

Effect of vegetation size on the outcome of infective endocarditis in intravenous drug users

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ABSTRACT

Background: Infective endocarditis is one of the most important complications of injection drug use, which is associated with significant mortality and morbidity. The aim of this study was to evaluate the influence of vegetation size and localization on outcome and in-hospital mortality of infective endocarditis.

Patients and methods: A total of 34 patients were admitted to a university hospital in a four-year period and analyzed prospectively. Injection drug users were defined as patients who had injected drugs intravenously within the past 3 months before admission. The diagnosis of infective endocarditis was made on the basis of modified Duke's criteria.

Results: Totally, 38 episodes of endocarditis in 34 patients were identified. Patients were all male with the mean (\pm standard deviation) age of 30.4 ± 7.1 years. The affected valves were as follow: tricuspid valve in 26 cases (74.3%), mitral valve in 4 (11.4%), mitral and tricuspid valve in 4 (11.4%), and mitral and aortic valve in 1 (2.9%). The vegetation size was 10mm or less in 12 cases (34.29%), and more than 10mm in the remaining 23 cases (65.71%). Eight patients (21.1%) underwent surgery, however, unfortunately, nine (23.7%) died. Vegetations sized more than 10mm ($p < 0.033$), involvement of the left-sided valves ($p < 0.012$), and presence of more than one vegetation on TTE or TEE ($p < 0.05$) were associated with higher probability of death.

Conclusion: In contrast to some earlier studies which concluded that vegetations larger than 20mm are associated with higher mortality, our results revealed that the mortality rate increases even with smaller vegetations. In addition, the number and the location of vegetations also could affect the prognosis. Therefore, lower threshold for surgical interventions should be applied in patients with vegetations larger than 10mm.

Keywords: *Infective endocarditis, Vegetation, Outcome.*

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INTRODUCTION

Infective endocarditis (IE) is a classic complication of injection drug use (IDU) which has a different microbiology, involvement of cardiac valves, and prognosis in contrast with non-drug users. Infective endocarditis in this group of patients usually involves the tricuspid valve (58-

80%) and *Staphylococcus aureus* is the usual cause of the disease. It has a relatively good prognosis and the mortality rate is from 5% to 10%, depending on the series (1-3). Although several echocardiographic and clinical parameters have been used to predict outcome, to guide medical therapy, and to determine the need for surgical intervention, the exact predictors for poor outcome or the need for surgical interventions are not clearly determined in this group of patients. In native valve

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endocarditis, some studies had reported that the presence of vegetation, or vegetation size could be a predictor of outcome for a subgroup of patients who are at risk for the development of complications (4-6). Few studies have been performed to analyze this in right-sided endocarditis, or in injection drug users (7-9). For example, right-sided involvement, younger age, and lack of pre-existing heart disease or other underlying diseases have been thought to explain the better prognosis of *S. aureus* endocarditis among IDUs than in general population (10-12).

Vegetation size of more than 20mm is a recognized risk factor of adverse outcome in injection drug users with infective endocarditis (9,13,14). However, unfavorable outcome frequently occurs with vegetations smaller than 20mm; then this study designed to evaluate the role of vegetation size and localization on in-hospital mortality of such patients.

PATIENTS and METHODS

This prospective study has been carried out on patients admitted to Imam Reza hospital, Mashhad, north east of Iran, with the diagnosis of IE, during March 2001 to February 2005. Injection drug use and infective endocarditis were the inclusion criteria and the following initial data was collected at baseline: demographic characteristics, clinical and echocardiographic features, and outcome.

Injection drug users were defined as patients who had injected drugs intravenously within the past 3 months before admission. The diagnosis of infective endocarditis was made on the basis of modified Duke's criteria; two major criteria were growth of pathogen organisms on the blood sample (interpreted as "positive blood culture"), and visualization of vegetation or perivalvular abscess on the transthoracic or transesophageal echocardiography (TTE and TEE, respectively). The outcome of patients categorized as death or clinical cure. Blood cultures were obtained for all

patients under sterile conditions. Blood samples were cultured on standard media, and isolates were identified with standard microbiological tests using enzymatic or biochemical tests. All patients underwent TTE while TEE was achieved when appropriate. Valvular vegetation was defined as a localized mass of shaggy echoes adherent to a valve leaflet. Nonspecific valvular thickening was not interpreted as vegetation. The vegetative mass was measured in various planes. Size was measured by maximal length and width during freeze-frame analysis. A perivalvular abscess was defined as a circular echo density, without flow in its interior.

Analysis of risk factors associated with in-hospital mortality was performed for all cases with a definite diagnosis (modified Duke's criteria) and echocardiographic data. The following variables were analyzed: age, sex, clinical manifestations, blood culture result, vegetation size and site of involvement, clinical response, in-hospital cardiac surgery, and outcome. The association between categorical variables was analyzed with the chi-square test with the Yates correction or the Fisher's exact test (2-tailed) as needed. Statistical analysis was performed with the SPSS software package (version 11.0, SPSS Inc, Chicago, Ill). Statistical significance was defined as P value of less than 0.05.

