Original Article

A 20-year study on treating childhood infective endocarditis with valve replacement in a single cardiac center in China

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Background: Children with infective endocarditis (IE) have to undergo valve replacement instead of valve repair in China due to severe valve damage. The present study is to review our experience on surgical treatment of children with IE in reference to the incidence, pathologic status, diagnosis, surgical strategies and outcomes.

Methods: We reviewed 35 patients with a mean age of 13.7±2.2 years who were underwent valve replacement surgery for IE during the period from January 1993 to December 2013. Preoperative transthoracic echocardiographic (TTE) evaluation and transesophageal echocardiography during operation were performed in all patients. All the children underwent chart review and retrospective risk-hazard analysis.

Results: Among the patients surveyed congenital cardiac lesions were present in 15 (42.8%), rheumatic heart valve disease in 2 (5.7%) and previous heart surgery in 2 (5.7%). The median stay of intensive care unit was 6 days. Intraoperative findings showed that the endocarditis involved mostly the mitral and aortic valves (88.5%). Triple or quadruple valve involvement was found in one patient each. Ten-year freedom from IE-related death and re-intervention was 94.2% and 91.6%, respectively.

Conclusions: Children undergoing surgery for IE frequently have advanced disease with embolic complications. Although valve replacement is not the primary option for pediatric IE, the rate of 5-year survival and freedom from re-operation was optimal prognostically. Pediatric physicians should pay attention to the common clinical features of IE so that the native valve is preserved well.

Keywords: Children; infective endocarditis (IE); valve replacement

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Introduction

Infective endocarditis (IE) in children is an uncommon infection and was previously only a rare complication of rheumatic heart disease. In developed countries, majority of patients developing IE in childhood are the patients living with surgical repairs of congenital lesions (1). While in developing countries, where rheumatic heart disease is still prevalent, antibiotic prophylaxis for potential septic procedures is not routinely followed and late referral is common (2). In all age groups, IE leads to significant morbidity and mortality. Although IE occurs less in children than in adults, childhood IE leads to significant morbidity and mortality (3). If medical management fails or complications of endocarditis ensue, timely surgical intervention is crucial

for prognosis (4,5). Hickey *et al*. (6) have indicated that native valve preservation should be preferred in the children with IE. Though valve replacement confers to a high risk of repeat replacement at the 15th year (7), valve replacement is necessary in many Chinese children with IE because either they come to hospital with advanced clinical manifestations or their valves are damaged too severely where preservation of the values is not a feasible option.

The purpose of our study was to review the 20-year treatment experience of childhood IE with valve replacement surgery at our institution with regard to incidence, pathologic status, diagnosis, surgical strategies, operative mortality, recurrence of infection, re-operation, short-term and long-term surgical results.

Methods

We reviewed the cardiac surgery database of Shanghai Changhai Hospital (a 1,000-bed tertiary care teaching hospital with an annual cardiac operations of approximately 1,200) to identify the pediatric patients who had surgery for native valve endocarditis (NVE) from January 1993 to December 2013. A total of 35 children (23 boys, 12 girls), with a mean age of 13.7±2.2 years, underwent surgery for IE. They represent 9% of the total 388 cardiovascular surgical procedures performed for IE at our institution during that period. The acute clinical events present on admission or before surgery were recorded. Preoperative transthoracic echocardiographic (TTE) evaluation was performed in all patients. All patients had three sets of blood cultures (with two bottles per set), separated from each other by at least 1 h, and obtained from different venipuncture sites over 24 h. The review of these patients was approved by our institutional committee for human research. Follow-up was available to a mean of 9.5±3.6 years after surgery with a total of 160 patient years.

The patients' temperature was controlled and monitored for over 2 weeks before the surgery. The mean time from surgery after the diagnosis of IE was 3–21 days. Congestive heart failure, accompanying other heart diseases, persistent sepsis and systemic emboli were considered as the primary indication for operation. All operations were performed through a median sternotomy on full cardiopulmonary bypass between the 2 venae cava and the ascending aorta. Mild systemic hypothermia (28–30 ℃) was used in all the patients. Myocardial protection was identical for all patients and consisted of an anterograde cold blood crystalloid cardioplegia with topical ice slush.

Our principles of surgical intervention for IE consisted of uncompromising and thorough excision of all infected material and tissues, cutting back until healthy tissues were identified and followed by appropriate reconstruction. If the infection extended to the annulus or surrounding structures, a radical resection of the abscess and patch reconstruction of the annulus and adjoining structures was accomplished with fresh autologous pericardium. When infection was limited to the leaflets of the native valve, valve repair or simple replacement was performed. Valve repair was preferred option when adequate valve tissue was left after complete excision of infected material. When infection had extended to or beyond the annulus, as seen with abscess formation, then surgical intervention consisted of radical resection of all infected tissue, followed by reconstruction as necessary with valve replacement.

