The Role of Transthoracic Echocardiography in the Early Diagnosis of Infective Endocarditis in Pediatrics

Ali Akbar Zeinaloo, MD, S. Hameed Mirkhani, MD and Mortaza Niazee, MD

Abstract

Background- The role of transthoracic echocardiography and the sensitivity rate of blood culture in the early diagnosis of infective endocarditis(IE) are not defined accurately in Iranian childhood population.

Methods- Thirty-six episodes of IE were evaluated in 36 children admitted to hospitals affiliated with Tehran University of Medical Sciences during a 5-year period (1996-2000). The patients' major complaints, clinical findings, the medication they had been receiving and their tests and echocardiographic data were studied.

Results- The average age was 10.38±3.348 years. Overall, the male/female ratio was 2:1; fever was the most common complaint (100%). Sixty-six percent of the patients had fever more than 7 days. Congenital heart disease was the most common underlying disease (66%), followed by rheumatic heart disease (RHD, 22%). Congestive heart failure (CHF) was present in 30.5% of the cases. Blood cultures were positive in 42%, and vegetations were seen in 83.4% by 2-dimensional echocardiography (echo). Blood culture and echo sensitivity and specificity were 45 vs. 90.5 ($p<0.001$) and 60 vs. 75 ($p<0.05$), respectively. The most common site of vegetation was the aortic valve area, followed by the tricuspid valve. *Staphylococus aureus* was the most common infecting microorganism. There were 6 deaths (16.6%) due to different causes. Indicators for mortality include negative cultures, infection with *S. aureus*, large vegetation and CHF. All mortalities had left-sided vegetations ($p<0.05$).

Conclusions- In contrast to the high sensitivity of blood cultures in IE in developed countries, in the developing countries the result of blood culture is not reliable. Therefore, echocardiography can play a major role in the early diagnosis of IE and can change the outcome of this potentially serious illness ***(Iranian Heart Journal 2004; 5(3):16-22).***

Key words: Infective endocarditis■ children■ blood culture■ transthoracic echocardiography

Infective endocarditis (IE), one of the most dangerous cardiac conditions, occurs when the infecting microorganism attacks the valves or their related areas of the heart. Nowadays, most children afflicted with endocarditis suffer from some complicated congenital heart disease (CHD).

The modern categorization is based on the etiology and cause under the general heading, infective endocarditis.[1, 2, 3] Infants under one year of age constitute less than 10% of the cases.[9] In recent decades, those patients having undergone heart surgery to live a normal life have been added to the list of high-risk groups.

Another factor contributing to the increasing cases of the endocarditis is the declining attention of the physician, the dentist and the cardiac patient to preventive measures.

Fever is a constant sign (56 to 100 percent), and anorexia, lethargy, arthralgia, muscle pain and loss of weight are among

From the Division of Pediatric Cardiology and Cardiac Surgery Unit, Children`s Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran. Corespondence to: Ali Akbar Zeinaloo, MD, Medical Education Center, Nosrat Ave. , Tohid Sq., Tehran, Iran. Tel: 021-6921185, 021-6921144 Fax: 021-6921228 e-mail: zeinaloo@sina.tums.ac.ir

the commonest signs. The administration of antibiotics before cultures of the blood may reduce cases of positive test results to 50 to 60 percent. Although antibiotics and surgical procedures have proved effective treatment, infant death rates of 20 to 25 percent have been reported[3], and in the patients with a larger invading microbial mass and heart complications, the rate may increase up to 50 or 60 percent. Another reason for the high mortality rate is the deterring nature of some such organisms as staphylococcus and fungi, which may cause numerous large infectious vegetations and increase the risk of emboli, abscess, heart failure and cerebral hemorrhage. A delay in the diagnosis of the disease may be due to the nonspecific symptoms.

With the introduction of echocardiography into the area of medicine, there is much greater hope for a prompt diagnosis of endocarditis.

