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Changes in Patient Characteristics of Infective Endocarditis with Congenital Heart Disease: 25 Years Experience in a Single Institution

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Background and Objectives: The profile of infective endocarditis (IE) has changed and is now showing an increasing prevalence of IE among congenital heart disease (CHD) patients. We studied the change of clinical profiles of IE over the past 25 years in patients with CHD at a single institution.

Subjects and Methods: We reviewed medical records retrospectively for 325 patients diagnosed with IE between January 1, 1987, and March 31, 2012. We analyzed and compared the differences in patient characteristics and outcomes between 1987-2000 (group A) and 2001-2012 (group B).

Results: Over the 25-year period, 93 cases of IE in CHD patients were diagnosed (59 cases in group A and 34 cases in group B). Ventricular septal defect was the most common underlying cardiac disease observed during the entire period. The most common causative pathogen was *Streptococcus* in both groups. Group A contained 16 cases (27.1%) that had undergone cardiac surgery, whereas this number was 19 (55.8%) in group B. The number of patients who had undergone palliative care or surgery using prosthetic materials was higher among group B patients ($p<0.001$). Surgical procedures due to uncontrolled infection were performed in three cases in group A and 10 cases in group B.

Conclusion: Infective endocarditis and CHD show a close correlation, and the profile of IE patients can change in line with an increase in the survival rate of patients with complex CHD and the improvement of surgical techniques. Ongoing reassessment and the systematic management of these patients is crucial in the prevention and treatment of IE. **(Korean Circ J 2014;44:37-41)**

KEY WORDS: Infective endocarditis; Heart disease, congenital.

Introduction

Infective endocarditis (IE) is a disease that can cause serious complications, and the risk of IE is higher in patients with underlying heart disease.[1)] Over the past several decades, IE was commonly associated with rheumatic heart disease and degenerative valvular heart disease. However, the profile of IE has since changed, with an increasing prevalence of IE among congenital heart disease (CHD) patients.[2-4)]

Reports on the clinical features of CHD with IE in different countries[5)6)] indicate that the occurrence of IE has different features according to medical status, culture, and the region involved.[7-9)]

In Korea, there has been an increased survival rate of patients with CHD, but little is known about the occurrence of IE in these patients. Therefore, we reviewed cases of IE over the past 25 years at a single institution, and studied the change in theclinical profiles of IE in patients with CHD.

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Subjects and Methods

Study patients

We searched the Severance Cardiovascular Hospital database for CHD patients diagnosed with IE between January 1, 1987, and March

Table 1. Baseline demographic characteristics of the two study groups (n=93)

Items	Group A (n=59)	Group B (n=34)	p
Sex (n, male : female)	25 : 34	13 : 21	0.934
Age (years±SD)	17.9±14.7	24.4±18.6	0.072
Age <1 year of age (n, %)	5 (8.5)	2 (5.9)	0.834
1 year≤age≤18 years of age (n, %)	26 (44.1)	14 (41.2)	0.687
Age >18 years of age (n, %)	28 (47.4)	18 (52.9)	0.761
Cyanotic CHD (n, %)	10 (16.9)	17 (50)	0.001

Group A: IE cases with CHD between 1987-2000, Group B: IE cases with CHD between 2001-2012. SD: standard deviation, IE: infective endocarditis, CHD: congenital heart disease

31, 2012. Modified Duke criteria[10] were used for the diagnosis of IE, and the diagnosis of IE was made when the patients could be classified as suffering from definite endocarditis.

Data were collected from a retrospective review of patients' records, which included patient demographics, history of CHD, causative organism, clinical course, complications, morbidity, and mortality. We divided the patient data into two periods; group A of previously treated patients, hospitalized between 1987 and 2000; group B of more recently treated patients, hospitalized between 2001 and 2012. We analyzed and compared the differences in patient characteristics and outcomes between the two groups.

Statistical analyses

Datawere analyzed using Statistical Package for the Social Sciences (SPSS) 20 for Windows (SPSS Inc., Chicago, IL, USA). Means were analyzed using the Student t-test. For categorical data analysis we used the chi-square test. A p of less than 0.05 was considered statistically significant.

Results

Demographic characteristics

During the 25-year period, 325 cases in 309 patients with IE were treated at our hospital. Of these, 93 cases (28.6%) across 87 patients, composed of 59 cases in group A (56 patients) and 34 cases in group B (31 patients), were diagnosed as having an underlying CHD. Five patients were patients with recurring symptoms; three patients in group A (56 patients) and two patients in group B (31 patients). Only one patient had recurring symptoms three times, in group B.

The mean age ofthe patients was 17.9±14.7 years of age in group A and 24.4±18.6 years of age in group B; the difference was not statistically significant. There were no statistically significant differences between the groups in age: five cases (8.5%) in group A were younger than 1 year compared to two cases (5.9%) in group B. Twenty eight cases (47.4%) in group A were older than 18 years compared to 18 cases (52.9%) in group B, and 26 cases (44.1%) in group A were between 1 and 18 years, compared to 14 cases (41.2%) in group B. However, the prevalence of cyanotic CHD {Tetralogy of Fallot (TOF), pulmonary atresia with ventricular septal defect (VSD), Ebstein's anomaly, double-outlet right ventricle, and transposition of the great arteries} was significantly higher in group B than group A (p=0.001) (Table 1).