Data were procured from institutional medical records detailing patient demographics, pre-intervention echocardiography and angiography, operative procedures, subsequent clinic attendances and autopsy reports in the advent of death. Data were analyzed by using SPSS statistical software (Version 15.0). Data are presented as frequencies, medians with ranges, means with standard deviations or odds/hazard ratios with 95% confidence intervals (CI) as appropriate. Actuarial time-related outcomes were calculated by using Kaplan-Meier principles. In the case of missing data, mean values were imputed and the frequency of the missing data was indicated. Statistical significance was considered as $P<0.05$.

Results

Clinical characteristics

The characteristics of the patients are shown in *Table 1*. Endocarditis was active in 32 patients and healed in 3 (8.6%) patients with a mean age of 13.7±2.2 years. Predisposing factors were found in 17 (48.6%) patients, with rheumatic heart valve disease in 2 (5.7%), and congenital heart disease (CHD) in 15(42.8%). Previous sternotomy had been performed on one patient for VSD repair and patent ductus arteriosus ligation, and another patient had undergone patent ductus ligation via thoracotomy.

Most of the patients had constitutional and non-specific features of systemic sepsis such as lethargy, malaise and fever. While physical signs associated with adult IE such as nail clubbing, Osler's nodes, Janeway lesions or splinter hemorrhages were uncommon. About

Table 1 Characteristics of all the patients in the present study

Characteristics	Number	%
Mean age (mean ± SD (years	13.7±2.2	
Male gender	23	65.71
Active IE	32	91.43
Healed IE	3	8.57
Predisposing factors	17	48.57
RHD	2	5.71
VSD	5	14.29
ASD	2	5.71
VSD and ASD	1	2.86
Marfan syndrome	1	2.86
Abnormal left coronary artery	1	2.86
Bicuspid aortic valve	3	8.57
Previous surgical interventions		
VSD repair and patent ductus arteriosus ligation	1	2.86
Patent ductus arteriosus ligation	1	2.86

IE, infective endocarditis; RHD, rheumatic heart disease; VSD, ventricular septal defect; ASD, atrial septal defect.

Table 2 The predominant clinical features and lab findings of the patients

Clinical features	Number	%
Lethargy	31	88.57
Malaise	33	94.29
Fever	30	85.71
Cough	14	40.00
Shortness of breath	20	57.14
Nail clubbing	1	2.86
Oedema	6	17.14
Embolization	2	5.71
Myocardium abscess	1	2.86
Leukocytosis	32	91.43
Anemia	2	5.71
Arrhythmia	1	2.86

Table 3 The microbial population in the blood cultures from childhood infective endocarditis patients

Microorganisms	No. of patients	%
Streptococcus viridans	8	22.86
Streptococcus acidominimus	1	2.86
Streptococcus constellatus	1	2.86
Staphylococcus aureus	8	22.86
Staphylococcus epidermidis	2	5.71
Other bacteria	2	5.71
Culture-negative endocarditis	13	37.14

32 (91.43%) patients had elevated inflammatory markers or leukocytosis. Some patients had anemia, myocardium abscess, thrombocytopenia, and high level of creatinine. The diagnosis of embolism event was based on clinical signs and data derived from non-invasive procedure. Clinical embolization had occurred preoperatively in 2 (5.71%) patients (*Table 2*).

Different microorganisms were grown in blood cultures (n=22) (*Table 3*). *Staphylococci* and *Streptococci* were seen in equal number of patients. The preoperative TTE findings showed that the aortic and mitral valves were the primary sites of infection, while the pulmonary and tricuspid valves were less frequently involved (*Table 4*). Two valves involvement was seen in 3 (8.6%) patients. CHD was present in 15 (42.8%) children. The sites of infection associated with different heart defects are shown in *Table 5*.

Operative procedure

The distribution of operative procedures is shown in *Table 6*. Aortic value replacement (AVR) was the common procedure performed. Valve replacement has to be performed on many children with IE where there is advanced damage of valves, and the most frequently used valve was Regent mechanical valve with size ranged from 12 to 18. The superior leaflet, tendon and papillary muscle were preserved when mitral valve replacement (MVR) was performed. The patient suffering from coronary artery embolization underwent coronary artery bypass grafting and the embolus was removed.