Transthoracic echo, especially the two dimensional type, is of great sensitivity and accuracy in detecting vegetations, even in the veins (80% sensitivity and 36–85 percent specificity). With the advanced techniques of echocardiography, vegetations as large as 2-3mm are detectable. Negative echo does not necessarily reject the likelihood of the disease, yet the accuracy of echo in detecting vegetations on the healthy valves and heart or simple heart conditions is much greater than congenital heart disease.[3,7] Two-dimensional echo determines mitral valve motion abnormalities due to inflammation (before the development of vegetations) or detects the effects of developed vegetations on the normal function of natural or artificial valves. Thus, Doppler echo contributes for more accurate diagnosis. It can even indicate infectious vegetations in patients with negative blood culture tests.[5, 10] The accuracy of echocardiography in detecting artificial valve endocarditis is considerably low.[10] Although blood culture test is the most accurate paraclinical confirmation and a gold standard index for infective endocarditis, in the reports of the in-patient cases in Iran and some other countries the positive test results range between 27 and 73 percent.[1, 11, 21, 22]

This study aims at making a comparison between the accuracy and sensitivity of blood cultures with the echocardiographic data of the patients hospitalized in a period of five years (1996–2000) for infective endocarditis.

Methods

A clinical research with non-randomised simple sampling, this study studied 40 cases, four of whom were excluded due to early discharge or death before a definite diagnosis was made. Among the 36 patients were 24 boys and 12 girls with the average age of 10.38±3.348 years (range 2-15 years of age), who were admitted between 1996 and 2000. Those suspected of infective endocarditis or cases of prolonged fever were hospitalized. The patients' major complaints, clinical findings, the medication they had received, their tests and echocardiography results were studied. The commonest complaint was fever. So, the patients were divided into two groups: those with an early diagnosis (having fever for less than one week) and those with a delayed diagnosis (having fever longer than one week). Three consecutive blood culture tests were given on admission. Other essential serological and hematological tests were also performed at the onset.

A Vingmed 750 apparatus was used to augment Doppler two-dimensional color echocardiography for each of these patients after their admission. During the course of treatment, they underwent echocardiography so that the vegetations could be controlled and their response to treatment be measured. The judgment was

based on the Duke diagnostic criteria. All echocardiographies were performed by a pediatric cardiologist. The treatment plan, based on positive or negative blood cultures (positive echocardiography), followed the protocol of the American Society of Cardiology (ASC) for 4 to 8 weeks, and the response to treatment was controlled by vegetations follow-up. None of these patients had transesophageal echocardiography. None had artificial valves. Those who did not respond to medication underwent surgery to remove the vegetations (three cases: one fungal and two staphylococcal).
Research ethics were fully observed during the course of study. Statistical analyses were analyzed with *t*–test and Kruskal-Wallis.

Results

The ratio of female-male patients was 1/2 as 24 (66.5%) of the 36 patients were boys and 12 (33.5%) were girls. The average age was 10.38±3.348 years; 61% of the patients were between 10 to 15 years of age and 34% 4-10 years; and only 5% were under four years old. Twenty-four cases (66.6%) had fever more than one week, and in 12 cases the fever lasted less than a week (Table I). All the cases had heart murmur. In 30.5% of the cases, congestive heart failure; in 22%, cerebral complications (cerebral embolism, bleeding or brain abscess); in 19%, emboli to lungs and kidneys; in 2.7% spleen abscess; and in 5.5%, pericarditis were observed. In 15 cases, the blood culture test was reported positive (42%) and in 21 cases negative (58%, Table II).

Table I: The lapse between the fever onset and the treatment given to the endocarditic patients.

Time period	Number	Percent	Mortality
Fever fewer than seven days (early diagnosis)	12	33.3	0
Fever longer than seven days (delayed diagnosis)	24	66.6	6
Total	36	100	6

Table II. Positive/negative blood culture tests and the bacterial species in the endocarditic patients.

