

JOURNAL CLUB CRITIQUE

Early surgery for native valve infective endocarditis

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Expanded abstract

Citation

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. Of the 39 randomly 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].

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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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References

1. Fedeli U, Schievano E, Buonfrate D, Pellizzer G, Spolaore P: **Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system.** *BMC Infect Dis* 2011, **11**:48.
2. Correa de Sa DD, Tleyjeh IM, Anavekar NS, Schultz JC, Thomas JM, Lahr BD, Bachuwar A, Pazdernik M, Steckelberg JM, Wilson WR, Baddour LM: **Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota.** *Mayo Clin Proc* 2010, **85**:422-426.
3. Shimizu H, Ross RK, Bernstein L, Pike MC, Henderson BE: **Serum oestrogen levels in postmenopausal women: comparison of American whites and Japanese in Japan.** *Br J Cancer* 1990, **62**:451-453.
4. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS; American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease).** Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008, **52**:e1-142.
5. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons, Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B: **ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons.** *Circulation* 2006, **114**:e84-231.
6. Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, Casalta JP, Gouvenet J, Derumeaux G, Iarussi D, Ambrosi P, Calabró R, Riberi A, Collart F, Metras D, Lepidi H, Raoult D, Harle JR, Weiller PJ, Cohen A, Habib G: **Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study.** *Circulation* 2005, **112**:69-75.
7. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Müller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL; ESC Committee for Practice

- Guidelines: **Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer.** *Eur Heart J* 2009, **30**:2369-2413.
8. Fabri J Jr, Issa VS, Pomerantzeff PM, Grinberg M, Barretto AC, Mansur AJ: **Time-related distribution, risk factors and prognostic influence of embolism in patients with left-sided infective endocarditis.** *Int J Cardiol* 2006, **110**:334-339.
 9. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, Hoskin TL, Mirzoyev Z, Anavekar NS, Enders F, Moustafa S, Mookadam F, Huskins WC, Wilson WR, Baddour LM: **The impact of valve surgery on 6-month mortality in left-sided infective endocarditis.** *Circulation* 2007, **115**:1721-1728.
 10. Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG Jr: **Changing patient characteristics and the effect on mortality in endocarditis.** *Arch Intern Med* 2002, **162**:90-94.
 11. Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, Corey GR, Spelman D, Bradley SF, Barsic B, Pappas PA, Anstrom KJ, Wray D, Fortes CQ, Anguera I, Athan E, Jones P, van der Meer JT, Elliott TS, Levine DP, Bayer AS; ICE Investigators: **Staphylococcus aureus endocarditis: a consequence of medical progress.** *JAMA* 2005, **293**:3012-3021.
 12. San Román JA, López J, Revilla A, Vilacosta I, Tornos P, Almirante B, Mota P, Villacorta E, Sevilla T, Gómez I, Del Carmen Manzano M, Fulquet E, Rodríguez E, Igual A: **Rationale, design, and methods for the early surgery in infective endocarditis study (ENDOVAL 1): a multicenter, prospective, randomized trial comparing the state-of-the-art therapeutic strategy versus early surgery strategy in infective endocarditis.** *Am Heart J* 2008, **156**:431-436.

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