Contemporary In-Hospital and Long-Term Outcomes of Surgical Management for Fungal Endocarditis

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SUMMARY

Fungal endocarditis (FE) is a rare and fatal disease. The contemporary in-hospital and long-term surgical outcomes of FE have not been adequately evaluated. This study describes our experience with the surgical management of FE.

Eight FE patients who underwent surgery in our center from January 2004 to November 2016 were included in this study. Seven had fungal prosthetic valve endocarditis (PVE) and one fungal native valve endocarditis (NVE). The Bentall operation, Cabrol operation, and mitral valve replacement were performed in 4, 3, and 1 patient, respectively. The overall in-hospital mortality rate was 25% (2/8). The follow-up was completed in all surviving patients and the mean follow-up time was 55.5 ± 63.3 (range, 1-154) months. Two late deaths occurred at 2 months and 4 months after discharge. The other patients recovered well during the follow-up.

FE is a devastating disease and surgical treatment has acceptable in-hospital and long-term mortality rates. (Int Heart J 2017; 58: 516-520)

Key words: Fungus, Cardiac surgery, Mortality

Fungal endocarditis (FE) is an uncommon condition that accounts for 2% to 4% of all cases of infective endocarditis (IE).1) Despite advances in its treatment, FE is an extremely devastating disease associated with high mortality and recurrence rates.2) It is highly challenging to establish a diagnosis of FE. Candida and Aspergillus species are the most frequent etiologic fungi responsible for FE.3,4)

A combined antifungal and surgical treatment for FE is recommended by guidelines,2,5) but some patients are poor surgical candidates. Due to the rarity of FE and the low rate of surgical intervention that ranges from 10% to 38% of all cases, few studies have reported contemporary in-hospital and long-term surgical outcomes for FE, especially in Asian populations.6-8) An improved understanding of the role of surgical treatment for FE has important clinical implications. Taking these needs into account, we conducted a retrospective study to summarize our experience to provide information about the contemporary in-hospital and long-term outcomes of the surgical management of FE.

METHODS

Patients: This retrospective cohort study was carried out at Zhongshan Hospital of Fudan University. From January 2004 to November 2016, 790 IE patients underwent cardiac surgery in our center and 8 consecutive FE patients were enrolled in this study. The diagnoses for all enrolled FE patients were further confirmed by intraoperative findings and histological examination. The study protocol was approved by the Ethics Committee of Zhongshan Hospital of Fudan University and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient involved in this study.

Echocardiography and microbiology: Transthoracic echocardiography was performed for all IE patients preoperatively. Transoesophageal echocardiography was performed if necessary. All echocardiographic studies were conducted according to standard techniques by experienced echocardiographers. Microbiological information was obtained from blood cultures, intraoperative tissue sample cultures, and histological examinations.

Surgical treatment and antifungal therapy: Surgical decisions were based on the clinical judgement by a multidisciplinary team according to conventional guidelines. The indications of surgical treatment predominantly included uncontrolled infec-
tion, heart failure, and prevention of embolic events. All procedures were carried out by median sternotomy and use of extracorporeal circulation. After careful and radical debridement of the infected valves and perivalvular abscesses, excised tissues were sent for microbiology culture and histological examination. The Bentall operation was typically performed for aortic root replacement. If coronary ostia or tight adhesions carried a risk of strong traction at the level of the reimplanted ostia, we opted for the Cabrol approach. Antifungal therapy was initiated from the suspicion or diagnosis of FE and continued for at least 6 weeks after the operation.

Data collection and follow-up: The relevant medical records of all enrolled patients were investigated and analyzed retrospectively. Early PVE was defined as occurring within 1 year of surgery and late PVE beyond 1 year. Postoperative respiratory failure was defined as the need for mechanical ventilation for more than 48 hours or re-intubation. Postoperative acute renal dysfunction was defined as a least a 2-fold increase in plasma creatinine associated with urine production less than 0.5 mL/Kg/hour × 12 hours. In-hospital mortality was defined as death occurring during the same hospitalization or within 30 days after the operation. Follow-up started from the date of discharge, by telephone interview with patients or their relatives or reviewing outpatient records. Follow-up was completed for all patients with a mean duration of 55.5 ± 63.3 (1-154) months. Quantitative variables are presented as the mean ± SD or range.

