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PROJECT REPORT

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DECLARATION

I , Dr. AJEET ARULKUMAR S J, hereby declare that the project in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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GLOSSARY

IE	Infective endocarditis
PVE	Prosthetic valve endocarditis
NVE	Native valve endocarditis
RHD	Rheumatic heart disease
AVR	Aortic valve replacement
MVR	Mitral valve replacement
DVR	Double valve replacement
NYHA	New York Heart Association
TEE	Transesophageal Echocardiogram
TTE	Transthoracic echocardiogram
CONS	Coagulase Negative staphylococcus
AF	Atrial fibrillation
RVOT	Right ventricular outflow tract
CCF	Congestive cardiac failure
PVT	Prosthetic valve thrombosis
INR	International normalized ratio
PT	Prothrombin time
OAC	Oral anticoagulants

Report I

A STUDY OF THE CLINICAL PROFILE AND CHANGING EPIDEMIOLOGY OF INFECTIVE ENDOCARDITIS IN INDIA- 11 YEAR STUDY

Introduction

Infective endocarditis (IE) is a microbial infection of the endothelial surface of the heart. Even in the modern era of advanced medical, surgical and critical care interventions, it remains a disease that is associated with considerable morbidity and mortality[1,2].Neither the incidence nor the mortality rate of IE has declined significantly, although the pattern of the disease appears to be changing globally[3,4,5]

This is principally because of an increase in degenerative valvular disease in the elderly, placement of prosthetic valves, and exposure to invasive procedures and nosocomial bacteremia[6]. In some series, Staphylococcus aureus has emerged as the most common cause of IE and rates of Streptococcus viridans seem to decrease. [7,8,9].

However the epidemiology, clinical, and microbiologic spectrum of infective endocarditis is significantly different in developing countries compared to the western world. These differences can be attributable to multiple factors including significantly higher incidences of rheumatic heart disease and uncorrected congenital heart disease, excessive and improper use of antibiotics, late clinical presentation, and worse outcomes.[10] IE in India occurs in relatively young patients with underlying rheumatic and congenital heart diseases. The blood culture is negative in high proportion of cases, the diagnosis is often delayed, and the mortality is substantial[11,12,13].

While the literature from developed countries is abundant in data highlighting various aspects of infective endocarditis only a few studies have been published locally. How far the changes in the epidemiology of endocarditis (i.e. changes in the causative organisms, patient profile and outcomes) have occurred in India is not clearly known.

There is a need to collect the data from our community and compare it with the world literature to analyze if the changing epidemiology of IE is also seen in our country

This study was undertaken with these specific objectives in mind.

Review of the literature

Infective endocarditis has been recognized for more than 5 centuries. The earliest description of the vegetative lesion of IE is attributed to Lazarus Riverius (1589–1655)[14].In 1709 Giovanni Lancisi (1654–1720) recorded additional observations in De SubitaneisMortibus during his tenure as Vatican physician to Pope Clement XI,[15]. In 1806, Jean NicolauseCorvisart first used the term vegetations to describe the characteristic macroscopic excrescences seen in IE[16]. Despite these descriptions, it was not until the mid-19th century that a connection was made between vegetative lesions and systemic inflammation (Boullard, 1841)[17]. The Gulstonian lectures by Sir William Osler to the Royal College of Physicians in 1885 created the impetus for the systematic study of IE[18]. As Osler had said "It is of use from time to time to take stock ,so to speak ,of our knowledge of a particular disease, to see exactly where we stand in regard to it , to inquire to what conclusions the accumulated facts seem to point ,and to ascertain in what direction we may look for fruitful investigations in the future". With these words, Osler began the three seminal lectures on endocarditis to the Royal College of Physicians of London in 1885.

Even as late as the early 1900s a fatal outcome was virtually inevitable and resulted from sepsis, emboli and cardiac failure. Attempts at treatment included ligation of an infected PDA, use of anti meningococcal and antipneumococcal sera. The introduction of penicillin in the early 1940s provided the first dramatic breakthrough. It was the turning point for the treatment of infective Endocarditis and in terms of lives saved and prolonged, it outweighs any subsequent innovation.

Epidemiology

The distribution of IE has changed considerably. In the first half of the 20th century, IE was predominantly a complication of rheumatic heart disease. The median age of patients with IE has gradually increased from 30 to 40 years in the preantibiotic era to 47 to 69 years in the late 20th century[19]. Older patients present with more subtle clinical manifestations than the younger ones to the degree that correct diagnosis is missed in two thirds of them early in the course of the disease. It is postulated that their vulnerability is related to a decrease in the activity of their immune system and to the dysfunction of the heart and other organs that marks the aging process. In contrast to the age, the estimated incidence of IE in the Western population has remained unchanged over the past two decades at 1.7 - 6.2 cases per 100,000 patient years, despite the dramatic reduction in the incidence of rheumatic heart disease over the last half-century[20,19.]A review of contemporary case series encompassing a total of 3784 episodes of IE between 1993 and 2003 found a median incidence of 3.6/100 000 population/year with a progressive increase in relation to age2.

Infective endocarditis occurs at least twice as often in men than women3. This ratio increases with age. This sexual distribution generally is not dependent of the specific infecting organism. However, women less than 35 years of age are disproportionately involved in cases of enterococcal endocarditis[21].

Predisposing factors

Almost any structural cardiac lesion of the heart may give rise to IE as long as it can result in formation of a sterile platelet/fibrin thrombus, the indispensable precursor of all types of IE. The specific type of cardiac abnormality underlying a given case of IE is closely associated

with certain characteristics of the patient (age, history of drug abuse .or immunosuppression) and the nature of the infecting organism .Bacteria such as streptococcus viridans, with a low invasive potential, opportunistically infects abnormal heart valves. *S. aureus*has the ability to infect normal valvular structures.

