment, an early surgery strategy is associated with improved clinical outcomes by effectively decreasing systemic embolism in patients with IE. (Circulation. 2010;122[suppl 1]:S17–S22.)

Key Words: infective endocarditis ■ vegetation ■ embolism ■ heart valve surgery

Despite recent advances in diagnosis and treatment, infective endocarditis (IE) remains associated with high mortality and morbidity. The leading causes of mortality are congestive heart failure (CHF) attributable to valvular dysfunction and stroke caused by embolization of vegetation.1,2 Urgent surgery is particularly beneficial in IE patients with CHF related to acute mitral or aortic regurgitation, but indications for surgical intervention to prevent systemic embolism remain controversial. Patients with large vegetations are at high risk of embolism.3,4 However, surgery on the basis of vegetation size alone is controversial, and the 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines5 recommend surgery as a class IIa indication only in patients with recurrent emboli and persistent vegetation. The timing of surgery to prevent embolism is also important, because the risk of embolism is especially high during the first 2 weeks following the initiation of effective antibiotic treatment, and the benefits of early surgery should be balanced against the potential risks of operative mortality, postoperative relapse, and prosthetic valve dysfunction.6,7 Taking into account recent advances in surgical techniques, the revised 2009 European Society of Cardiology guidelines8 recommend urgent surgery as a class IIb indication in patients with isolated very large vegetations (>15 mm in diameter). Additionally, early identification of patients at high risk of embolism by transesophageal echocardiography, as well as increased experiences with vegetation excision and valve repair, have raised arguments for early surgery. However, the usefulness of such surgery to prevent embolic events has yet to be established, and there have been no studies comparing early surgery performed under embolic indications with a watchful waiting strategy in patients with IE. The primary goal of the present study was to compare clinical outcomes of early surgery performed within 1 week of diagnosis with those of a conventional treatment strategy based on present guidelines in IE patients with embolic indications only.
A prospective registry, commencing in 1998 and using a standard case report form, has included all consecutive patients with IE undergoing echocardiography at our hospitals. Case report forms, including patient demographics, clinical presentations, and echocardiographic data, were stored in an electronic database as in previous studies. Clinical follow-up data on study patients were collected annually and entered into the database. From January 1998 to December 2006, 376 eligible patients were diagnosed with definite IE, a total of 132 patients were consecutively enrolled in this study. IH indicates in-hospital.

Methods

Study Population

A prospective registry, commencing in 1998 and using a standard case report form, has included all consecutive patients with IE undergoing echocardiography at our hospitals. Case report forms, including patient demographics, clinical presentations, and echocardiographic data, were stored in an electronic database as in previous studies. Clinical follow-up data on study patients were collected annually and entered into the database. From January 1998 to December 2006, 376 eligible patients were diagnosed with definite IE according to the Duke criteria (Figure 1). A total of 132 patients, who had a definite diagnosis of left-sided native valve endocarditis and were potential candidates for early surgery to prevent systemic embolism, were consecutively enrolled at the Asan Medical Center (n=105) and Seoul National University Hospital (n=27). In line with the 1998 ACC/AHA guidelines on surgical indications for IE, the exclusion criteria were defined as patients with severe CHF; IE complicated by heart block; annular or aortic abscess; or destructive pericarditis at the time of diagnosis, and/or poor medical status, such as presence of malignancy. Patients with prosthetic valve IE, right-sided vegetations, and small vegetations with diameter of <5 mm were also excluded (Figure 1). The choice of early surgery or conventional treatment for each patient with IE was at the discretion of each attending physician, who explained the potential benefits of early surgery, the operative risks and complications associated with prostheses, and assigned great importance to the preferences of individual patients. Whereas a conventional strategy was chosen for 68 patients (CONV group), early surgery was performed on 64 patients (OP group) within 7 days after diagnosis of IE. Patients in the CONV group were referred for surgery before completion of scheduled antibiotic therapy, if they developed CHF, if vegetation size increased despite antimicrobial therapy, or if vegetation persisted after recurrent embolism. Informed consent was obtained from each patient, and the study protocol was approved by the ethics committees of our institutions.