RESULTS

During the study period, 38 episodes of IE occurred in 34 patients. Using modified Duke's criteria, all the diagnosed patients had "definite" IE, having 2 major criteria in 22 cases (57.9%), and 1 major criterion with 3 minors in 16 other cases (42.1%). All episodes occurred in male patients with the mean age of 30.4±7.1 years (ranging from 18 to 52 years). 4 patients experienced a second episode of IE.

Fever was the most common complaint in our setting (31 cases, 81.6%), followed by fatigue (16

cases, 42.1%), dyspnea (16 cases, 42.1%), cough (13 cases, 34.2%), sweats (13 cases, 34.2%), chills (12 cases, 31.5%), and hemoptysis (12 cases, 31.5%). The average length of symptomatic period, before presentation, was 13.2 days.

During the initial physical examination, 34 cases (89.4%) had fever (oral temperature of $\geq 38^{\circ}\text{C}$), while the average body temperature was 39.1°C . Cardiac murmur was evident in 24 cases (63.1%), and Janeway lesions, Osler's node, and splinter hemorrhage were seen in 3, 1, and 1 patients, respectively. The course of disease had been complicated by deep vein thrombosis (6 cases, 15.7%), cerebrovascular events (3 cases, 7.8%), meningitis (2 cases, 5.2%), gastrointestinal (GI) bleeding (1 case, 2.6%), and myocardial infarction (1 case, 2.6%).

Complete results of echocardiographic interventions of 35 cases were analyzed. All patients underwent TTE, while 8 cases (22.9%) underwent TEE. On TTE, tricuspid valve was involved in 26 cases (74.3%), and the frequency of mitral valve involvement alone, and mitral and tricuspid valves together, was equal; each in 4 cases (11.4%). In one case (2.9%), mitral and aortic valves were involved simultaneously. Totally, 26 cases had one vegetation on TTE (74.3%), 7 cases had 2 (20.0%), 1 case had 3 (2.9%), and 1 case had 4 vegetations (2.9%). The vegetation size was 1cm or less in 12 cases (34.3%), and more than 1cm in the remaining 23 cases (65.7%).

Among 8 patient underwent TEE, TEE findings were compatible with TTE in 6 cases (75.0%). In one patient with normal TTE result, small vegetation (4mm) was seen on tricuspid valve, and in another patient in whom TTE had shown vegetation on mitral valve, vegetation on aortic valve accompanied with aortic insufficiency was also noted.

Empirical antibiotic therapy began after admission, on the basis of clinical situation of the patient, severity of the disease, co-morbidities, and considering the unusual practices for injecting the

drug, and then changed in view of antibiotic susceptibility pattern of isolated organism.

Among 38 episodes of endocarditis, 9 cases (23.7%) died because of different complications of endocarditis. Averagely, death occurred 9.2 days following the admission.

To evaluate the influence of vegetation size and localization on the course of disease and ensuing death, the echocardiographic findings were compared in two categories of deceased and survivors, in consideration of statistical significance. Statistically significant association was noted between the left-sided heart involvement and ensuing death ($p < 0.012$) (Figure 1).

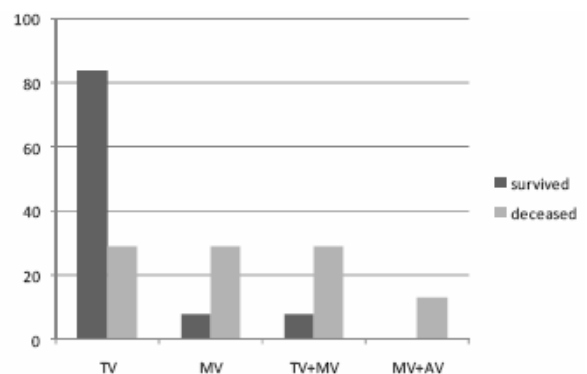


Figure 1. Association between death and site of involvement

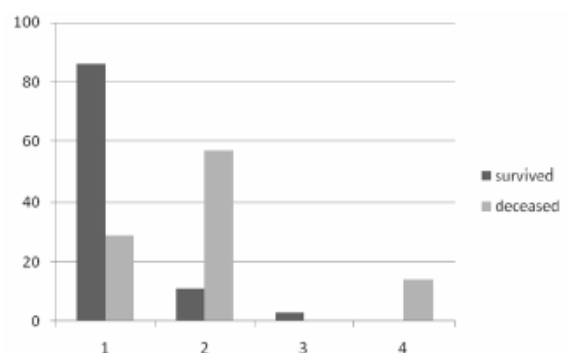


Figure 2. Association between death and number of vegetations

Furthermore, statistical analysis shows that there is an association between death and presence of more than one vegetation (figure-2) on TTE

($p=0.050$). There was an association between death and presence of vegetation which had a diameter of 10mm or more (figure 3) ($P=0.033$).