In the case of mitral valve prolapse (MVP) *with significant regurgitation*, the risk of developing IE is increased by 10-100 fold[22], whereas for prosthetic valves and for patients with prior IE the risk for valvular infection may be increased more than 100 fold[23].

In the early years of heart valve replacement, its incidence was as high as 10%[24]. Presently prosthetic valve endocarditis accounts for 10–15% of most series with an overall incidence of 0.1–2.3%/patient year[25]. The greatest risk of infection occurs within two months of implantation (early PVE). In some studies mechanical prosthesis appear to be associated with a higher risk for early PVE[26] and bioprosthesis appear to be associated with higher risk of late PVE[27]. However there were also reports which did not demonstrate any such difference[28]. Early infection peaks two months after surgery and is often caused by S *epidermidis* or *S. aureus*, whereas the spectrum of late infection mirrors that of native valve disease.After the first year, the rate of infection averages about 0.3%.

Although RHD has become an uncommon predisposing factor for IE in the developed world, it remains the largest cardiac risk factor for IE in the developing countries accounting for approximately 50% of cases. The lifetime risk for patients with RHD to develop endocardial infection is 6%[29]. The majority of cases of IE complicating RHD occurs in females (67%) of cases, and involves the mitral valve (85%).

Mitral valve prolapse accounts for up to 30% of cases of native valve endocarditis in the developed countries. It has supplanted RHD as the chief underlying condition for the IE of younger patients4. Mitral valve prolapse is found in approximately 5% of the population. The increased risk of endocarditis is largely confined to patients with prolapse, thickened valve leaflets (>5 mm), and mitral regurgitation murmur, especially among men and patients older than 45 years[30].

Overall, congenital heart disease is the underlying factor in 5% of adult IE. Among congenital heart diseases, the tetrology of Fallot exhibits the greatest incidence of IE. Even when surgically corrected, it remains a significant factor for the development of endocardial infection. Approximately 25% of tetrology patients who undergo and anastomotic correction develop infection at the surgical site. This is attributed to turbulent flow at the site where vessels are joined. Secundum atrial septal defect and pulmonary stenosis pose negligible risks for IE, probably because of the minimal pressure gradient across these lesions[31] The risks of congenital aortic stenosis becoming infected is directly proportional to the pressure gradient across the valve.

An emerging population at risk for IE consists of patients with health care–associated infections. In developed countries IE is attributed to a health care–related exposure in nearly 25% of the patients[32].

Pathogenesis

The hallmark of IE is persistent endocardial or endovascular infection causing continuous bacteremia. There are substantial experimental data to suggest that host endothelial damage is the key predisposing insult, with subsequent platelet and fibrin deposition and creation of a receptive

milieu for bacterial colonization during episodes of transient bacteremia [33]. Platelet-fibrin deposition occurs spontaneously on abnormal valves and at sites of cardiac endothelium injury or inflammation and are called nonbacterial thrombotic endocarditis (NBTE)[34,35].Bacteremia is the event that converts NBTE to IE. Common sources of bacteremia include skin, surgical wounds, the periodontal space, indwelling intravascular catheters, and the urinary and gastrointestinal tracts. Bacteria that have entered the bloodstream must be able to adhere to the damaged endothelium, exposed extracellular matrix, or areas of fibrin deposition[36].

Clinical Manifestations and Complications

The clinical presentation of IE ranges from subtle, chronic fatigue with low-grade fevers, weight loss, and malaise, to an abrupt onset of fulminant acute pulmonary edema brought on by massive acute aortic regurgitation. Four processes contribute to the clinical picture: (a) the infectious process on the valve, including the local intracardiac complications; (b) septic or aseptic embolization to virtually any organ; (c) constant bacteremia, often with metastatic foci of infection; and (d) circulating immune complexes and other immunopathologic factors[37]. The clinical features differ, in part, depending on the primary infection site. Endocarditis simulates a wide variety of disorders, including other infectious diseases, malignancies, and connective tissue diseases. It should be part of the differential diagnosis of any unusual or febrile illness in patients with underlying heart disease. Bacteremia itself can also cause clinical findings such as fever and systemic toxicity. Most patients with IE develop symptoms within 2 weeks of the inciting bacteremia [38]. However in some patients with candidemia causing IE or with intraoperative or perioperative infection of prosthetic valves, the incubation period may be prolonged (5 months or more).

Fever is usually present in the current era, but may be absent (5% of the cases), especially in the setting of CHF or other comorbid condition, immunosuppressive therapy, advanced age, or previous antibiotic therapy[39]. Nonspecific symptoms such as anorexia, weight loss, malaise, fatigue, chills, weakness, nausea, vomiting, and night sweats are not unusual. Audible heart murmurs occur in over 85% of the cases, but may be absent with right-sided or a mural infection. The classic changing murmur and the development of a new regurgitant murmur (usually aortic insufficiency) are uncommon and occur in 5% to 10% and in 3% to 5% of the cases, respectively. When present, these are diagnostically useful signs and usually complicate acute staphylococcal disease. Over 90% of patients who demonstrate a new regurgitant murmur develop CHF.