Blood culture test	Number	Percent	Response to medical treatment	Mortality
Negative	21	58.3	88.5	3
Staphylococcus aureus	8	22.2	62.5	3
Brucella	3	5.5	100	--
Enterococcus	2	8.5	100	--
Streptococcus viridans	1	2.75	100	--
Fungus (Aspergillus)	1	2.75	medication + surgery	--
Total	36	100	82.5	6

Eighty percent of the patients were CRP positive. In 30 cases (83.4%), vegetations as large as 2-12 mm were observed; and in 6 cases (16.6%), there were no vegetations. They, however, showed cardiac valve damage and insufficiency. The most common site of vegetations was the aortic valve (27.5%). Tables III and IV display the sizes and sites of vegetations, mortality rates and the response to treatment, respectively. Echocardiography specificity was 75% with a sensitivity of 90.5%, while blood culture tests showed a specificity of 60% with a sensitivity of 45% ($P<0.05$ and $P<0.001$). The response to treatment was controlled with echocardiography, and CRP extended as high as 82.5%. In one case of fungal infection (Aspergillus), the aortic valve was replaced, and the culture test performed during the surgical operation turned out positive. In 6 cases which led to death (16.6%), the following observations were in common: Positive CRP, vegetations larger than 5 mm, delayed diagnosis, negative blood culture tests or *Staphylococcus aureus*, vegetations on the aortic valve or left ventricle and congestive heart failure. In this study, 20 cases (56%) had congenital cardiac anomaly, the commonest ones being VSD, TF, and PDA respectively. In addition, two of them had Blalock-Taussig shunts. There were eight (22%) cases of cardiac rheumatism and another eight (22%) cases with no congenital heart disease (one case

of Marfan's syndrome, and one case of mitral valve prolapse).

Table III. Vegetation frequency and size regardless of sites

Vegetation size	No. of cases	Ratio (percent)	Mortality	Positive blood culture tests (person)
larger than 5 mm	25	69.4	6	8
smaller than 5 mm	5	14	0	3
without vegetations	6	16.6	0	4
Total	36	100	6	15

Table IV. Frequency and sites of vegetations in different heart areas

Vegetation areas	Number of cases	Prevalence (percentage	Echocardiography finding(%)	Mortality
Aortic	10	27.5	27.5	3
Mitral valve	8	22.5	22.5	1
Tricuspid valve area & right ventricle	8	22.5	22.5	1
Pulmonary valve and PDA sites	2	5.5	5.5	0
Left ventricle	2	5.5	5.5	1
Without vegetation	6	16.6	--	0
Total	36	100	83.5	6

Discussion

Knowing infective endocarditis as a lethal disease to which congenital heart diseases contribute, the researchers do not expect this disease in infancy; however, in recent years, due to the cardiac surgery at lower ages and increasing use of cardiac catheters, it has been on the increase.[1, 2,4,5,9, 14] The prevalent age, which used to be 8.5 years in the 1960s, has increased to 13 years in the present decade.[1, 2, 14,15] Similarly, the cases which used to be rare in newborns and children under the age of two have increased in the last decade[2, 9], and there has been a prevalence of 3% in the autopsies of newborns.[9] In the present study, the average age was 10.38 with 5% of the cases being under 4 years of age. In Sultanzadeh's report, 22.5% of the patients were under the age of 5[22] . Martin et al., who studied over a period of 35 years, reported that 10% of their 76 endocarditic patients were under one year of age.[15]

In the present study, 56% of the cases were those with some CHD and 22% with RHD. Adnan and Jeffrey reported such cases to be 70% and 10%, respectively where 40% of the CHD cases, especially those of cyanotic type had already undergone heart surgery.[1,2] Sultanzadeh et al. reported 60% of the cases to be those with CHD and 35% with RHD.[22] This study and the one conducted by Rajib et al. show that the role of RHD in endocarditis and in healthy valves and in those with mitral valve prolapse in older age groups is still more prominent in our society.[16] In this study, the patients with ventricular septal defect comprised 38% of the sample, while in the world health reports this is as low as 23%.[4, 14] In Jeffrey's report, the risk of endocarditis with a VSD background is the second highest, with tetralogy of Fallot occupying the first position. Furthermore, in 9.7% of such cases, endocarditis does occur.[2] In Sultanzadeh's report, 65% of the patients already suffered from VSD.[22]

