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Clinical predictors of in-hospital death and early surgery for infective endocarditis: Results of CArdiac Disease REgistration (CADRE), a nation-wide survey in Japan

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ABSTRACT

Background: The benefit of early surgery for IE is yet to be determined in non-Western countries. We conducted this study to evaluate the role of early surgery in infective endocarditis (IE) in Japan.
Methods: IE admissions in Japan were prospectively registered using a nation-wide WEB-based registration system (CArdiac Disease REgistration, CADRE). The impact of early surgery on in-hospital mortality was assessed in native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). Risk factors for in-hospital death were assessed by multiple logistic regression analysis. The propensity score for early surgery was calculated to adjust the impact of early surgery.
Results: From September 2006 to May 2009, 348 NVE and 81 PVE were registered. In NVE, early surgery was preferable in every quartile stratified with the propensity score and the summary odds ratio (OR) and 95% confidence interval (CI) was 0.12 (0.05–0.31). The predictors of in-hospital death were *Staphylococcus aureus* infection (OR 3.5, 95% CI 1.26–9.7), heart failure (OR 6.74, 95% CI 2.43–18.7) and early surgery (OR 0.07, 95% CI 0.03–0.2). In PVE, the predictors of in-hospital death were age (OR 1.09, 95% CI 1.01–1.18), *S. aureus* infection (OR 5.8, 95% CI 1.4–24.01) and heart failure (OR 7.44, 95% CI 1.81–30.67), whereas early surgery was not (OR 0.51, 95% CI 0.12–2.16).
Conclusion: Early surgery for NVE is associated with improved survival in a wide range of clinical subgroups in Japan. In PVE a survival benefit of early surgery is not clear.

1. Introduction

Infective endocarditis (IE) is a life threatening disease. Although surgery is advocated as an effective treatment, the surgical indication is different between native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE) [1,2]. Current criteria for early surgery for NVE are heart failure due to valvular dysfunction, persistent bacteremia, abscess formation, involvement of virulent microorganism and high risk of embolism [1–3]. In PVE, dehiscence of the prosthetic valve and PVE occurred early after previous surgery (<12 months) in addition to the criteria for NVE are accepted as the early surgical indication [1,2]. However, they are mostly based on the opinion of the experts or the observational studies and no randomized controlled trials are available. Observational studies using propensity models have yielded conflicting results on the role of early surgery in NVE, as well as in PVE [4–12]. This may be partly due to the difference in the period when these studies were performed. Recent advances in surgical procedure and perioperative management may change the surgical outcomes. Most of the literatures on this issue are from the Western countries; there are a few reports from Japan and most of them are small, conducted in one or two institutions [13–15].

We conducted a prospective nation-wide registration study to evaluate the role of early surgery in the treatment of NVE and PVE in the recent clinical practice in Japan using a propensity model and define the subsets in which early surgery is recommended.

2. Methods

2.1. Patients

We conducted a nation-wide WEB-based registration of cardiac diseases consisted with teaching hospitals in Japan, named CADRE, an acronym of CArdiac Disease

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REgistration; CADRE-IE is a branch of it. Physicians at each institution were in charge of the treatment and registered the data anonymously. The diagnosis of IE was made by the modified Duke criteria [16]. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the National Cerebral and Cardiovascular Center. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. We analyzed the patients with NVE and PVE separately (Fig. 1).

2.2. Definition

Early surgery was defined as replacement or repair of the affected valve or correction of anatomical abnormality and/or debridement during the index hospitalization for IE. *Early PVE* and *late PVE* were defined as PVE which occurred within or after 6 months from the previous valvular surgery, respectively. *Chronic disease* as one of other background factors was defined as steroid usage, hemodialysis, diabetes mellitus, cancer or liver cirrhosis. *Paravalvular complications* were defined as the presence of paravalvular abscess or new fistula. *Major complications* were defined as paravalvular complications, valvular perforation, congestive heart failure, new conduction defect, intracranial complications or other vascular embolism. We used in-hospital mortality as the outcome measure. Patient comorbidities and postoperative complications were defined according to The Society of Thoracic Surgeons Adult Cardiac Surgery Database (http://209.220.160.181/STSWebRiskCalc261/support_definitions.html). *Heart failure* was diagnosed based on careful history and physical exam, or by one of the following criteria: 1. Paroxysmal nocturnal dyspnea; 2. Dyspnea on exertion due to heart failure; 3. Chest X-ray showing pulmonary congestion; 4. Pedal edema or dyspnea, and receiving diuretics; or 5. Pulmonary edema.