The classic peripheral manifestations were previously found in up to one half of the cases with IE of prolonged duration; however, the prevalence has significantly decreased in recent years. Clubbing may be present if the disease is of long duration, and may recede with therapy. The complete syndrome of hypertrophic osteoarthropathy is rare. Splinter hemorrhages are linear red to brown streaks in the fingernails or toenails. Petechiae are found after a prolonged course, and usually appear in crops on the conjunctivae, buccal mucosa, palate, and extremities. These lesions are initially red and non blanching, but become brown and barely visible in 2 to 3 days. Petechiae may result from either local vasculitis or emboli. Osler nodes are small, painful, nodular lesions usually found in the pads of fingers or toes and occasionally in the thenar eminence. They are 2 to 15 mm in size and are frequently multiple and evanescent, disappearing in hours to days. Osler nodes are rare in acute cases of IE. They are not specific for IE because they may be seen in systemic lupus erythematosus, marantic endocarditis, hemolytic anemia, and gonococcal infections and in extremities with cannulated radial arteries. Janeway lesions are

hemorrhagic, macular, painless plaques with a predilection for the palms or soles. They persist for several days and are thought to be embolic in origin. They occur with greater frequency in staphylococcal IE. Roth spots are oval, pale, retinal lesions surrounded by hemorrhage and are usually located near the optic disk. They occur in less than 5% of the cases of IE and may also be found in anemia, leukemia, and connective tissue disorders such as systemic lupus erythematosus. Splenomegaly is more common in patients with IE of prolonged duration. Splenic septic emboli are common during IE, but localized signs and symptoms may be absent in approximately 90% of patients with this complication[40].

Major embolic episodes, as a group, are second only to CHF as a complication of IE and occur in at least one third of cases. Embolic events are infrequent after 2 weeks of therapy[41] Splenic artery emboli with infarction may result in left upper quadrant abdominal pain with radiation to the left shoulder, a splenic or pleural rub, or a left pleural effusion. Renal infarctions may be associated with microscopic or gross hematuria, but renal failure, hypertension, and edema are uncommon. Retinal artery emboli are rare (occurring in <2% of cases) and may be manifested by a sudden complete loss of vision. Pulmonary emboli can be a complication of right-sided IE. Coronary artery emboli usually arise from the aortic valve and may cause myocarditis with arrhythmias or myocardial infarction. Major vessel emboli (affecting the femoral, brachial, popliteal, or radial artery) are more frequent in fungal endocarditis.

Neurologic manifestations occur in 20% to 40% of the cases and may dominate the clinical picture, especially in staphylococcal IE. Stroke is the most common neurologic complication of IE, occurring in 9.6% of patients. Patients with mitral valve IE have a greater risk of stroke than patients with aortic valve IE[42].

Laboratory Testing- Blood Cultures

The blood culture is the single most important laboratory test performed in a diagnostic workup for IE. The bacteremia is usually continuous and low-grade (80% of the cases have less than 100 CFU/mL of blood)[43]. In approximately two thirds of the cases, all blood specimens drawn yield positive results on culture[44]. When bacteremia is present, the first two blood cultures yield the etiologic agent more than 90% of the time. The sensitivity of blood cultures for the detection of streptococci is particularly susceptible to prior antibiotic therapy and is also affected by the media employed. The interpretation of positive blood cultures requires consideration of their likelihood of causing IE. The following organisms are considered to be likely causes of IE when isolated from two or more blood cultures: S. aureus, viridans streptococci, enterococci (if acquired in the community and not nosocomial), S. sanguis, and group G streptococci. False-positive results are likely to be present when organisms such as Propionibacteriumspp, Corynebacteriumspp, Bacillus spp, and coagulase-negative staphylococci are recovered from a single blood culture or a minority of blood culture results. However, because these organisms are also capable of causing IE, it is important to determine if there is persistent bacteremia present as opposed to contamination with skin flora.

Other Blood Laboratory Tests

The utility of other blood laboratory tests in the diagnosis of IE is limited. Anemia is nearly always present (70%-90% of cases), especially in subacute cases, and has the characteristics of the anemia of chronic disease, with normochromic, normocytic indices. Thrombocytopenia occurs in 5% to 15% of the cases and leukocytosis is present in 20% to 30% of cases. The differential count is usually normal, but there may be a slight shift to the left. The

erythrocyte sedimentation rate (ESR) is nearly always elevated (90% to 100% of cases), with a mean value of 57 mm/hour found in one large series[44]. The C-reactive protein concentration is virtually always elevated in IE and is a nonspecific finding. Recently, procalcitonin has been shown to be a better diagnostic marker than C-reactive protein in patients with suspected IE[45].

Echocardiography

Since its first use in the diagnosis of IE in 1973, echocardiography has become paramount in the process of evaluating IE[46]. It is crucial in detecting vegetations, echogenic distinct masses from the adjacent valve with independent motion from the valve itself. Vegetations have characteristic findings of a shaggy dense band of irregular echoes in a nonuniform distribution on one or more leaflets. TTE should be performed in all patients in whom IE appears to be a reasonable diagnosis. TTE has variable sensitivity for the detection of vegetations (<50% to >90% positive), indicating that a negative study does not exclude IE. the sensitivity of TTE for detecting vegetations is highest in right-sided IE; (c) false-positive results are extremely rare; (d) only technically adequate studies are of value, a characteristic that heavily depends on the experience of the person performing the examination; and (e) patients with a vegetation • identified by echocardiography are at an increased risk for subsequent systemic emboli, CHF, the need for emergency surgery, and death, especially with aortic valve involvement.

TEE is more sensitive than conventional TTE in the detection of intracardiacvegetations (approximately 95% versus 60%-65%), particularly in the setting of prosthetic valves[47]. The superiority of TEE over TTE is evident in the detection of small vegetations; therefore, TEE should be considered in patients with suspected IE and negative results on TTE. Other recent

investigations have demonstrated TEE to be superior in the diagnosis of valvular perforation and pacemaker IE[48].