The patients in this study all had fever (100%) on admission, and 66.6% of them had fever longer than 7 days. Martin, Durack and Van Hare had announced fever as the commonest symptom and reported that 90% of their patients had fever on admission.[12, 13, 14] Ashraf et al. reported that in 69.4% of their cases, echocardiography was recommended to detect endocarditis due to prolonged fever.[7] Prognostic reports give the figures 92% and 50% for fever lasting shorter than seven days and delayed diagnosis, respectively.[3,5,12] In this study, all the patients in the first group (100%) and 74% in the second group responded to the

treatment. Altogether, delayed diagnosis and prolonged fever are considered a serious risk factor.

The positive blood culture tests in the world health statistics are reported at 90-98%, which is reduced to 68% for the administration of antibiotics before the culture.[2, 9, 17, 18] In the studies by Jeffrey, Ashraf or Adnan, the negative blood culture tests were reported to be 5-15%.[1,2,7] In Moradmand et al. and Sultanzadeh's reports, the positive blood culture tests were reported as 46.6% and 27.5%, respectively; and in the 10-year study of Ragib from India, the result was only 43.2%.[22, 21, 16] In the present study, the positive blood culture test was 42%, which differs drastically from the world statistics but hardly shows any significant difference from those reported in Iran or India. The low positive blood culture tests in this study may be due to any of the following reasons: Taking antibiotics before the test; the low volume of the blood specimen used for the culture; higher technical error, which could also be due to the lack of special growth medium for microorganisms of slow growth, molds; and anaerobes. Such factors may be a good reason for the reduction of blood culture sensitivity from 98% in other reports to 45% in the present study.

Congestive heart disease is quoted to be 30% in several reports.[1, 2, 3, 8, 21] In this study, it was 30.5% with a death rate of 36.5%. Heart disease has always been a serious risk factor and worsens the prognosis.

In several reports, nervous system complications in endocarditis are reported to be 20%.[1, 2, 8, 9, 19] In the present study, this was found to be 22%, which showed no significant difference. The specificity and sensitivity of transthoracic echocardiographies in the children department were reported to be 36% and 100%, respectively.[2, 5, 6] Van Hare and Kavey quote the echocardiography sensitivity as high as 80% and the specificity 70%.[13,14] Duke considers vegetations in echocardiography as a major criterion which is comparable with blood culture test.[12] Ashraf et al. from Michigan Children`s Hospital quotes this sensitivity as 46.2% in the patients with positive blood culture tests who manifested weak clinical symptoms for endocarditis.[7]

In this study, sensitivity and specificity were found to be 90.5% and 75% respectively, which proves this indicator to be an important means for the early diagnosis. When the blood culture test is negative in more than 50% of the cases, reliance on echocardiography results is a good prognosis for the patient.

Serum C-reactive protein usually increases at the onset, and a normal state is gradually restored during a successful treatment.[2,20] In this study, those with clinical signs who did not respond to treatment had strongly positive CRP, and 3 out of the 6 deceased ones had positive CRPs.

The mortality rate in this study was only 16.6%, and such risk factors as staphylococcal vegetations, congestive heart failure, lasting fever, negative blood culture test and standing positive CRP were present. Unlike Ragib's report of a 43.2% mortality rate[16], the death rate in the present study matches statistics reported elsewhere.

Conclusion

In conclusion, in contrast to the high sensitivity of blood cultures in IE in developed countries, in the developing countries the result of blood culture is not reliable; therefore, echocardiography can play a major role in the early diagnosis of IE and can change the outcome of this potentially serious illness. Officials are requested to pay special attention to the factors resulting in the low sensitivity of blood culture tests.

Acknowledgements

Thanks are due to our colleagues in the Children's Medical Center and Imam's Hospital Children Department for their selfless contributions to this study. In addition, we express our gratitude to Ms. Samadi Khameneh, Ms. Kharazi, Ms. Hamidi, Miss. Pedram and Ms. Sabeti for their conscientious cooperation.