Clinical and Echocardiographic Data

The following clinical data were collected during hospitalization: comorbidities, predisposing heart disease, manifestations of IE, results of blood cultures, and antibiotic therapy. Comorbidity was assessed using the Charlson comorbidity scale, which assigns weights to specific comorbid disease states. All patients were treated according to the American Heart Association guidelines, and treatment plans were optimized by close cooperation between cardiologists, infectious disease specialists, and cardiac surgeons. All patients underwent transthoracic echocardiography within 24 hours after hospitalization, and transesophageal echocardiography was performed on 117 patients (88.7%) to evaluate the vegetation in detail and to detect complications related to IE. The degree of aortic and mitral regurgitation was assessed semiquantitatively or using quantitative methods and classified as mild, moderate, or severe. Maximal length and mobility of the vegetation were evaluated as previously described.

Surgical Procedure

All procedures were performed with the use of a standard cardiopulmonary bypass. In patients with mitral valve (MV) IE, repair was preferred when possible, most often with excision of vegetation and reconstruction with autologous pericardium. Aortic valve (AV) or MV replacements were successfully performed using mechanical or bioprosthetic valves at the discretion of the surgeon. In the OP group, 32 patients (50%) underwent valve surgery within 48 hours after enrollment, and the remaining 32 patients (50%) were treated with surgery within 7 days. Median time from diagnosis to operation was 2.5 days (interquartile range, 1 to 5 days). In 29 patients with MV involvement, 10 and 19 patients underwent MV repair and MV replacement (MVR), respectively. AV replacement (AVR) was performed in 28 patients with AV involvement. In 7 patients with dual-valve involvement, dual-valve replacement was performed in 5 patients, and 2 patients received MVR plus AV repair and AVR plus MV repair, respectively. Concomitant coronary artery bypass graft operation at the time of valve surgery was performed on three patients (4.7%).

In the conventional treatment group, 40 (59%) patients underwent valve surgery before discharge (n=32; median time to operation, 28 days; interquartile range, 16 to 34 days) or during follow-up (n=8); 13 (32.5%) AVR, 14 (35%) MVR, 8 (20%) MV repair, and 5 (12.5%) dual-valve replacements were performed. Concomitant coronary artery bypass graft operation at the time of valve surgery was performed on 1 patient (2.5%).

Follow-Up and End Points

Data were obtained until May 2009, during annual visits to the outpatient clinic or by telephone interviews. Deaths were classified as cardiovascular or noncardiovascular on the basis of medical records. For 2 patients lost to follow-up, data on vital status, dates, and causes of death were obtained from the Korean national registry of vital statistics. We retrospectively reviewed the data that were prospectively collected in an electronic database.

The primary end point was a composite of embolic events that occurred after diagnosis of IE, cardiovascular mortality, and recurrence of IE during follow-up. Diagnosis of embolic event was based on clinical symptoms, signs, and follow-up computerized tomography scans. Specific diagnosis of cerebral embolism was eventually confirmed by an experienced neuroradiologist during the clinical course, and, in addition to computerized tomography scanning, additive brain MRI was performed if indicated.
Table 1. Baseline Characteristics of Patients (OP Group) Who Underwent Early Surgery and Those (CONV Group) Who Underwent Conventional Treatment

<table>
<thead>
<tr>
<th></th>
<th>OP Group (n=64)</th>
<th>CONV Group (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45.9±15.9</td>
<td>51.1±17.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>39 (60.9)</td>
<td>47 (69.1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (9.4)</td>
<td>9 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>11 (17.2)</td>
<td>12 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>2 (3.1)</td>
<td>3 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Embolism on admission</td>
<td>10 (15.6)</td>
<td>14 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity index</td>
<td>0.42±0.83</td>
<td>0.37±0.88</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>60.0±8.2</td>
<td>60.8±8.3</td>
<td></td>
</tr>
<tr>
<td>Vegetation site, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV</td>
<td>28 (43.8)</td>
<td>19 (27.9)</td>
<td></td>
</tr>
<tr>
<td>MV</td>
<td>29 (45.3)</td>
<td>42 (61.8)</td>
<td></td>
</tr>
<tr>
<td>AV+MV</td>
<td>7 (10.9)</td>
<td>7 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Vegetation diameter, mm</td>
<td>15.6±5.7</td>
<td>12.6±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;15 mm, n (%)</td>
<td>34 (53.1)</td>
<td>46 (67.6%)</td>
<td></td>
</tr>
<tr>
<td>≥15 mm, n (%)</td>
<td>30 (46.9)</td>
<td>22 (32.4)</td>
<td></td>
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<tr>
<td>Vegetation mobility</td>
<td>3.71±0.56</td>
<td>3.47±0.65</td>
<td>0.025</td>
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<tr>
<td>Valvular disease severity</td>
<td></td>
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<td>0.001</td>
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<tr>
<td>Mild-to-moderate, n (%)</td>
<td>8 (12.5)</td>
<td>26 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>56 (87.5)</td>
<td>42 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Microbiological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>8 (12.5)</td>
<td>9 (13.2)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>1 (1.6)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Viridans streptococcus</td>
<td>29 (45.3)</td>
<td>38 (55.9)</td>
<td></td>
</tr>
<tr>
<td>Enterococcus</td>
<td>5 (7.8)</td>
<td>5 (7.4)</td>
<td></td>
</tr>
<tr>
<td>HACEK</td>
<td>3 (4.7)</td>
<td>3 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture-negative</td>
<td>18 (28.1)</td>
<td>11 (16.2)</td>
<td></td>
</tr>
</tbody>
</table>