Diagnostic Criteria

IE is typically a syndrome diagnosis based on the presence of multiple findings rather than a single definitive test result. Practical and logical case definitions for IE are important for both clinicians and researchers who study this complex disease. Accurate identification and classification of patients of IE are important in defining the natural history, complications, epidemiology, and treatment outcomes.

Pelletier and Petersdorf published the first formal case definition based on their 30-year experience caring for patients with IE in Seattle, Washington. Although this first case definition was specific for the diagnosis of IE, it lacked sufficient sensitivity. Subsequently, von Reyn and colleagues developed the first stratified diagnostic criteria[49]. This was superseded in 1994 by Durack et al. when they published the Duke Criteria for the diagnosis of IE that incorporated additional clinical factors and echocardiographic data[50]. The Duke criteria was revised in 2000 by Li et al. to increase the sensitivity for detection of cases related to *S. aureus* bacteremia, as well as to account for culture-negative IE[51]. These modified Duke criteriahave now been adopted in the latest guidelines from the European Society of Cardiology. Nevertheless, the sensitivity of these criteria is significantly weakened in culture negative patients and in countries where echocardiography, modern serology, and molecular techniques remain poorly resourced.

The modified Duke Criteria for the diagnosis of IE are provided in Table below.

Definition of IE According to the Modified Duke Criteria

Definite IE

Pathologic criteria

Microorganisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen

Pathologic lesions, vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis

Clinical criteria

2 Major criteria

1 Major criterion and 3 minor criteria

5 Minor criteria

Possible IE

1. 1 Major criterion and 1 minor criterion
2. 3 Minor criteria

Rejected

1. Firm alternate diagnosis explaining evidence of IE
2. Resolution of IE syndrome with antibiotic therapy for 4 d
3. No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for 4 d
4. Does not meet criteria for possible IE

Definition of Terms Used in the Modified Duke Criteria for IE Diagnosis

Major criteria

Blood culture findings positive for IE

Typical microorganisms consistent with IE from 2 separate blood cultures. Viridans streptococci, Streptococcus bovis, HACEK group, or Staphylococcus aureus, Community-acquired enterococci, in the absence of a primary focus

Microorganisms consistent with IE from persistently positive blood culture findings, defined as:2 positive culture findings of blood samples drawn 3 or most of 4 separate culture findings of blood (with first and last sample drawn 1 h apart)

Single positive blood culture for Coxiellaburnetii or antiphase I IgG antibody titer 1:800

Evidence of endocardial involvement

Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least possible IE by clinical criteriaor complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absenceof an alternative anatomic explanation, Abscess, New partial dehiscence of prosthetic valve (including new valvular regurgitation; worsening or changing of preexisting murmur not sufficient)

Minor criteria

Predisposition, predisposing heart condition, or intravenous drug use

Fever, temperature 38°C

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages,and Janeway lesions

Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor

Microbiological evidence:

Positive blood culture finding but does not meet a major criterion or serologic evidence of active infection with organismconsistent with IE

Echocardiographic minor criteria eliminated

Treatment

Certain general principles have been accepted that provide the framework for the current recommendations for treatment of IE. A prolonged course of therapy is necessary to eradicate microorganisms growing in valvularvegetations. Bactericidal, rather than bacteriostatic, antibiotics should be chosen to decrease the possibility of treatment failure or relapses. Parenteral antibiotics are recommended over oral drugs in most circumstances because of the importance of sustained antibacterial activity. Likewise, antibiotic combinations can produce a rapid bactericidal effect. This is seen with synergistic combinations such as penicillin plus an aminoglycoside effective against most viridans streptococci or enterococci. Recently, guidelines for outpatient parenteral antibiotic therapy for IE have been published. These guidelines outline a conservative approach (inpatient or daily outpatient follow-up) during the critical phase (first 2 weeks of treatment) when complications are most likely, followed by outpatient parenteral therapy for the continuation phase of antibiotic therapy[52]. Patients selected for outpatient therapy should respond clinically to inpatient therapy and be without evidence of metastatic or intracardiac complications. They also should be hemodynamically stable, compliant, and capable of managing the technical aspects of intravenous therapy. Such patients require careful, regular monitoring and should have prompt access to medical care should complications occur.

The American Heart Association (AHA) in 2005 updated specific treatment guidelines based on the microbiologic etiologic agent1.

Surgical therapy

Valve replacement has become an important adjunct to medical therapy in the management of IE and is now used in at least 25% of the cases. The major indications in the past

have been persistent infection and heart failure in both adults and children. The AHA Committee on IE, working from data reported in the recent literature, has identified the following echocardiographic features in IE as associated with a potential increased need for surgical intervention: (1) persistent vegetations after a major systemic embolic episode, (2) large (>1 cm in diameter) anterior mitral valve vegetations, (3) 1 or more embolic events during first 2 weeks of antimicrobial therapy, (4) increase in vegetation size after 4 weeks of antibiotic therapy, (5) acute aortic or mitral insufficiency with signs of ventricular failure, (6) heart failure unresponsive to medical therapy, (7) valve perforation or rupture, (8) valvular dehiscence, rupture, or fistula, (9) new heart block, and (10) large abscess1[,35].

The hemodynamic status of the patient, not the activity of the infection, is the critical determining factor in the timing of cardiac valve replacement. Surgery should not be delayed because a full course of antibiotic therapy has not been completed or the patient is still bacteremic. Although not systematically studied, most studies suggest that if there is evidence of active IE at the time of valve replacement surgery, antibiotic therapy should be continued postoperatively for 2 to 6 weeks[55].