References

1. Adnan S, Dajani, KA: Infective endocarditis. In: Heart Disease in Infants, Children and Adolescents. Fifth and Sixth editions, Baltimore, Williams & Wilkins, 1995: 1541- 1553 & 2000: 1297- 1308.

2. Strake JR: Infective endocarditis. In: Textbook of Pediatric Infectious Diseases. 4th edition, Philadelphia, W. B. Saunders Company, 1998, pp. 315- 335.

3. Bisno Al, Dismakes WE, Durack DT: Antimicrobial treatment of infective endocarditis due to viridans streptococci, enterococci and staphylococci. JAMA, 1989; 26: 1471.

4. Friedman RA, et al: Infective endocarditis in children. In: The Science and Practice of Pediatric Cardiology. 2nd edition, Baltimore, Williams and Wilkins, 1989, pp. 1759- 1775.

5. Rbel RE, Liv F: Review identification of high risks in infective endocarditis and role of echocardiography. European Heart Journal 1995; 16: 588- 602.

6. Saiman L. Prince A, Gersony WM: Pediatric infective endocarditis in the modern era. J Pediatr 1993; 122: 847- 853.

7. Ashraf MA, Simpson PM: The role of Transthoracic echocardiography in the diagnosis of infective endocarditis in children. Arch Pediatr Adolesc Med 1999; 153 (9): 950- 954.

8. Steckelberg JM, Wilson WR: Risk factors for infective endocarditis. Infect Dis Clin North Am 1993; 7: 9- 19.

9. Remington JS: Endocarditis in newborn. In: Infectious Diseases of The Fetus and Newborn Infant. Fifth edition, Philadelphia, W. B. Saunders Company, 2000, pp. 1563- 1566.

10. Gonsalez AM, Vilcher F: Perivalvar abscess associated with endocarditis; clinical features and diagnostic accuracy of two-dimensional echocardiography. Chest 1993; 109: 88- 93

11. Karalis DG, Bansal RC: Transesophageal echocardiographic recognition of subaortic complications in aortic valve endocarditis: clinical and surgical implications. Circulation 1992; 89: 353- 362.

12. Durack DT, Lukes AS, Bright DK: New criteria for diagnosis of infective endocarditis, utilization of specific echocardiographic findings. Am J Med 1994; 96: 200- 209.

13. Kavey REW, Frank DM: Two-dimensional echocardiographic assessment of infective endocarditis in children. Am J Dis Child 1983; 137: 851- 856.

14. Van Hare GF, Ben-Shachar G, Liebman J, et al: Infective endocarditis in infants and children during the past 10 years: a decade of change. Am Heart J, 1984; 107: 1235- 1240.

15. Martin JM, Niches WH, Wald ER: Infective endocarditis: 35-year experience at a children's hospital. Clin Infect Dis 1997; 24(4): 657- 690.

16. Rajib E, Anil C, Jagmohan V, et al: Active endocarditis observed in an Indian hospital from 1981-1997. Am J Cardiol 1992; 70(1): 1453- 80.

17. Swaminathan S, Rither SB: *Enterococcus avium* endocarditis in an infant with tetralogy of Fallot and a Blalock-Taussig shunt. Pediat Cardiol 1999; 20 (3): 227-8.

18. Baorto E, Bayne RM: Culture-negative endocarditis caused by *Bartonella henselae*. J Pediatr 1998; 132(6): 1051- 4.

19. Selton HB, Suty C: Infective endocarditis in patients with negative blood cultures: Analysis of 88 cases from a one-year nationwide survey in France. Clin Infect Dis 1995; 20: 501- 506.

20. MacCarthney AC, Orange GU: Serum C-reactive protein in infective endocarditis. J Clin Pathol 1998; 41: 44 – 48.

21. Moradmand S, Rasoolinejad M: The result of surgery on vegetation in endocarditis (43 cases). The Journal of Faculty of Medicine, Tehran University, 2000, 58 (1): 45-50.

22. Soltanzadeh MH, Ameed MH: Study of infectious endocarditis in children (in Tehran), Proceedings of 11th International Congress of Pediatrics, Sept. 1999; pp. 386-393.