RESULTS

Patients demographics and characteristics: From January 2004 to November 2016, 8 definite FE patients who underwent cardiac surgery in our center were enrolled in the study. There were 5 males and 3 females, and the mean age of the patients was 39.6 ± 11.9 years (range, 23-53 years). The organisms were Aspergillus in 5 patients and Candida in 3 patients. Five patients were early PVE, two late PVE, and one NVE. The clinical features of all patients are summarized in the Table. Before the operations, all patients were classified as New York Heart Association (NYHA) functional class III or IV. Fever was present in all patients. Stroke occurred in one patient and peripheral embolisms were detected in 4 (50%). Blood culture was only positive in two patients infected with Candida. The most frequent predisposing risk factor was a history of previous cardiac surgery, and intravenous drug use and an immunocompromised state were not present in these patients. Preoperative echocardiographic findings are summarized in the Table. Vegetations and perivalvular abscesses were common echocardiographic signs of FE. The Figure shows one FE patient with perivalvular abscess.

Operative data: Detailed surgical strategies are summarized in the Table. The Bentall operation was performed in 4 patients, the Cabrol modification operation in 3 patients, and mitral valve replacement in one patient. The mean cardiopulmonary bypass (CPB) time was 199.9 ± 53.3 (range, 106-261) minutes, and the mean aortic cross clamping (ACC) time was 106.6 ± 35.7 (range, 41-157) minutes. Mechanical valves were used in all patients. Because of restricted availability at our center, homografts were not used.

In-hospital mortality and morbidity: There were two in-hospital deaths. One patient died because of incurable low cardiac output after withdrawal of the CPB support. Another patient died because of intracerebral hemorrhage 7 days after the MVR operation. The pacemaker was implanted in two patients due to complete atrioventricular block postoperatively. Two patients suffered from acute renal dysfunction and recovered without dialysis. The mean ventilation time was 16.1 ± 10.1 (range, 8-37) hours, and one patient needed re-intubation. The mean postoperative ICU stay was 3.3 ± 1.9 (range, 1.5-6.5) days, and the mean postoperative in-hospital duration was 28.3 ± 13.1 (range, 11-51) days. The volume of drainage for the first 24 hours was 480.0 ± 303.9 (range, 220-1090) mL.

Long-term mortality: The follow-up was completed for all surviving patients and the mean follow-up time was 55.5 ± 63.3 (range, 1-154) months. Two late deaths occurred during the follow-up. One patient died because of recurrent and uncontrolled infection 2 months after discharge, and another died due to brain embolism 4 months after discharge. The other patients recovered well during the follow-up.

DISCUSSION

In this study, we summarize our experience with the surgical management of FE. Surgical treatment has acceptable inhospital and long-term mortality rates. A combined antifungal and surgical management for FE is recommended.

FE is most prevalent in patients who are intravenous drug abusers, immunocompromised, recipients of prolonged antibiotics, parenteral nutrition, prosthetic heart valves, or those who have had previous cardiac surgery. Multifactorial risk factors in a single patient might be more likely to cause FE. In our study, previous cardiac surgery was the most frequent risk factor for FE. No intravenous drug abusers or patients with an immunocompromised state were found in this study, which may be due to a referral bias.

FE has no special clinical manifestation compared with bacterial endocarditis. Fever of unknown origin was the most common clinical manifestation, and changing heart murmurs were recorded in some FE patients. FE should be considered in patients with uncontrolled fever of unknown origin or septic emboli, especially in those with previous cardiac surgery. Echocardiography and CT scan may provide valuable information for the diagnosis of FE. Large vegetations and perivalvular abscesses are frequent signs of FE.

The diagnosis of fungal endocarditis can be very challenging, because most of the time, blood cultures are negative or take a long time to yield growth. The sensitivity of detection of Candida in blood culture is about 50%-75%; however, the blood culture yield for Aspergillus endocarditis is estimated to be only 4%. In our study, only two patients had positive blood cultures for Candida. Sometimes the diagnosis of FE is only made upon histopathological examination of the explanted valve, infected foreign grafts, or peripheral emboli. Detection of a constituent of the cell wall of fungi, such as mannan, 1,3-β-D-glucan, and galactomannan, is a diagnostic adjunct for FE. Recently, molecular methods, such as polymerase chain reaction, may be helpful for the diagnosis of FE.