Table 4 Pre-operative evaluation of cardiac involvement in children with endocarditis

Pre-operative evaluation	Number	%
Sites of infection		
Mitral valve	17	48.57
Aortic valve	14	40.00
Tricuspid valve	1	2.86
Aortic valve and pulmonary valve	1	2.86
Mitral valve and aortic valve	2	5.71
Echocardiographic findings		
Aortic insufficiency	18	51.43
Mitral insufficiency	20	57.14
Tricuspid insufficiency	24	68.57
Mitral stenosis	2	5.71
Aortic valve stenosis	2	5.71
Mitral valve prolapse	7	20.00
Impaired ventricular function	19	54.29
Abscess formation	1	2.86

Table 5 The association of the sites of infection and different heart defects in the patients

Heart defect	Sites of infection			
	MV	AV	PV	TV
VSD				
Sub-arterial	–	2	1	–
Sub-crest	–	2	–	–
Perimembranous (with PDA or not)	2	–	–	–
Sub-arterial with ASD and valsalva aneurysm	–	1	–	–
ASD	2	–	–	–
Bicuspid aortic valve	–	3	–	–
Marfan syndrome	1	–	–	–
Abnormal left coronary artery	–	1	–	–

MV, mitral valve; AV, aortic valve; PV, pulmonary valve; TV, tricuspid valve; VSD, valsalva aneurysm; PDA, patent ductus arteriosus; ASD, atrial septal defect.

Table 6 The surgical strategy adopted for the patients with IE

Surgery strategy	Number	%
AVR	7	20.00
AVR + VSD repair	1	2.86
AVR + MVP	1	2.86
AVR + reconstruction of the aortic root + VSD repair	1	2.86
AVR + MVP + excision of vegetations from PV and repair + excision of abscess from myocardium	1	2.86
AVR + reconstruction of the aortic root	1	2.86
AVR + VSD repair + reconstruction of the outlet portion of right ventricle	1	2.86
AVR + VSD repair + ASD repair + excision of valsalva aneurysm	1	2.86
AVR + paravalvular tissue repair	1	2.86
MVR	5	14.29
MVR + TVP	6	17.14
MVR + TVP + ASD repair	2	5.71
MVR + VSD repair	1	2.86
MVR + CABG + embolus removal	1	2.86
MVR + bentall	1	2.86
DVR	1	2.86
MVP	2	5.71
TVR	1	2.86

AVR, aortic valve replacement; VSD, ventricular septal defect; MVP, mitral valve repair; PV, pulmonary valve; MVR, mitral valve replacement; ASD, atrial septal defect; TVP, tricuspid valve repair; CABG, coronary artery bypass grafting; DVR, double valve replacement; TVR, tricuspid valve replacement.

Outcome

All patients were placed under postoperative antibiotic regimens for a period of 4 to 6 weeks. The median intensive care stay was 6 (range, 3–26) days. Important postoperative complications included rhythm disturbances in two with AF and supraventricular tachycardia, the underlying mechanism may be injuries due to surgery and inflammation in CPB,

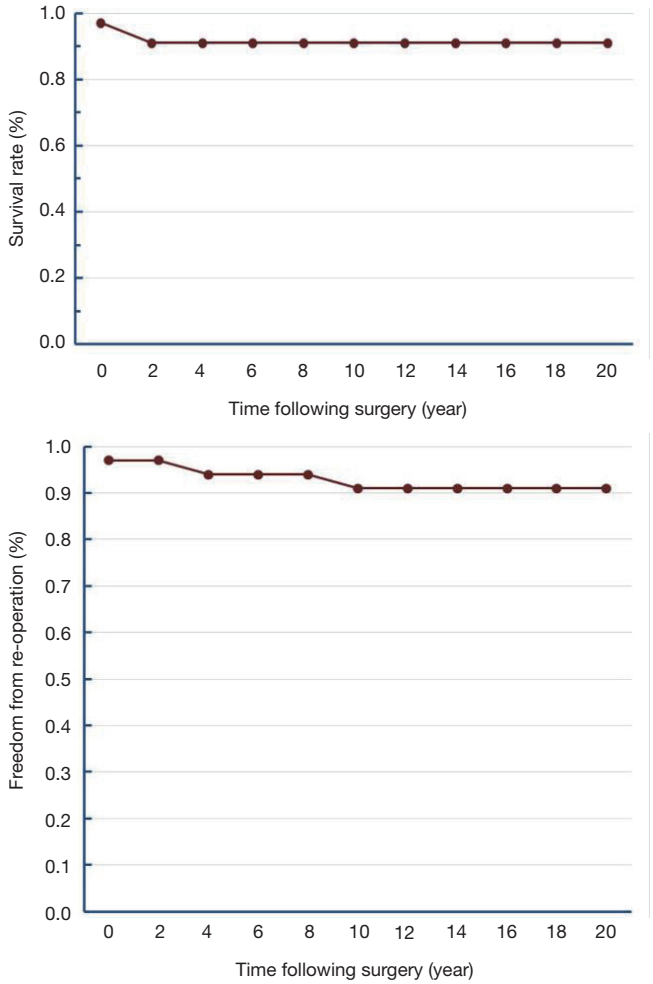

Figure 1 Survival rate and freedom from re-operation. (A) Survival after surgical intervention for infective endocarditis (valve replacement, n=35). There was only one early death attributable to abscess formation of the root of aorta one month after operation. One patient died after re-AVR surgery for infective endocarditis of the mechanical aortic valve in two years after the first surgery. One-year survival was 97% and 5-year survival was 94%. (B) Freedom from re-operation after surgical intervention for infective endocarditis. Freedom from re-operation: 1-year, 97%; 5-year, 94%; 10-year, 91%. AVR, aortic value replacement.

the both patients were treated with anti-arrhythmia drugs and recovered without recurrence. We also recorded aortic root abscess in one, and superior vein compression in one patient a year after operation.