Table 2. Underlying congenital heart disease

Diagnosis (%)	Group A (n=59)	Group B (n=34)	p
VSD	27 (45.7)	12 (35.3)	0.487
ASD	8 (13.5)	1 (2.9)	0.105
ECD	4 (6.7)	1 (2.9)	0.679
PDA	7 (11.9)	3 (8.8)	0.693
TOF	4 (6.8)	8 (23.5)	0.087
PA with VSD	0 (0)	6 (17.6)	0.002
DORV	5 (8.5)	2 (5.9)	0.684
PAPVR	2 (3.4)	0 (0)	0.454
Bicuspid AV	1 (1.7)	0 (0)	0.454
Ebstein's anomaly	1 (1.7)	0 (0)	0.454
TGA	0 (0)	1 (2.9)	0.176

Group A: IE cases with CHD between 1987-2000, Group B: IE cases with CHD between 2001-2012. VSD: ventricular septal defect, ASD: atrial septal defect, ECD: endocardial cushion defect, PDA: patent ductus arteriosus, TOF: tetralogy of fallot, PA: pulmonary atresia, DORV: double-outlet right ventricle, PAPVR: partial anomalous pulmonary venous return, AV: aortic valve, TGA: complete transposition of the great arteries, IE: infective endocarditis, CHD: congenital heart disease

Associated heart disease

The most commonly associated heart disease was VSD in 39 cases (41.9%) followed by TOF, at 12 cases (12.9%), and patent ductus arteriosus at 10 cases (10.7%). Non-cyanotic heart diseases such as VSD were the main cardiac conditions in group A, whereas cyanotic heart diseases, such as TOF and pulmonary atresia with VSD, composed the main cardiac conditions in group B (Table 2).

We compared the incidence of IE in patients with or without prior cardiac surgery for underlying CHD. Of the total cases with CHD (n=93), we found 58 cases (62.3%) that had not, any cardiac surgery, and 35 cases (37.6%) that had undergone corrective or palliative

cardiac surgery upon the diagnosis of IE. Group A (n=59) included 16 cases (27.1%) that had undergone cardiac surgery, whereas this number was 19 (55.8%) in group B (n=34); this difference was statistically significant (p=0.004). Those patients who underwent corrective surgery consisted of 15 cases in group A, but only eight cases in group B. However, patients who had undergone palliative care or surgery using prosthetic materials increased in group B to 11 cases compared to only one case in group A, which was statistically significant (p<0.001) (Table 3).

Causative microorganism

The most commonly identified causative microorganism in both groups was *Streptococcus*, with *Staphylococcus aureus* identified in one case in group A and five cases in group B. There were unique bacteria identified in group A, including *Acinetobacter anitratus*, *Citrobactoer freundi*, and *Serratia marocescens*. *Candida albicans* was also identified in three cases in group A. Thirty-five cases (37.6%) did not have an identified microorganism observed in blood cultures, and there was no statistical significance between the two groups (group A, 26 cases; group B, 9 cases; p=0.113) (Table 4).

Treatment

All patients who were diagnosed as having IE, were hospitalized and treated with an intravenous injection of antibiotics. The mean hospital stay was 48 days; 44 days in group A and 50 days in group B. Of these patients, 13 cases underwent early surgical procedures due to uncontrolled infections after the intravenous injection of antibiotics and increased complications, such as heart failure. Surgical procedures were performed in three cases in group A (two cases were for a removal of vegetation, and one case was valvuloplasty

Table 3. Proportion of infective endocarditis according to prior cardiac surgery

History of operation	Group A (n=59)	Group B (n=34)	p
Patients without prior cardiac surgery (%)	43 (72.9)	15 (44.1)	0.033
Patients with prior cardiac surgery (%)	16 (27.1)	19 (55.9)	0.004
Corrective surgery	15 (25.4)	8 (23.5)	0.801
Palliative surgery or prosthetic material	1 (1.7)	11 (32.4)	<0.001

Group A: IE cases with CHD between 1987-2000, Group B: IE cases with CHD between 2001-2012. IE: infective endocarditis, CHD: congenital heart disease

Table 4. Causative microorganism

Microorganism	Group A (n=59)	Group B (n=34)	p
Number of cases documented by blood culture (n, %)	33 (55.9)	25 (73.5)	0.113
Gram (+) organism			
Staphylococci			
Staphylococcus aureus			
Methicillin-sensitive	2	2	0.568
Methicillin-resistant	2	3	0.263
Staphylococcuscoagulase negative			
Staphylococcus epidermidis	1	2	0.271
Streptococci			
Viridans streptococcus	15	13	0.195
Others	4	1	0.429
Enterococcus			
Enterococcus faecalis	1	1	0.690
Gram (-) organism			
Acinetobacter anitratus	2	0	0.278
Citrobactoer freundi	2	0	0.278
Serratia marocescens	1	0	0.445
Pseudomonas aeruginosa	0	3	0.020
Fungi			
Candida albicans	3	0	0.181

Group A: IE cases with CHD between 1987-2000, Group B: IE cases with CHD between 2001-2012. IE: infective endocarditis, CHD: congenital heart disease

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with vegetation removal), and 10 cases in group B (nine cases required valvuloplasty, and one case had vegetation removal only).