Concerning the extremely high mortality rate among those who receive medical treatment alone, an early and aggressive surgical treatment is recommended. Indications for
<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/Age</th>
<th>Preoperative Characteristics</th>
<th>Previous surgery</th>
<th>Organism</th>
<th>Echocardiographic findings</th>
<th>Infected valve</th>
<th>Surgery/Valve type</th>
<th>Antifungal therapy</th>
<th>In-hospital Outcome</th>
<th>Follow-up outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/53</td>
<td>Fever</td>
<td>AVR (4 m) for AR</td>
<td>Aspergillus (Not specified)</td>
<td>Vegetation; perivalvular leak; perivalvular abscess</td>
<td>A</td>
<td>Bentall/Mechanical</td>
<td>L-AmB 8w</td>
<td>Alive</td>
<td>Alive (154m)</td>
</tr>
<tr>
<td>2</td>
<td>M/44</td>
<td>Fever</td>
<td>DVR (1.5 m) for rheumatic heart disease</td>
<td>Aspergillus fumigatus</td>
<td>Vegetation; perivalvular leak</td>
<td>A</td>
<td>Bentall/Mechanical</td>
<td>I 2w then L-AmB 6w</td>
<td>Alive</td>
<td>Died (2m after discharge)</td>
</tr>
<tr>
<td>3</td>
<td>M/36</td>
<td>Fever; spleen embolism; IE History</td>
<td>Bentall (2 m) for BAV, dilated aortic root, IE</td>
<td>Aspergillus fumigatus</td>
<td>perivalvular leak</td>
<td>A</td>
<td>Cabrol/Mechanical</td>
<td>V 3w (iv) then V 3m (po)</td>
<td>Alive</td>
<td>Died (4m after discharge)</td>
</tr>
<tr>
<td>4</td>
<td>F/53</td>
<td>Fever; spleen and lower limb embolism</td>
<td>MVR (9 y) for MS</td>
<td>Candida albicans</td>
<td>Vegetation</td>
<td>M</td>
<td>MVR/Mechanical</td>
<td>L-AmB</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M/23</td>
<td>Fever; stroke; lower limb embolism</td>
<td>Bentall (5 m) for AR, dilated aortic root</td>
<td>Aspergillus flavus</td>
<td>Vegetation; perivalvular abscess</td>
<td>A</td>
<td>Cabrol/Mechanical</td>
<td>M 3w V 3w (iv) then V 3m (po)</td>
<td>Alive</td>
<td>Alive (86m)</td>
</tr>
<tr>
<td>6</td>
<td>M/24</td>
<td>Fever; lower limb embolism; IE History</td>
<td>AVR (6 y) for BAV, AR, IE</td>
<td>Candida albicans</td>
<td>Vegetation; perivalvular abscess</td>
<td>A</td>
<td>Cabrol/Mechanical</td>
<td>V 2w (iv) then F 6w 5FC 6w</td>
<td>Alive</td>
<td>Alive (86m)</td>
</tr>
<tr>
<td>7</td>
<td>M/36</td>
<td>Fever</td>
<td>Bentall + TAR (4 m) for aortic dissection</td>
<td>Candida albicans</td>
<td>Vegetation; perivalvular leak; perivalvular abscess</td>
<td>A</td>
<td>Bentall/Mechanical</td>
<td>M</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F/48</td>
<td>Fever</td>
<td>ASD repair (20 y)</td>
<td>Aspergillus (Not specified)</td>
<td>Vegetation; perivalvular abscess</td>
<td>A</td>
<td>Bentall/Mechanical</td>
<td>C 4w then V (po)</td>
<td>Alive</td>
<td>Alive (1m)</td>
</tr>
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</table>

AVR indicates aortic valve replacement; MVR, mitral valve replacement; DVR, double valve replacement; TAR, total arch replacement; ASD, atrial septum defect; AR, aortic valve regurgitation; MS, mitral valve stenosis; BAV, bicuspid aortic valve; A, aortic valve; M, mitral valve; L-AmB, liposomal amphotericin B; I, Itraconazole; V, voriconazole; M, Micafungin; F, fluconazole; 5FC, 5-fluorocytosine; C, caspofungin; W, week, m, month; and y, year.
surgical intervention are uncontrolled infection, the risk of emboli dissemination, and hemodynamic instability and heart failure. Surgical treatment is always difficult in FE patients, especially in PVE patients. The principle of surgical treatment is careful and thorough debridement of all infected tissues, which is key for later recovery and survival. Aortic root replacement, using the Bentall or Cabrol approach, is usually needed for infections in the aortic valve because of the high percentage of perivalvular abscesses. The current guideline recommends amphotericin B with or without flucytosine or echinocandin for Candida IE and voriconazole with or without echinocandin or amphotericin B for Aspergillus IE, combined with surgical removal of infected tissues, followed by chronic suppressive therapy with oral azoles. In high-risk patients presenting with prolonged fever, empiric antifungal therapies are necessary and should be given with sufficient term and dose. Due to persistent fever and a worsening clinical condition, misdiagnosed FE patients may miss the opportunity for surgery. Thus, FE mandates an aggressive treatment strategy, even when the patients still have fever and a negative blood culture. With the advent of new and effective antifungal agents, surgery may be safer than before.

Several limitations should be noted in the interpretation of our research. First, it was conducted at tertiary centers, and we cannot rule out the possibility that our patients might represent a selected cohort from referral centers with severer conditions. Second, the sample size was relatively small, although our cardiovascular center is the largest one in East China.

**Disclosure**

**Conflict of interest:** None of the authors have any conflict of interest.

**References**


J Cardiol 2013; 112: 111-6.