In contrast to left-sided IE in which CHF is the usual indication for surgical intervention, persistent infection is the indication for surgery in over 70% of patients with right-sided IE. Most of the patients are narcotic addicts, with IE caused by organisms that are difficult to eradicate with antimicrobial therapy alone (e.g., fungi, gram-negative aerobic bacilli). Tricuspid valvulectomy with valvuloplasty is now the procedure of choice for refractory right-sided IE.. However, eventual tricuspid valve replacement is usually required for progressive right heart failure[53,54].

Most patients with PVE (except those with late disease caused by penicillin-sensitive viridans streptococci) require valve replacement. Valve replacement is also necessary in a significant proportion of patients with IE on native valves after a medical cure; aortic involvement is a predictor of the need for surgery.

Medical therapy alone is inadequate and virtually all patients with periannular extension should undergo cardiac surgery. A small number of patients with significant comorbidities can be treated without surgical intervention, especially those without heart block, echocardiographic evidence of progression, or valvular dehiscence or insufficiency. Issues surrounding the surgical options can be complex, especially if there has been neurologic bleeding or significant comorbid disease.

Mortality

The most frequent causes of death in IE, in approximate order, are neurologic and septic complications, CHF, embolic phenomena, rupture of a mycotic aneurysm, complications of cardiac surgery, lack of response to antimicrobial therapy, and PVE[55]. The current in-hospital mortality rate for patients with IE is 10% to 20%1,[56].The one year mortality approaches 40%[57].

Infective-Endocarditis in India

While the estimated incidence of IE in the Western population has remained unchanged over the past two decades such estimates are not available from India. Even assuming the lowest incidence, at least 17,000 episodes of IE must be occurring per year in India[58]. From the published series[10,11,12,13] it is apparent, as may be expected, that IE in India occurs in relatively younger patients with underlying rheumatic and congenital heart diseases. The blood culture is negative in high proportion of cases, the diagnosis is often delayed, and the mortality is

substantial. In comparison with the western series, Indian series have a higher incidence of RHD and lower incidence of MVP. Reported endocarditis in IV drug abusers in Indian series is rare. Surgery for IE was performed less often in Indian studies compared to the West.

Choudhary R et al[12] analyzed the clinical data from 186 patients (133 males and 53 females) with 190 episodes of infective endocarditis (IE) occurring between January 1981 and July 1991 from PGI, Chandigarh. The mean age was much lower (25 ± SD 12 years). Rheumatic heart disease was the most frequent underlying heart lesion accounting for 42%. This was followed by congenital heart disease in 33% and normal valve endocarditis in 9%. Twenty-four patients had either aortic regurgitation (n = 15) or mitral regurgitation (n = 9) of uncertain etiology. Prosthetic valve infection and mitral valve prolapse were present in only 2 patients each. A definite predisposing factor could be identified in only 15% patients. Only 1 patient had history of intravenous drug abuse. Commonest infecting organisms were staphylococci (37 cases) and streptococci (34 cases). Garg et al[11]studied a total 198 episodes of Duke "definite"infective endocarditis (IE) in 192 patients observed over 10 years in SGPGI,Lucknow. [141 males and 51 females, mean age 27.6+1-12.7 years (range 4-68 years)]. Majority of patients (76.5%) were below 40 years of age. Rheumatic heart disease (RHD) was the commonest underlying heart disease (present in 46.9% patients). None of their patients were intravenous drug abusers. Blood cultures were positive in 67.7% (streptococci in 23.2%, staphylococci in 19.7%, gram negative in 13.6%, enterococci in 8.1%, polymicrobial and fungal in 1.5% episodes each).

Aims of the study

1. To study the epidemiology, clinical profile, management and outcome of patients with infective endocarditis treated in our hospital over the last 11 years
2. To analyze if the changing epidemiology of IE noted in the developed countries is also seen in our country.

Methods and Materials

The case records of all patients admitted to the SreeChitraTirunal Institute for Medical Sciences and Technology in Trivandrum with a diagnosis of IE during the period January 2000 to December 2010 were analyzed. Only the patients who met definitive criteria according the modified Duke's criteria for IE were included[50]. Patients who had incomplete records were not taken into the study. All the patients included in the study had at least 3 samples for cultures (aerobic and anaerobic). In case the initials were negative and in PVE additional tests were done for fungal and other fastidious organisms.

The overall cohort was divided into 2 groups – Group 1 included patients admitted betweenJanuary 2000 - December 2005(First 6 years of study) and Group 2 included those admitted between January 2006 - December 2010 (Last 5 years of the study). All baseline parameters, investigations, treatment, complications and outcomes were analyzed between the 2 groups. Follow up of the patient was analyzed from the outpatient case records.

Statistical analysis

All statistical analysis was done using SPSS 14 (SPSS Inc, Chicago, Illinois). Data were expressed as mean ± SD. Comparison between Group 1 and Group 2 as well comparison between NVE and PVE were made using students paired T Test. A p value <0.05 was considered to be statistically significant

Results

A total of 237 patients were included for analysis. Group 1 (patient admitted during the first 6 years of the study) constituted 103 patients (43.5%) and group 2 constituted 134 patients (56.5%).

Group	Admission Date	Duration	Number	Percent
Group 1	January 2000 - December 2005	6 years	103	43.5
Group 2	January 2006 - December 2010	5 years	134	56.5

Table 1

Age

The mean age of the entire cohort was 36.4 (±15.6) years. The mean of those in Group 1 was 33.7 ±15.0 years whereas those in Group 2 were 38.6 ±15.9. The majority of the patients were between 30 to 39 years old in both groups.

