Early surgery for native valve infective endocarditis

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**Expanded abstract**

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Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Sohn DW: Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med* 2012, 366: 2466-2473.

Background
The timing and indications for surgical intervention to prevent systemic embolism in infective endocarditis (IE) remain controversial. This trial compares clinical outcomes of early surgery and conventional treatment in patients with IE.

Methods
Objective: To determine the effect of early surgery (<48 hours) to decrease the rate of death or embolic events as compared with conventional treatment for IE.

Design: Prospective randomized trial.

Setting: Two academic medical centers in Korea.

Subjects: Adult patients with left-sided, native-valve IE and a high risk of embolism.

Intervention: Valve repair or replacement with removal of vegetation within 48 hours of random assignment versus no early surgery.

Outcomes: Composite primary endpoint of in-hospital death and embolic events occurring within 6 weeks after random assignment. Secondary endpoints, at 6 months, included death from any cause, embolic events, recurrence of IE, and repeat hospitalization due to the development of congestive heart failure.

Results
Thirty-seven patients were assigned to the early-surgery group (<48 hours), whereas 39 were assigned to conventional therapy, 27 patients (77%) underwent surgery during the initial hospitalization and three during follow-up. One patient (3%) in the early-surgery group and nine (23%) in the conventional-treatment group reached the primary endpoint (hazard ratio (HR) 0.10, 95% confidence interval (CI) 0.01 to 0.82; *P* = 0.03). There was no significant difference in all-cause mortality at 6 months in the early-surgery and conventional-treatment groups (3% and 5%, respectively; HR 0.51, 95% CI 0.05 to 5.66; *P* = 0.59). The rates of the composite endpoint of death from any cause, embolic events, or recurrence of IE at 6 months were 3% in the early-surgery group and 28% in the conventional-treatment group (HR 0.08, 95% CI 0.01 to 0.65; *P* = 0.02).

Conclusions
Early surgery in patients with IE and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.

Commentary
Even with recent advancement in modern health science, infective endocarditis (IE) remains a disease associated with significant morbidity and mortality [1]. Its incidence increased from 5 to 7.9 cases per 100,000 person-years in Minnesota from 1970 to 2007 [2]. The role of surgical intervention is increasing, and better outcomes are being realized [3]. Current guidelines of the American Heart Association (AHA) favor early surgical intervention in heart failure, but indications for surgery to prevent systemic embolization are not clear [4,5]. Although the European Society of Cardiology has strongly recommended urgent surgery (within a few days) for a vegetation size of greater than 10 mm in an effort to prevent systemic embolization, evidence to support this aggressive approach is based mainly on observational studies [6,7]. Several randomized control trials (RCTs) have been conducted to determine choice and duration of antibiotics for IE, but no RCT regarding timing and indication of surgery is available. Early surgery may be beneficial since most emboli occur during the first week following the start of therapy, and the majority of these are cerebral emboli, which lead to poor outcomes [8].
This study was designed to address the role of timing of surgery in the prevention of systemic embolization in patients without heart failure but with large vegetations (>10 mm). All 39 patients in early intervention group underwent surgery, whereas only 30 (77%) of the 39 patients in the conservative group had surgery, presumably because it was felt to be indicated. In the conservative group, eight (21%) had indications for urgent surgery (mean time of 6.5 days after random assignment), and 22 (56%) had elective surgery after 2 weeks because of left ventricular dysfunction. The early-surgery group had no embolic events, whereas the conservative group had eight (21%) cases of documented systemic embolization (0% versus 21%, \( P = 0.005 \)). All embolic events occurred during the first 6 weeks (primary endpoint). In both groups, there was no significant difference in mortality at 6 weeks (3% versus 5%, \( P = 1.00 \)) or 6 months (secondary endpoint). The results of this study suggest that early surgical intervention significantly reduces the incidence of major embolic events without altering other short- and long-term endpoints. This study is important because it is the first randomized clinical trial to address a subgroup of patients with large vegetations without heart failure.

The significance of this study lies in the low pre-existing morbidity of the patients and the potential for real improvement in quality of life if significant embolization is avoided. Given the findings of the study, the AHA may modify its recommendations on the treatment of patients with IE and large vegetations. Interestingly, the overall mortality was lower in this study than the other observational studies of IE (5% versus 27%) [9]. This lower mortality may be related to strict inclusion criteria and excluding patients with complicated IE. Another possibility for the observed lower mortality in all subjects may be related to low incidence of *Staphylococcal* infection, an important risk factor for death in IE [10,11]. This study does not include patients with prosthetic valve, major stroke, and right-sided endocarditis, and this makes its recommendations limited in scope. Furthermore, though it is an RCT, it is not blinded, and this can cause ascertainment bias. Thus, it is difficult to generalize these results to all patients presenting with IE and large vegetations.

Although this is a small RCT, it signals a new era in conducting RCTs to determine optimal surgical approaches for patients with IE. Interestingly, in 2008, a larger RCT testing optimal timing of surgery for IE was also initiated (NCT00624091) [12]. That study is ongoing and is testing the role of timing of surgery for other indications, such as prosthetic heart valves and complicated IE. It will be interesting to see whether early surgery remains superior for preventing complications in this larger diverse group of patients.

**Recommendation**

Early surgical repair of patients with left-sided IE and large vegetations results in a markedly reduced incidence of long-term embolic complications without altering mortality as compared with using antibiotics alone and elective surgical repair.

**Abbreviations**

AHA, American Heart Association; IE, infective endocarditis; RCT, randomized control trial.

**Competing interests**

The authors declare that they have no competing interests.

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