CNS, coagulase negative Staphylococcus; HACEK, Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella; LV, left ventricular.

**Statistical Analysis**

The present intention-to-treat analysis assessed results obtained after early surgery and conventional treatment in a cohort of 132 patients with left-sided valve IE, treated in 2 institutions over a period of 9 years.

Categorical variables are presented as numbers and percentages and were compared with the χ² test and Fisher’s exact test. Continuous variables are expressed as means±SD and were compared using the t test. To evaluate in-hospital events, logistic regression analysis was performed. Variables significantly associated with such events in single-variable analysis were included as candidate predictors in stepwise logistic regression analysis. Variables with significance P<0.10 were included in the multivariate model. Five-year survival and event-free survival curves were constructed using Kaplan–Meier estimates and compared using the log-rank test. For Kaplan–Meier analysis, we analyzed all clinical events by time to first event. Because patients were not randomly assigned to 1 of the 2 treatment strategy groups, we performed adjustment for factors favoring selection of early surgery by use of propensity score matching.5,14 The propensity scores were estimated without regard to outcome variables, using multiple logistic regression analysis. All prespecified covariates were included in full nonparsimonious models for treatment with early surgery versus a conventional strategy (Table 1). This model yielded a concordance index of 0.76, indicating a good ability to differentiate between patients receiving conventional therapy and those undergoing early surgery. For development of propensity score–matched pairs without replacement (a 1:1 match), a greedy 531-digit match algorithm was used, as described previously.15 After propensity score matching, baseline covariates were compared between the 2 groups using the paired t test for continuous variables and the McNemar or marginal homogeneity test for categorical variables. In the propensity score–matched cohort, the risks of clinical end points were compared with Cox’s regression models, with robust SEs that accounted for clustering of matched pairs. All reported probability values were 2-sided, and a value of P<0.05 was considered statistically significant. SAS software, version 9.1 (SAS Institute, Inc, Cary, NC), was used for statistical analyses.

**Results**

**Patient Characteristics**

The study included 132 IE patients, with a mean age of 49±17 (17–80) years, and 65% of patients were men. Table 1 summarizes the characteristics of patients who underwent early surgery versus conventional treatment. There were no significant differences between the 2 groups in terms of age, diabetes mellitus, hypertension, or atrial fibrillation. Vegetations were more frequently located on the mitral valve in the CONV group, although it was not statistically significant. Patients in the OP group had more mobile and larger (15.6±5.7 versus 12.6±4.6 mm, P<0.001) vegetations and higher incidence of severe valvular heart disease (88% versus 62%, P=0.001) (Table 1). Propensity score matching for the entire population yielded 44 matched pairs of patients. In the matched pairs, there was no significant between-group difference for any covariate.

**Comparison Between Surgical and Conventional Treatment Groups**

The in-hospital mortalities between study patients and excluded patients, in whom urgent surgery was needed or early surgery was not indicated owing to poor medical conditions, were significantly different (3.0% versus 19.9%, P<0.001) (Figure 1). There were 2 in-hospital deaths in the OP group; the causes of death were cardiac tamponade and cerebral mycotic aneurysm rupture. In the CONV group, there were 2 in-hospital deaths caused by aggravation of congestive heart failure and cerebral embolism.