AGE	Group 1	Group 2	Entire Cohort
1 to 9	4.9 (5)	3.7 (5)	4.2 (10)
10 to 19	16.5 (17)	8.2 (11)	11.8 (28)
20 to 29	18.4(19)	21.6 (29)	20.3 (48)
30 to 39	27.2 (28)	25.4 (34)	26.2 (62)
40 to 49	17.5 (18)	17.9 (24)	17.7 (42)
50 to 59	12.6 (13)	12.7 (17)	12.7 (30)
>60	2.9 (3)	10.4 (14)	7.2 (17)

Table 2

Sex

Majority of the patients were males (63.2%). It did not differ between the 2 groups (62.1% vs. 64.1%). The overall sex ratio was 1.72: 1.

Predisposing Cardiac conditions

Overall Prosthetic valve was the most common predisposing factor accounting more 35.9% of all cases. However in Group 1 the most common predisposing factor was congenital cardiac lesions accounting for 36.9%. The incidence of degenerative heart diseases (including coronary artery disease related mitral regurgitation) was very low in both the groups (1.9 % and 2.2% respectively). Similarly only 7 patients (3%) had structurally normal hearts.

Predisposing factors	**Group 1**	**Group 2**	**Entire Cohort**
Prosthetic valve	29.1 (30)	41.0 (55)	35.9 (85)
Rheumatic heart disease	27.2 (28)	29.1 (39)	28.3 (67)
Congenital anomalies	36.9 (38)	14.9 (20)	24.5 (58)
Mitral valve prolapse	3.9 (4)	8.2 (11)	6.3 (15)
CAD/degenerative	1.9 (2)	2.2 (3)	2.1 (5)
Normal	1.0 (1)	4.5 (6)	3 (7)

Table 3

Congenital Heart disease

There was significant decrease in the incidence of congenital anomalies in Group 2 when compared to group 1 (14.9% vs. 36.9%). Among the congenital heart disease the most common

lesion was bicuspid aortic valve (43.1%). Other common congenital lesions included TOF (17.2%), VSD (15.9%) and RSOV (3.4%).

Congenital anomaly	Group 1	Group 2	Entire Cohort
Bicuspid valve	36.8 (14)	55 (11)	43.1 (25)
Tetrology of Fallot	21.1 (8)	10 (2)	17.2 (10)
Ventricular septal defect	21.1 (8)	5 (1)	15.5 (9)
Rupture of sinus of Valsalva	5.3 (2)	0 (0)	3.4 (2)
Others	15.8 (6)	30 (6)	20.7 (12)

Table 4

Organism Isolated

Overall 35.4% of the patients had cultures negative IE. The most common organism isolated in the cohort was alpha hemolytic streptococci (17.7%) followed by Enterococci (11.4%). Staphylococcus aureus was isolated in only 10 patients (4.3%) of which 3 had Methicillin resistant Staphylococcus aureus (MRSA). Candida was isolated in 9.7% and CONS in 9.3%. Mixed infections occurred in 5 patients

Organism	Group 1	Group 2	Entire Cohort
Culture Negative	37.9 (39)	33.6 (45)	35.4 (84)
Streptococci (Alpha hemolytic)	19.4 (20)	16.4 (22)	17.7 (42)
Streptococci (Others)	1.0 (1)	0.0 (0)	0.4 (1)

Enterococci	8.7 (9)	13.4 (18)	11.4 (27)
Staph Aureus	2.9 (3)	3.0 (4)	3.0 (7)
CONS	5.8 (6)	11.9 (16)	9.3 (22)
MRSA	0.0 (0)	2.2 (3)	1.3 (3)
Diphtheroid	1.9 (2)	0.7 (1)	1.3 (3)
Pseudomonas	3.9 (4)	5.2 (7)	4.6 (11)
E. Coli	1.0 (1)	0.0 (0)	0.4 (1)
Acinetobacter	2.9 (3)	0.7 (1)	1.7 (4)
Candida	12.6 (13)	7.5 (10)	9.7 (23)
Others	0.0 (0)	3.0 (4)	1.7 (4)
Mixed	1.9 (2)	2.2 (3)	2.1 (5)

Table 5

Presenting Features

Fever was the most common presenting complaint (93.7%) of the cohort. The average duration of fever was 43.9 ± 44.4 days. 40.9% had a fever of at least 1 month duration and a significant minority had fever of more than 3 months (18%).

Fever	**N=237**	**Percent**
No fever	15	6.3
>1 month	97	40.9
> 2 month	45	19

> 3 month	18	7.6

Table 6

Specific lesions

Among those with NVE the most common significant valve lesion was Aortic regurgitation (45.7%) followed by Mitral regurgitation (34. 9%). Both Aortic stenosis and Mitral stenosis were less common (8.1% and 11.3% respectively). In NVE the presence of Aortic stenosis was significantly more among those who died in hospital.

Specific Lesions	**Total (%)**	**Among Mortality (%)**	**P value**
Mitral regurgitation	34.9	43.2	0.87
Aortic regurgitation	45.7	64.9	0.01
Aortic stenosis	8.1	10.8	0.82
Mitral stenosis	11.3	13.5	0.94

Table 7

Prior Infective endocarditis

27 patients (11.4%) had a prior episode of IE and were admitted for recurrence, of which 4 patients had 2 episodes of IE in the past.

