Impact of early surgery in the active phase on long-term outcomes in left-sided native valve infective endocarditis

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Objective: We sought to evaluate the impact of early surgery in the active phase on long-term outcomes in patients with left-sided native valve infective endocarditis.

Methods: Clinical data were retrospectively reviewed in 212 consecutive patients with left-sided native valve infective endocarditis from 1990 to 2009. Early surgery in the active phase (within 2 weeks after the initial diagnosis) was performed in 73 patients, and the conventional treatment strategy was applied in 139 patients. In the conventional treatment group, 99 patients underwent late surgical intervention. To minimize selection bias, propensity score was used to match patients in the early operation and conventional treatment groups. Major adverse cardiac event was defined as a composite of infective endocarditis-related death, repeat surgery, and recurrence of infective endocarditis during follow-up.

Results: The mean follow-up period was 5.5 years. In-hospital mortality was lower in the early operation group than in the conventional treatment group (5% vs 13%, $P = .08$). For 57 propensity score-matched pairs, the estimated actuarial 7-year survivals free from infective endocarditis-related death and major adverse cardiac events were significantly higher in the early operation group than in the conventional treatment group (infective endocarditis-related death: 94% ± 5% vs 82% ± 5%, $P = .011$, major adverse cardiac events: 88% ± 5% vs 69% ± 7%, $P = .006$, respectively).

Conclusions: Compared with conventional treatment, early surgery in the active phase was associated with better long-term outcomes in patients with left-sided native valve infective endocarditis. Further prospective randomized studies with large study populations are necessary to evaluate more precisely the optimal timing of surgery in patients with native valve infective endocarditis. (J Thorac Cardiovasc Surg 2011;142:836-42)

⊕ Supplemental material is available online.

The optimal timing of surgical intervention in patients with left-sided native valve infective endocarditis (IE) has not been clarified, and considerable controversy remains regarding the role of early surgery. Early surgical intervention in the acute or active phase of IE in the presence of uncontrolled sepsis, shock, and organ failure raises concerns about high operative mortality and risk of relapsing IE. On the other hand, postponing surgery to complete a course of antimicrobial therapy could increase embolic risk and cause extensive cardiac tissue damage, which result in more difficult repair, progressive cardiogenic shock and organ failure, and increased mortality.

Recent studies have investigated the impact of surgical intervention for left-sided IE and suggested benefits of valve surgery.[1-6] However, these studies were limited by a short follow-up. Moreover, improved long-term outcomes by early surgery for left-sided IE have not been clearly shown because of the lack of controlled trials and the inherent biases of observational studies. The present study compared the long-term clinical outcomes of patients with left-sided native valve IE who underwent early surgery in the active phase with patients who received the conventional treatment strategy. We tried to minimize the inherent biases in treatment selection and prognostic imbalances using propensity analyses and multivariable modeling.

MATERIALS AND METHODS
Study Population
From 1990 to 2009, 212 patients with active left-sided native valve IE who were admitted to the Kobe City Medical Center General Hospital were enrolled. All patients met the modified Duke criteria for definite or possible endocarditis. For patients with multiple episodes of endocarditis, the first episode was considered as the index episode.

Clinical Data
Clinical data were retrospectively reviewed in 212 consecutive patients with IE. From medical records, we extracted data on sociodemographics, comorbid conditions, previous heart disease, microorganisms isolated,

echocardiographic findings, occurrence of IE complications, timing and type of cardiac surgery, euroSCORE, and outcomes. We evaluated both the additive and logistic euroSCOREs to assess the operative risk at the time of admission.

In the present study, the median time between IE diagnosis and surgery was 8 days in patients who underwent operation during the initial antibiotic therapy (n = 100). Of these, 50 patients underwent surgery within 7 days and 23 patients underwent surgery within 8 to 14 days after the initial diagnosis. As a result, approximately 75% of the patients underwent operation within 14 days. During the 14-day period after the initial diagnosis, the risk of embolism has been reported to be higher than after 14 days.[7,8] We think that surgery within this period could be a reasonable therapeutic option with the purpose of avoiding new embolic events. Thus, we defined early operation as surgical intervention within 2 weeks and late operation as surgical intervention more than 2 weeks after the initial diagnosis of IE. The indications for valve surgery in this study population were as follows: heart failure unresponsive to medical therapy, persistent infection, repeat embolization, high embolic risk, and presence of perivalvular extension of IE. In addition, the late operation was indicated in patients undergoing conventional treatment because of residual severe regurgitation after the resolution of infection. Repeat surgery was defined as the second cardiac surgery excluding the first surgical intervention for IE.

