Injection Drug Use and Outcomes After Surgical Intervention for Infective Endocarditis

Nabin K. Shrestha, MD, MPH, Jennifer Jue, MD, Syed T. Hussain, MD, Jason M. Jerry, MD, Gosta B. Pettersson, MD, PhD, Venu Menon, MD, Jose L. Navia, MD, Amy S. Nowacki, PhD, and Steven M. Gordon, MD

Departments of Infectious Disease, Internal Medicine, Cardiothoracic Surgery, Psychiatry, Cardiology, and Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio

Background. **Infective endocarditis (IE) requiring surgical intervention in patients who actively inject drugs poses treatment challenges. Decisions regarding the need for operation are affected by concern for relapse of IE from ongoing injection drug use (IDU). The purpose of this study was to evaluate the effect of active IDU on outcomes after operation for IE.**

Methods. **All patients with IE surgically treated at Cleveland Clinic from July 1, 2007 to July 1, 2012 were identified from the Cleveland Clinic Infective Endocarditis Registry and the Cardiovascular Information Registry. Of 536 patients operated on for IE during the study period, 41 (8%) actively injected drugs. The primary outcome of the study was death or reoperation for IE.**

Results. **Patients who injected drugs had poorer survival free of reoperation, and the risk of events varied with time. In a multivariable Cox proportional hazards model, using time-dependent covariates, IDU was associated with a higher hazard of death or reoperation between 90 and 180 days (hazard ratio [HR], 9.8; 95% confidence interval [CI], 2.7–35.3) but not before 90 days (HR, 0.38; 95% CI, 0.05–3.1) or after 180 days (HR, 1.8; 95% CI, 0.8–3.8). Among patients who injected drugs, reoperation and death contributed equally to the outcome, whereas among patients who did not inject drugs, reoperation for IE was far less common.**

Conclusions. **Between 3 and 6 months after operation for IE, patients who inject drugs have a hazard of death or reoperation that is about 10 times that of patients who do not inject drugs. Before and after, the HRs are much smaller and not statistically significant.**

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Infective endocarditis (IE) is a disease with substantial morbidity and mortality. Recent incidence rates of IE in Olmsted County, Minnesota have been reported to be 5.0 to 7.9 cases per 100,000 person-years [1]. In older studies in the United States and Europe, the annual IE incidence rates ranged from 17 to 59 cases per million [2–4]. In the past, the predominant risk factor for IE was rheumatic heart disease, but other risk factors have gained prominence [1, 5, 6]. These include injection drug use (IDU) [7, 8], prosthetic valves [9–11], degenerative valvular disease [12], intravascular devices [13], and hemodialysis [14, 15].

IDU is a burgeoning public health problem, especially among young adults aged 20 to 35 years [16]. The drugs commonly used include heroin, cocaine, and amphetamines [17]. Heroin addiction is no longer an inner city problem—most current heroin addicts are white, are from small urban or nonurban environments, and started their opioid use with prescription narcotics [18, 19]. This changing demographic is fueled at least in part by increasing abuse of prescription narcotics. Between 1999 and 2008, there was a sharp increase in the number of opioids prescribed in the United States and a parallel rise in the number of individuals admitted for the treatment of opioid addiction [20]. The incidence of IE in patients who inject drugs has been reported as ranging from 1% to 5% per year in the United States [16]. The number of hospitalizations for IE resulting from IDU has increased in recent years [21].

Current guidelines on the treatment of IE by the American Heart Association and European Society of Cardiology include recommendations for surgical intervention when there are severe complications from the disease. Indications for operation include heart failure, uncontrolled infection, and prevention of systemic embolism [22–24]. Among the IDU population, patients are at risk of recurrent infection from continued IDU [7]. Data on long-term outcomes of surgically treated IE in patients who inject drugs are limited and also conflicting. Both increased risk of reoperation [25] and equivalent risk of reoperation [26], compared with patients who do not inject drugs, have been reported. Given the high economic cost of surgical treatment for IE, knowledge of outcomes after operation among patients who inject drugs will help make informed decisions regarding treatment options for these patients.

The aim of this study was to compare survival free of reoperation among surgically treated patients with IE

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Address correspondence to Dr Shrestha, Cleveland Clinic, 9500 Euclid Ave, G-21, Cleveland, OH 44195; e-mail: shrestn@ccf.org.

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who inject drugs and surgically treated patients with IE who do not inject drugs.