There was one early death due to abscess formation in the root of aorta in 1 month after AVR for IE of aortic valve. One patient who had undergone double valve replacement (DVR) was infected by *Streptococcus* again after 2 years post-surgery, and was cured by antibiotics. One patient was diagnosed to have dissection of descending aorta 7 years after surgery, and was found to have anticoagulation complications after 1 year. One patient died after Re-AVR surgery for IE of the mechanical aortic valve in 2 years after the first AVR surgery. While the other one was cured by re-AVR surgery for IE of the mechanical aortic valve 10 years after the first AVR surgery (*Figure 1*).

Discussion

IE is an uncommon infection in childhood and occurs primarily in children with CHD (8), while rheumatic heart disease is a rarely seen in developed countries (3,9). IE in children leads to significant morbidity and mortality. Although rheumatic heart disease is still prevalent in China, it is not an important cause of IE in children unlike in Pakistan (10). In the 1990's, *Staphylococcus aureus* (*S. aureus*) endocarditis was less frequent than the *Streptococcus* endocarditis with prevalence ranging from 8% to 30% (11). A population-based study from 1970 to 2000 in Minnesota, USA, showed predominant presence of viridans group *Streptococci* (VGS) in adult IE (12). We identified higher rates of *S. aureus* infections in our IE case series. The change in trend of etiological agents and increasing incidence of *S. aureus* in childhood IE has been reported in some recent case series (3,13-15). We observed IE by *S. aureus* and *Streptococcus* in equal number of patients and culture-negative endocarditis in 13 (37.1%). As to fungal endocarditis, we have not recorded patients in our center, and the related reports were only scatter cases. Reported prevalence rates of IE with negative blood cultures ranged between 10% and 30% and found even higher in Pakistan and Eastern Europe (16,17). One of the main causes of negative blood cultures in IE patients is antibiotic pretreatment. The antibiotic abuse was also said to be prevalent in China before the 21st century.

The rate of emergence of resistant and multi-resistant bacteria has increased during the past two decades, especially among gram-positive microorganisms and so in some IE cases surgical treatment is needed. The clinical manifestations of IE are predominantly vague and constitutional, rather than specific. The predominant clinical features of IE in our series were lethargy, malaise, fever and leukocytosis that led to misdiagnosis and improper treatment in some patients before final diagnosis was made. Valve replacements were performed in many children with

IE in China instead of valve repair because often the valve was damaged too severely to be preserved. In children with damaged AV who needed AVR, Ross procedure was reported to be alternative option in early years, but because of shortage of homograft and the difficulties of procedure, Ross procedure was scarce in China.

Some centers have reported their recent surgical experience with infective IE in children. In a 29-year study period by Hickey's group on 30 children under the age of 18, valve replacement was performed in 24% (6). They observed lower 5-year survival in patients who underwent valve repair operation. Monro's group studied 16 children with IE (18). Compared with Hickey's study, Monro's group reported prosthetic tissue IE in 19% of cases with similar anatomical distribution of infected valves, etiologic organisms and associated congenital heart defects (69%). Interestingly, they described slightly a higher rate of cusp perforation, abscess formation or chordal rupture which may explain higher valve replacement rate of 63%. Preservation of native valve in childhood IE patients in China is difficult, although many doctors feel that valve repair is better than valve replacement (18). Factors such as expense for treatment, transportation inconvenience, and neglect of the common early clinical features affect the surgical option of IE treatment in the developing country. In Hickey's group, the rate of 10-year freedom from re-operation was 60%±18%, while it was 91% in our study.

From our experience, we found that valve replacement was not worst option as thought before, even the rate of 5-year survival and freedom from re-operation of the patient who underwent valve replacement is better than that of the patient who underwent valve repair operation, although it is not the primary choice for the children with IE. Preservation of the native valve will improve late survival, freedom from re-operation and functional outcomes. The first contact pediatric doctors should pay attention to the common clinical features of IE to diagnose the condition early and consider early referral so that the native valve as far as possible could be preserved, especially in the developing countries.

Limitations

The present study is limited by the smaller number of subjects and the unknown population denominator of children diagnosed with IE during the study period. However, it serves to emphasize that valve replacement may be better than valve repair if done early in the disease process.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The review of these patients was approved by our institutional committee for human research.

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