2.3. Statistics

We used Fisher's exact test to compare the prevalence of characteristics between two groups unless otherwise indicated. To compare numerical data between two groups, an unpaired *t*-test was used. We used univariable and multivariable logistic regression analyses to assess the impact of variables on in-hospital death. For multivariable analyses, we incorporated early surgery and the variables which were significant in univariable analyses. To adjust backgrounds between the early surgery and medication arms, we constituted a propensity score predicting early surgery. We included to the propensity models the variables which were disproportionate between the arms and the variables which could potentially influence the decision making of early surgery (Supplementary Tables 1 and 2). C-statistics of the models in NVE and PVE cohorts were 0.80 and 0.82, respectively. NVE patients were analyzed in the quartiles stratified with the propensity score. Unadjusted mortalities and odds ratios of propensity score stratified strata were estimated. In the PVE cohort we did not use propensity score to stratify the patients, because the small number of the PVE patients precluded valid stratification. Early PVE was not incorporated into the models in PVE because this variable was undefined in considerable number of patients. Subgroup analyses were conducted for the clinically relevant subgroups using the logistic regression models with interaction terms and adjustment with a propensity score as a logit transformation. Two-sided probability (P) value <0.05 was accepted as indicating statistical significance. A software package (PASW Statistics 18; IBM Corporation, Somers, NY, USA) was used for statistical analysis.

3. Results

We registered 513 patients from 118 teaching hospitals between September 2006 and May 2009 (Fig. 1). Patients without outcome data and those transferred to other hospitals for further treatment were excluded. We also excluded 10 NVE patients with a pacemaker and 8 PVE patients who had underwent valve repair without valve replacement. The remaining 348 NVE patients and 81 PVE patients were analyzed.

3.1. Background of NVE patients

In the 348 NVE patients, 237 patients underwent early surgery and 111 patients were treated medically. The patient background is shown in Table 1. The early surgery arm was younger and was accompanied with less congenital heart disease, higher rates of a negative result in blood culture, aortic valve involvement and multiple valvular vegetations. It was also characterized by higher rates of paravalvular complications, valvular perforation, heart failure and a lower rate of in-hospital death (Table 1). When stratified with a propensity score, the major background variables were well balanced within the strata (Supplementary Table 3).

The microbiological characteristics of the entire NVE cohort were comparable to the previous reports [9,17]. Viridans group streptococci were the leading cause of causative organisms (29%). Both *Staphylococcus aureus* and other streptococci were the second prevalent organisms (15%). Coagulase-negative staphylococci and enterococci species were the other major organisms. Negative results in blood culture were found in 20%. The surgical indications and procedures for NVE were provided as Supplementary Tables 4 and 5. The most frequent indications for surgery in NVE were high risk for embolism and worsening heart failure (48% and 45%, respectively).

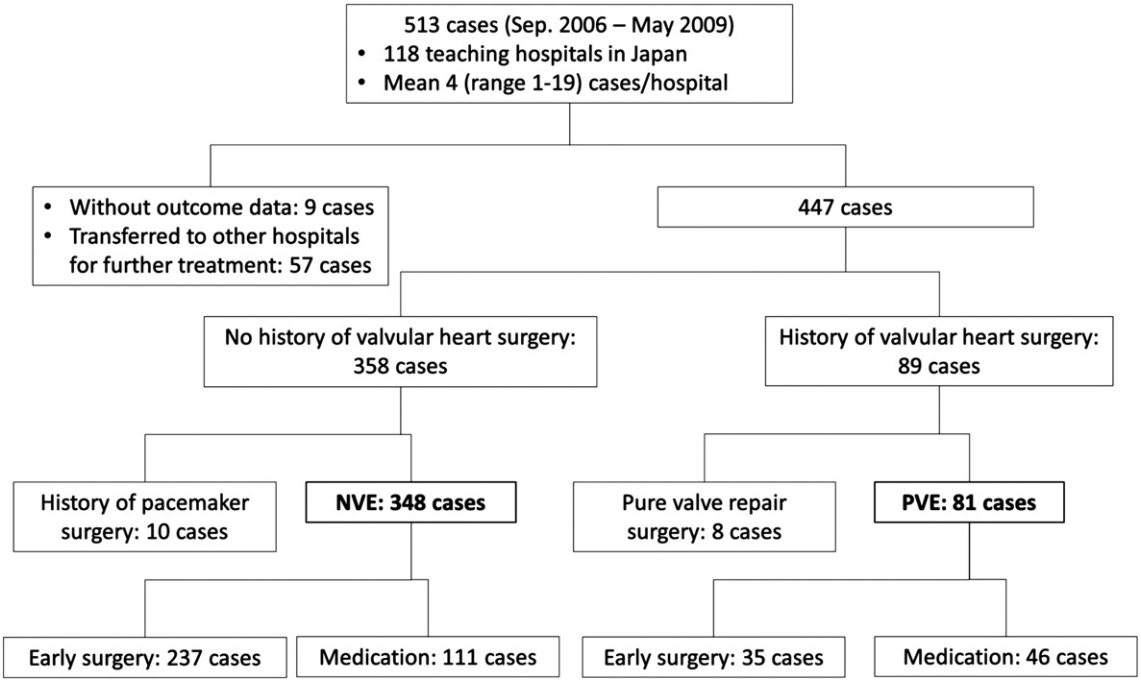

Fig. 1. Description of the patient population. NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.