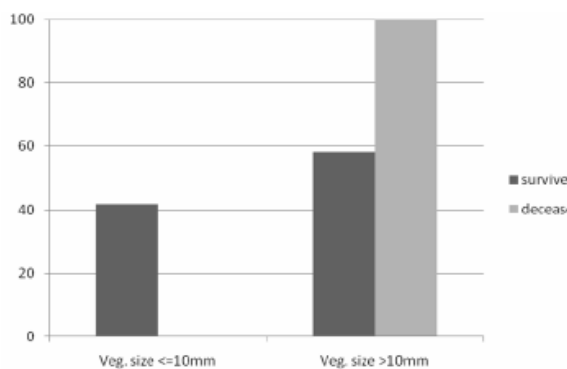


Figure 3. Association between death and vegetation size

DISCUSSION

Infective endocarditis is a common cause of bacteremia in injection drug users (IDU) which affected men more often than women. Unlike non-drug users, who generally present with the symptoms of greater than 2 weeks' duration (15), most addicts with IE present within the first week of illness with signs indicative of severe acute infection (1,16), which usually includes acute onset of fever, chills, and dyspnea. Cough is frequently present, and may be associated with blood-streaked sputum. Osler's node and Janeway lesions are rare and splenomegaly occurs in only 10 to 15 percent of cases. Heart murmurs are found with variable frequency, and if tricuspid valve involved, they are heard in 35 to 72 percent of patients (16). Fever, fatigue, and dyspnea were the most common complaints of patients evaluated in this study. Cough and hemoptysis spotted in 34.2% and 31.5% of patients at the time of presentation, respectively; 42.1% of patients complained of dyspnea. Janeway lesions detected in 7.8% and Osler's node were observed in 2.6% of the patients. Evidences of splenomegaly were postulated in 15.7% of cases, either in physical examination or on ultrasonography. Heart murmurs were revealed in

63.1% of the patients, and were the second most common finding in physical examination after fever (89.4% of cases).

IE in IDUs most commonly affected tricuspid valve (9,17-21); however, in some recently performed studies, left-sided (1,21,22) and multiple (23) valves involvement were observed with more frequency. Involvement of pulmonary valve is still rare, and is about 1% (17,18).

Tricuspid vegetations are often large and may be in excess of 20mm (17), and in rare situations, they reach in a size which leads in misdiagnosis as cardiac tumors on TTE. The TTE is at least equivalent to the TEE for detecting right-sided lesions (24). Hence, in patients with high probability of IE, a TTE might be performed first, and if negative a TEE may be ordered. In addition, TEE might be reserved for patients suspected to have left-sided involvement, or those with perivalvular lesions, such as valve ring abscess or perforation, or a vestigial eustachian valve. It is important to recognize that a negative TEE does not rule out endocarditis. In this study, TTE resulted in visualization of vegetation in 34 cases of 35 cases that underwent this procedure (97.1%). TEE findings were compatible with TTE in 75.0% of cases. After performing TEE, vegetation was observed in a patient with negative TTE, and in another patient with vegetation on mitral valve in TTE, vegetation on aortic valve was seen. Altogether, involvement of right and left sided valves occurred in 74.3% and 13.2% of cases, respectively. Valves of the right and left side of the heart were affected simultaneously in 11.4% of the patients.

Many studies conducted to evaluate the parameters that may affect the prognosis (13,14,25-29), and the following parameters are recognized as important ones: age, sex, prosthetic valve endocarditis, comorbidities, immunosuppression, presence of a vegetation, the result of blood and vegetation tissue culture, hemoglobin and CRP levels, surgical intervention, need for urgent

surgery, and occurrence of different complications during admission (including severe sepsis, congestive heart failure, renal failure, and major neurologic events).

The relationship between vegetation size and the likelihood of death assessed in several studies (25,26,30,31). In one study, vegetations larger than 20mm were associated with a 33% mortality rate, compared with 1.3% for patients with vegetations smaller than 20mm ($p<0.001$) (9). Vegetation size of 20mm or more was a predictor of death in other studies (13,32), while another study concluded that the vegetation size greater than 15mm associated with higher mortality rate (26). In our study, in-hospital mortality was higher in those with vegetations larger than 10mm ($p<0.033$). Involvement of the left-side of the heart ($p<0.012$) and more than one vegetation on TTE or TEE ($p<0.05$) were associated with higher probability of death, either.

In summary, in contrast to earlier studies which concluded that vegetations larger than 20mm are associated with higher mortality, our results revealed that mortality rate increases even with smaller vegetations (the mortality was higher in patients with vegetations larger than 10mm). In addition, the number and the site of vegetations could affect the prognosis. Therefore, lower threshold for surgical interventions should be observed in patients with vegetations larger than 10mm.

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