There were no embolic events in the OP group, and 14 embolic events in the CONV group during hospitalization. The embolization sites were the central nervous system (5 patients), spleen (1), kidney (4), femoral artery (3), and mesenteric artery (1). Two patients with embolic events required emergency surgery, 1 with mesenteric infarction and 1 with femoral artery embolism.

The median follow-up time was 1348 days (interquartile range, 1957 to 728 days) in the OP group and 1454 days (interquartile range, 2234 to 770 days) in the CONV group (P=NS). During follow-up, 1 patient died in the OP group, resulting from CHF after valve surgery, and 2 patients died in the CONV group. One patient died of CHF, and 1 patient with end-stage renal disease experienced sudden cardiac death during hemodialysis. With regard to recurrence of IE, no patients in the OP group and 1 patient in the CONV group experienced recurrence. In the latter patient, the recurrence...
aggravated preexisting CHF, leading to the need for valve surgery during active-phase IE.

Follow-up thromboembolisms occurred in 2 patients in the OP group and 2 in the CONV group. In the OP group, 1 patient experienced embolic stroke caused by improper anticoagulation therapy because of use of a herbal medication, and 1 experienced major stroke, resulting in craniectomy. In the CONV group, 1 instance of mechanical valve thrombosis and 1 patient with a cerebral infarct were noted.

There were no significant differences in terms of in-hospital mortalities and long-term survival rates between the 2 groups (Table 2 and Figure 2). The estimated actuarial 5-year event-free survival rate was 93±3% in the early surgery group and 73±5% in the CONV group, and the overall event-free survival rates were significantly different between the 2 groups (P = 0.0016; Figure 3A). For the 44 propensity score–matched pairs, the estimated actuarial overall event-free survival rates were also significantly higher in the OP group than in the CONV group (P = 0.0024; Figure 3B), and the risk of attaining the composite end point was significantly lower in the OP group than in the CONV group (hazard ratio, 0.180; 95% confidence interval [CI], 0.052 to 0.627; P = 0.007). With regard to embolism, the risk of embolic events was significantly lower in the OP group than in the CONV group (hazard ratio, 0.126; 95% CI, 0.029 to 0.552; P = 0.006), and statistical significance was maintained in the 44 propensity-matched pairs (hazard ratio, 0.143; 95% CI, 0.032 to 0.640; P = 0.011).

In the CONV group, 15 (22%) patients underwent valve surgery before completion of scheduled antibiotic therapy because of CHF aggravation, and 17 (25%) were surgically treated because of severe valvular heart disease reaching surgical indications during initial admission. During follow-up, 8 (12%) patients in the CONV group underwent valve surgery; 2 operations were performed during readmission for CHF and 6 met the surgical criteria for valvular heart disease according to ACC/AHA guidelines during follow-up. The survival rates free of cardiac events or surgery were 71±5% at 1 year, 53±6% at 3 years, and 43±4% at 5 years, respectively. By Cox’s regression analysis, vegetation size was the only predictor of cardiovascular events (hazard ratio, 2.633 when diameter was ≥15 mm or otherwise; 95% CI, 1.044 to 6.642, P = 0.04) and cardiovascular events or surgery (hazard ratio, 1.868 when diameter was >15 mm or otherwise; 95% CI, 1.033 to 3.379, P = 0.039) in the CONV group.

### Discussion

The present study demonstrated that, in patients with IE, early surgery within 1 week after diagnosis was associated with improved long-term clinical outcomes via significant reduction in systemic embolic events compared to a conventional treatment strategy. Furthermore, we showed that such improvements in clinical outcome were achievable without increase in IE relapse or prosthetic valve–related problems. To the best of our knowledge, this is the first study to compare clinical outcomes after early surgery performed within 1 week of diagnosis with those of the conventional treatment strategy in IE patients with embolic indications alone. Moreover, this is a relatively large-scale study performed with an intention-to-treat protocol and targeted a homogeneous population of patients with left-sided
native valve endocarditis who were potential candidates for early surgery.