Progress

The most common complication was heart failure associated with valvular dysfunction in 29 cases (group A, 14 cases; group B, 15 cases), followed by eight cases of pulmonary embolism (group A, four cases; group B, four cases), and one case of brain artery infarction in group B. There was no surgical mortality. Total mortality numbered 5 (5.3%), one case in group A and four cases in group B. The cause of mortality was acute cardiopulmonary failure due to uncontrolled infection and complications.

Discussion

The treatment outcomes of patients with CHD have dramatically improved over the past several decades, with an increase in long-term survival. This has resulted in an increased number of CHD patients diagnosed with IE.[3] CHD has been reported as 9-28%,[3)5)] and 17-26%[11)12)] of the causes of IE in Korea, suggesting a causative role of CHD in IE. In our study, 28.6% of patients diagnosed with IE had underlying CHD. The high prevalence of IE at our institute compared to the other domestic institutes, in part, results from the increased survival rate of CHD patients due to improved treatment methods, as well as the increased number of patients undergoing long-term follow-up at our institute, which runs a CHD center.

Patients with CHD have a possibility of IE in their lifetime, but the occurrence rate differs according to the type of CHD. Uncorrected VSD patients showed a high risk for IE[13-15)] and, in our study, VSD was the most commonly observed underlying CHD in both groups A and B. However, the larger percentage of patients with a cyanotic complex cardiac anomaly were observed in group B. This was likely due to an improvement in the early detection of CHD and improved surgical techniques, such as use of prosthetic materials, with patients consequently undergoing those procedures earlier in life. Consequently, there was a decreased risk of IE due to unrepaired simple CHD and the improved long-term survival rate of patients with a complex cardiac anomaly. The differences between the two groups are probably due to the improved treatment modality and improved treatment outcomes.[13)16)]

In the year 2000, the year that divides the two study groups, Korea implemented a nationwide systemic change, separating the prescribing and dispensing of pharmaceuticals, and regulating the use of antibiotics under national guidelines.

Previous studies have shown that 2.5-31% of IE patients did not have an identified microorganism in the blood culture.[17] This is less than the 37.6% found in our study, and although we found no statistically significant differences between group A (44.1%) and group B (26.5%), we noticed a decreasing trend in group B. Considering that the most common cause of non-identifiable microorganism in IE is antibiotic use prior to acquiring a blood sample, the changed health system regulating the use of antibiotics may be associated with this change.

The prevalence of IE due to *Staphylococcus* has previously been reported as having increased in patients who underwent previous cardiac surgery, compared to IE due to viridians streptococci.[18] In our study, the most common pathogen of IE was viridians Streptococci in both groups, and IE due to *Staphylococcus* was comparably low. However, the prevalence rate of *Staphylococcus* infection in group B indicated an increase. IE due to fungus was reported to be dominant in patients who had previously undergone open heart surgery, were exposed to the long-term use of broad spectrum antibiotics, and had had intravenous catheter insertion.[19] IE due to fungus has previously been shown to be increasing,[20] but our study showed a decreasing tendency.

The most common complication reported in the literature was heart failure, at 15-65%,[21] which appears to be in line with the findings of 31.2% in our study. However, the number of patients who underwent a surgical correction of IE due to uncontrolled infection after the intravenous injection of antibiotics increased in group B to 29.4% (compared to 5.1% in group A), and this was higher than the 14%[22] reported previously. Given that the indication for surgery is "uncontrolled infection", surgical correction of IE has also increased in recent years. Mortality has been reported as between 7% and 8%,[15)23)24)] but we found an overall lower percentage (5.3%), although the mortality rate increased to 11.7% in group B. These results probably reflect the increased number of patients undergoing palliative treatment or prosthetic material surgery. Consequently, there was an increase in the number of IE high-risk patients[16] and likely an increase in uncontrolled infection, leading to a higher rate of surgical correction among IE patients.

This study has a number of limitations. Our study was a nonrandomized controlled trial conducted retrospectively by reviewing medical records, which may not properly reflect the medical technology status, environmental changes, and societal changes and their ramifications. Furthermore, we lacked data on antibiotic prophylaxis before high-risk procedures, such as dental procedures or gastro-intestinal tract manipulation. However, this study is meaningful in that a single protocol was able to be evaluated over a long period of time at a single institute.

In conclusion, IE and CHD present a close correlation, and the profile of IE patients can change according to the tendency of an early correction for CHD and the development of diagnostic modalities. These changes were likely due to an increase in the long-term

survival rate of patients with complex CHD and an improvement in surgical techniques, such as the use of prosthetic materials. Ongoing reassessment and the systematic management of these patients is crucial in the prevention and treatment of IE, especially for patients with complex CHD.

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