Prior IE	**Percentage**	**n=237**
No	88.6	(210)
Once	9.7	(23)

Twice	1.7	(4)

Table 8

Presenting Embolism

A total of 16.9 % of the cohort presented with a major embolic manifestation. This included 27 patients with CVA (11.4%) and 13 with peripheralembolism (5.5%).

Presenting Embolism	**Percentage**	**n=237**
None	83.1	(197)
CVA	11.4	(27)
Peripheral	5.5	(13)

Table 9

Vegetations

Only 21 patients (8.9%) did not have any vegetation. Majority of the vegetations were either 5 to 10 mm (36.3%) or 10 to 20 mm (28.3%) in size. 18 patients had vegetations that were larger than 20 mm.

Vegetations Size	**Percentage**	**n=237**
No Vegetations	8.9	(21)

< 5mm	19.0	(45)
5-10 mm	36.3	(86)
10 -20 mm	28.3	(67)
>20 mm	7.6	(18)

Table 10

Vegetations were equally distributed between native mitral valve, prosthetic mitral valve and native aortic valve (Approximately 21% in each site). Other sites included prosthetic aortic valve, RVOT, tricuspid valve. Both aortic and mitral valve were involved in 17 patients (7.2%).

Vegetations Location	**Percentage**	**n=237**
No Vegetations	8.9	(21)
Mitral valve	21.1	(50)
Aortic valve	21.9	(52)
Aortic + Mitral Valve	7.2	(17)
Mitral prosthesis	21.9	(52)
Aortic prosthesis	7.2	(17)
RVOT/RV	3	(7)
Tricuspid valve	5.1	(12)
Others	3.8	(9)

Table 11

Dyspnea

Majority of the patients were either in NYHA Class II (57%) or Class III (28.7%) during admission. 11 patients had NYHA class IV dyspnea.

Dyspnea	**Percentage**	**n=237**
Class 1	9.7	(23)
Class 2	57	135
Class 3	28.7	(68)
Class 4	4.6	11

Table 12

Atrial Fibrillation

Only 17.3% of the cohort had atrial fibrillation. In 12 patients the AF was documented for the first time during the evaluation for IE and presumed to be new onset AF precipitated by the infection.

Atrial Fibrillation	**Percentage**	**n=237**
No	82.7	(196)
Yes new	5.1	(12)
Yes old	12.2	(29)
Yes Overall	17.3	(41)

Table 13

Complications

74.3 % of the study population had some form of complication during the management for IE. These included CCF in 37.6%, Embolism in 34.6%, Thrombocytopenia in 32.1%, Para valvular Abscess in 24.1%, MODS/Sepsis in 22.8%, Valve Perforation in 8%, Conduction abnormalities in 4.6%, IC Bleed in 9.3%.

Complication	**Percentage**	**n=237**
Valve Perforation	8.0	(19)
Embolism	34.6	(82)
Thrombocytopenia	32.1	(76)
Congestive cardiac failure	37.6	(89)
Para valvular Abscess	24.1	(57)
Sepsis	22.8	(54)
Conduction	4.6	(11)
IC Bleed	9.3	(22)
Overall	74.3	(176)

Table 14

The most common embolism was to the central nervous system and manifested as stroke/Transient ischemic attackin 15.6%. 14 patients had multiple embolic phenomena and a single patient had embolus to the Coronary artery.

Embolism	**Percentage**	**n=237**
Stroke	15.6	(37)
Peripheral	8.4	(20)
Coronary	0.4	(1)
Others	4.2	(10)
Multiple	5.9	(14)
Overall	34.6	(82)

Table 15

Renal Dysfunction

Mean of the highest creatinine during initial hospital stay was 2.1 ± 1.4 mg%, the range being 0.5 mg% to 9.4mg %. More than half (54%) had a creatinine of more than 1.5 mg% and 20.7% had a value of more than 2.5 mg%.

Creatinine	**Percentage**	**n=237**
<1.5 mg%	109	46
>1.5 mg %	128	54
>2.5 mg%	49	20.7

Table 16

Surgical Intervention

Only 29 patients (12.2%) underwent surgical intervention during the initial hospital admission. AVR was the most common surgery performed.

Type Of Surgery	**n=29**	**Percent (n=29)**
AVR	8	27.6%
MVR	1	3.4%
DVR	2	6.9%
Redo AVR	3	10.3%
Redo MVR	3	10.3%
Redo DVR	3	10.3%
Others	9	(31)

MVR = Mitral valve replacement, **AVR =** Aortic valve replacement**, DVR=** Double valve replacement

Table 17

Medical therapy

Remaining 87.2% of the population received in-patient intravenous antibiotics. Antibiotics were prescribed according to the sensitivity report and according to standard recommendation in cases of culture negative endocarditis. Antibiotics were frequently changed in a given patient in view of drug intolerance and changing sensitivity patterns. Overall 57.8% required a change of antibiotics during initial admission. 43.8% required more than 4 antibiotics

and 6.7% required more than 6 antibiotics during the initial hospital stay. Commonly used antibiotics included Ampicillin, Gentamicin, Penicillin and Ceftriaxone.