The impact of surgery on clinical outcomes remains controversial.15–18 Vikram et al15 compared the impact of surgery on short-term mortality in a well-designed study, and they controlled for cohort heterogeneity and confounding variables related to the performance of valve surgery using propensity score matching, and the authors concluded that valve surgery for patients with IE was independently associated with reduced 6-month mortality. The report of the International Collaboration on Endocarditis study investigators17 demonstrated that the benefits of surgery were not uniform in all patients with native valve IE and that early surgery, in a subgroup of patients with the most severe indications for surgery, was associated with a significant reduction in mortality. In contrast, Aranki et al18 found that patients undergoing early surgery during the active phase of IE exhibited a higher mortality than did patients receiving conventional treatment for IE. Significant differences in clinical characteristics have been found between medical and surgical groups in previous observational cohort studies,15–18 and plausible explanations of discrepant results among studies include variations in the baseline characteristics of study populations.19 The present study also shows that the in-hospital mortalities were significantly different between patients with embolic indications only and those with need for urgent surgery or poor medical conditions. The in-hospital mortality and long-term survival were similar between early surgery and conventional treatment groups, because study patients with embolic indications showed similar clinical characteristics and made a homogenous population. Accordingly, it is understandable that the present study demonstrates more favorable outcomes, because the proportion of patients with poor prognostic factors was lower than in previous studies.15–18

With regard to the optimal timing of surgery, Tleyjeh et al.7 comparing clinical outcomes between patients receiving surgery within the first 11 days after admission (n=69) and after 11 days (n=60), showed that a longer time to surgery had a significant protective effect on mortality. In another recent investigation8 of a relatively large prospective cohort, the authors concluded that the effect on mortality of very early surgery (within 1 week) was not uniform, and surgery might be beneficial in patients with the most severe forms of IE including Staphylococcus aureus infection, CHF, and larger vegetations, but very early surgery was associated with an increased frequency of relapse and prosthetic valve dysfunction. However, in our present study, early surgery improved clinical outcomes without relapse of IE or prosthetic valve dysfunction. A plausible explanation of discrepant results among studies also lies in differences in patient characteristics, and 40% to 50% of the study population had prosthetic valve endocarditis, and approximately 30% had an annular abscess in previous reports.6,7 Although the optimal timing of surgery is still debatable, early surgery within 1 week after diagnosis in patients with embolic indications only may be justified, because the risk of embolism seems particularly high during the first week after diagnosis,19,20 and the benefits of surgery might be greatest if surgery is performed within that time. The short time interval (median, 2.5 days) from diagnosis to surgery might contribute to significant reduction of embolic events in the early surgery group.

In the conventional treatment group of the present study, vegetation size was the only predictor of embolic events. These findings are consistent with those of previous studies.3,4,20 Although the revised 2009 European Society of Cardiology guidelines2 recommend urgent surgery as a class IIb indication in patients with isolated very large vegetations, evidence for this proposal remains insufficient. Therefore, the results of the present study may assist in the identification of the exact role of surgical treatment when only isolated large mobile vegetation is detected.

Limitations
The present study was subject to the limitations inherent in a nonrandomized study. Early surgery group tended to have larger vegetation and also a higher prevalence of severe regurgitation. Therefore, both of these factors may have influenced simultaneously on making decisions of surgery. To minimize selection bias and confounding, we used propensity score matching, which has been shown to eliminate a greater proportion of baseline differences than do stratification or covariate adjustment.14 In the propensity score–matched cohort, the early surgery group persistently showed a significantly lower rate of end point attainment. Although the use of a propensity score–matched cohort to adjust for confounding in treatment selection is intended to control for such bias, the approach cannot completely remove the effect of confounding, and it appears that substantial problem of baseline characteristics mismatch regarding vegetation size, location of vegetation, and frequency of severe valvular heart disease might not be completely solved. In addition, considering the characteristics of our centers as tertiary referral hospitals, some selection bias is probably inevitable. Therefore, large-scale randomized studies are required. This study excluded patients with major stroke or poor medical conditions, and care should be taken that the results of this study are not applicable to patients with high operative risks.

Conclusion
Compared with conventional treatment, an early surgery strategy is associated with improved clinical outcomes by effectively decreasing embolic events in patients with IE. The results of this observational study suggest that early surgery can be a valuable therapeutic option to improve clinical outcomes in patients who have severe valvular disease and large vegetation.

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Disclosures
None.

References


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