Patients and Methods

Setting and Study Design

The study was a retrospective cohort study of patients treated surgically for IE. It was conducted at Cleveland Clinic, a large multispecialty tertiary care referral center. Patients with IE are evaluated and managed in consultation with a collaborative multispecialty heart valve team, including but not limited to cardiologists, infectious disease physicians, and cardiothoracic surgeons, as recommended by the most recent American Heart Association/American College of Cardiology guidelines [24].

Case Ascertainment and Inclusion and Exclusion Criteria

The study was approved by our institutional review board. Patients were identified from the Cleveland Clinic Infective Endocarditis Registry, which includes all patients $\geq$ 18 years treated for IE at Cleveland Clinic, and the Cardiovascular Information Registry, which includes all patients who undergo cardiac surgical procedures at Cleveland Clinic. All patients older than 18 years who were operated on for IE at Cleveland Clinic for the first time from July 1, 2007 to July 1, 2012 were screened for inclusion in the study. All patients who met Duke criteria for definite IE [27] were included. Patients were excluded if they did not have active IE or if they were not US residents. Active IE was defined as receiving antibiotic therapy for IE at the time of operation or having histopathologic or microbiologic evidence of active IE of the valves that were removed or repaired at operation.

Data Sources and Data Extraction

Data were collected through structured electronic queries and by manual review of the electronic medical record. Variables collected included patient demographics, comorbid medical conditions, predisposing factors for IE, whether patients injected drugs, echocardiographic findings, microorganism data, IE complications, and outcomes. Outcome variables collected included death or reoperation for IE. IDU was defined as the patient having injected drugs within 3 months before admission. Invasive disease was defined as extension of the invasive process beyond cusps or leaflets into the annulus or surrounding structures [28]. Mortality information was gathered from the electronic medical record, the Social Security Death Index database (when available), and from online publicly available data such as published obituaries.

Outcome Measures

The primary outcome was survival free of reoperation for IE. Secondary outcomes were reoperations and deaths.

Statistical Analysis

Unadjusted Kaplan-Meier curves with a log-rank test compared the survival free of reoperation among patients who injected and those who did not. A multivariable Cox proportional hazards model was created using all the variables included in Table 1. Looking at our descriptive table comparing the group who injected drugs and the group who did not, we saw that a number of characteristics differed among these groups, thus requiring adjustment. Log-negative-log survival plots and score processes derived from cumulative sums of martingale residuals over follow-up times were used to assess the proportional hazards assumption for each covariate. Several covariates appeared to violate the proportional hazards assumption when checked with a score process ($p < 0.10$). These included IDU, age, coronary artery disease (CAD), shock, metastatic infection, central nervous system (CNS) emboli, and all-purpose refined diagnosis–related group (APR-DRG) mortality risk. The time dependency of these covariates was investigated by including interactions with time (trichotomized at 90 and 180 days). Except for age and shock, all these covariates were found to be significantly associated with time and were entered into the model as time-dependent covariates. The cutoffs for the periods (trichotomization at 90 days and 180 days) were chosen based on the log-minus-log survival plot for IDU, the primary risk factor of interest, identifying time points at which the relative hazard appeared to change. Since our primary question involved whether or not IDU was associated with the outcome, this was forced into the model. We began by fitting the full model (containing all variables) and then removing any variable indicating no sign of an association with the outcome ($p > 0.50$). This model was assessed by our clinical IE expert coauthors to select from among the remaining variables those that possess the most clinically relevant information for treating patients with IE. This resulted in a reduced model, containing both statistically important and clinically relevant variables, in conformance with the recommended 10:1 ratio of events to degree of freedom, so as not to overfit the model [29]. A p value < 0.05 was considered significant. Analyses were performed with SAS, version 9.3 (SAS Institute, Cary, NC).

Results

From July 1, 2007 to July 1, 2012, 551 patients underwent operation for IE. Eight non-US residents and 7 patients without active IE were excluded. The remaining 536 patients were included in the study.

Baseline Characteristics of Included Patients

Univariable comparisons for patients who injected drugs and those who did not are presented in Table 1. Forty-one (8%) of the 536 patients operated on for IE during the study period injected drugs. Among the 41 patients who injected drugs, 31 (76%) injected heroin and 12 (29%) injected cocaine. IDU was significantly associated with younger age, a lower prevalence of diabetes mellitus, CAD, health care–associated IE, a higher prevalence of hepatitis C virus infection, a higher prevalence of previous IE, and a higher proportion of *Staphylococcus aureus* infection.