Outcomes

The end points of this study were IE-related death and major adverse cardiac event (MACE). MACE was defined as a composite of IE-related death, repeat surgery, and recurrence of IE during follow-up. Long-term outcome was determined through examination of medical records. IE-related death included cardiac death and death caused by the complications of IE, while excluding death obviously unrelated to IE, for example, death due to malignant disease and traffic accident.

Statistical Analysis

Differences between patients undergoing the early operation and patients receiving conventional treatment were compared using the chi-square test or Fisher exact test for categoric variables. Continuous variables are described as mean ± standard deviation, except for operative days and survivals (mean ± standard error), and compared with unpaired t tests. Because operative days after the onset were not normally distributed, the Mann–Whitney U test was performed to assess differences. Survival analysis was performed by Kaplan–Meier analysis, and differences in survival between groups were examined with the log-rank test.

To reduce selection bias, we performed rigorous adjustment for differences in the baseline characteristics by use of propensity score matching. By using multivariable logistic regression, a propensity score model was created to estimate the likelihood of early operation. A nearest-neighbor matching algorithm was used to match patients on the logit of the propensity score with a caliper width of 0.2 of the standard deviation of the logit of the propensity score. After propensity score matching, the baseline covariates were compared between the 2 groups with the paired t test or Wilcoxon signed-rank test for continuous variables and the McNemar test for categoric variables. Survival curves were constructed with Kaplan–Meier estimates and compared with the log-rank test. For Kaplan–Meier analysis, we analyzed all clinical events by time to first event. Data analysis was performed with SPSS software (Version 17.0; SPSS, Inc, Chicago, IL).

RESULTS
Patient Characteristics

Of the 212 patients, 73 underwent early operation and 139 received the conventional treatment. In the conventional treatment group, 99 patients underwent late surgical intervention and 40 patients received medical treatment alone. The baseline characteristics of the early operation group compared with the conventional treatment group are summarized in Table 1. Patients in the early operation group were more likely to have aortic valve involvement, heart failure, valve perforation, and large vegetations. The euroSCORE was higher in the early operation group than in the conventional treatment group. There were no significant differences in terms of causative microorganism and cerebrovascular complications between the 2 groups, and the most common causative microorganism in both groups was *Streptococcus* species.

Surgical Interventions

Surgery was performed at a median of 5 days after the initial diagnosis of IE in the early operation group and at a median of 45 days in the conventional treatment group. In the early operation group (n = 73), 53 patients had mitral valve endocarditis. Of the 53 patients, mitral valve repair was performed in 40 (75%). In patients who underwent late operation in the conventional treatment group (n = 99), 69 had mitral valve endocarditis and mitral valve repair was performed in 54 (78%). When the infection involved the aortic valve, aortic valve replacement was performed in 95% of all patients. Cardiopulmonary bypass time and aorta clamp time were significantly longer in the early operation group, whereas the operative complications were comparable between the 2 groups. Table 2 summarizes the surgical procedures.

Clinical Outcomes

The in-hospital mortality was lower in the early operation group (5% vs 13%, P = .08), whereas the operative mortality was comparable between the early operation group and the late operation group (5% vs 5%, P = .58).

In the conventional treatment group, 4 patients had new cerebral infarction or cerebral hemorrhage and 6 patients died during the initial hospitalization as the result of worsening heart failure and sepsis more than 2 weeks after the initial diagnosis of IE.

The mean follow-up period was 5.5 ± 5.1 years. There were 6 IE-related deaths and 7 non–IE-related deaths in the early operation group during follow-up, whereas there were 19 IE-related deaths and 6 non–IE-related deaths in the conventional treatment group. In addition, there were 8 repeat operations, 6 recurrences of IE, and no admission for heart failure in the early operation group, compared with 10 repeat operations, 5 recurrences of IE, and 6 admissions for heart failure in the conventional treatment group.

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