Antibiotics	**Percentage**	**(n=237)**
Ampicillin	31.2	(74)
Gentamicin	62.0	(147)
Penicillin	46.4	(110)
Ceftriaxone	30.8	(73)
Vancomycin	17.7	(42)
Cloxacillin	16.5	(39)
Ceftazidime	12.7	(30)
Amikacin	18.6	(44)

Table 18

Adverse effects to antibiotics were frequent (62%). The more common ones are mentioned in Table 19

Adverse effects	**Percentage**	**(n=237)**
Overall	62	(147)
Renal	41.4	(98)
Neutropenia	6.3	(15)
Allergy	12.7	(30)
Fever	4.2	(10)

Thrombocytopenia	19.8	(47)
Others	7.2	(17)

Table 19

Mortality

The overall in hospital mortality of the study population was 30%. Patients with PVE had a higher mortality (40%) than those with NVE (24.3%) and those in Group 2 had a lower mortality(27.6%) than those in Group 1 (33%)

Group	**Mortality rate**
Overall (n=237)	30.0
Group 1 (n=103)	33.0
Group 2 (n=134)	27.6
PVE (n=85)	40
NVE (n=152)	24.3

Table 20

The most common cause of death was CCF. Other causes included renal failure, MODS/ Sepsis, Intracranial Hemorrhage, Arrhythmia, Renal Failure and Heart block.

Cause of death	**Percentage**	**Number**
Refractory Heat failure	60.6	(43)

MODS/ Sepsis	46.5	(33)
Intracranial Hemorrhage	15.5	(11)
Arrhythmia	12.7	(9)
Renal Failure	29.6	(21)
Heart block	19.7	(14)

Table 21

Follow up

Of the 166 patients who were discharged alive majority 68.7% were in NYHA Class II. (Table22)

Functional class at discharge	**Percentage**	**(n=166)**
NYHA Class 1	25.3	42
NYHA Class 2	68.7	114
NYHA Class 3	4.8	8
NYHA Class 4	1.2	2

Table 22

Among those discharged alive 19 patients lost to follow up. The average follow up of the 147 patients (Discharged Alive and Follow up available) was 3.3 years.

Follow Up Available	**Percentage**	**Number (n=147)**
Died	11.4	19

<1 year	31.3	52
1-3 years	15.7	26
>3 yeas	41.6	69
> 5 years	28.3	47

Table 23

Comparison between Group 1 and Group 2

The difference between baseline characteristic of Group 1 and Group 2 is shown in Table. As evident Group 2 patients were older, had more PVE, but less congenital anomalies. Late presentation was more common in Group 1.

Baseline characteristic	**Group 1**	**Group 2**	**P value**
Age<21	21.4 (22)	11.9 (16)	0.050
Age>60	2.9 (3)	10.4 (14)	0.026
Male gender	62.1 (64)	64.2 (86)	0.746
Prosthetic valve	29.1 (30)	41.0 (55)	0.058
Rheumatic heart disease	27.2 (28)	29.1 (39)	0.745
Mitral valve prolapse	3.9 (4)	8.2 (11)	0.175
Congenital anomaly	36.9 (38)	14.9 (20)	<0.01

CAD/ Degenerative	2.9 (3)	1.5 (2)	0.451
Prior IE	11.7 (12)	11.2 (15)	0.913
Presenting Embolism	20.4 (21)	14.2 (19)	0.206
Fever >30 days	51.5 (53)	32.8 (44)	<0.01
Fever >60 days	25.2 (26)	14.2 (19)	0.031
NYHA Class 3/4	36.9 (38)	30.6 (41)	0.308
Vegetation	91.3 (94)	91.0 (122)	0.953

Table 24

The microbiological profile between the 2 groups show that although there was a trend toward more staphylococcal infections in Group 2, it was not statistically significant (p=0.06)

Microorganism	**Group 1**	**Group 2**	**p value**
Culture Negative	37.9 (39)	33.6 (45)	0.495
StreptococciSpp	20.4 (21)	16.4 (22)	0.432
Staphylococci Spp	8.7 (9)	17.2 (23)	0.06
Enterococci	8.7 (9)	13.4 (18)	0.259
Gram Negative Spp	9.7 (10)	8.2 (11)	0.687
Candida	12.6 (13)	7.5 (10)	0.184
Others	1.9 (2)	3.7 (5)	0.45

Table 25

There was no significant difference between management and outcomes between the 2 groups. Mortality was 33% in group 1 and reduced to 27.6% in Group 2.

Management /Outcomes	**Group 1**	**Group 2**	**p value**
Surgery	13.6(14)	11.2(15)	0.577
Complication	70.9(73)	76.9(103)	0.296
Valve Perforation	8.7(9)	7.5(10)	0.720
Embolism	39.8(41)	30.6(41)	0.140
Thrombocytopenia	34.0(35)	30.6(41)	0.580
CCF	40.8(42)	35.1(47)	0.369
Para valvularAbscess	26.2(27)	22.4(30)	0.495
MODS/ Sepsis	24.3(25)	21.6(29)	0.632
Creatinine>2.5 mg %	19.4(20)	21.6(29)	0.675
Conduction Abnormalities	3.9(4)	5.2(7)	0.627
Intracranial Bleed	10.7(11)	8.2(11)	0.516
Mortality	33.0(34)	27.6(37)	0.369

Table 26

Prosthetic valve endocarditis

Important Baseline characteristics of Prosthetic valve endocarditis are mentioned in table 27. More than 50% of the patients had a mitral prosthesis and rheumatic heart disease was most common underlying pathology

Baseline characteristics	Percent (n=85)
Age (Average)	40.1 ±12.9 years
Age<21	5.9(5)
Age>60	5.9(5)
Male	58.8(50)
Post MVR	50.6(43)
Post AVR	24.7(21)
Post DVR	24.7(21)
Prior IE	17.6(15)
Rheumatic heart disease	76.5(65)
Congenital anomaly	14.1(12)

Table 27

Comparison betweenPVE and NVE.

Compared to NVE, patients with PVE were older (40.1±12.9yearsvs. 34.4±16.7 years). Patients with PVE presented earlier – only 30.6% had fever more than 1 month compared to 46.7% in the NVE group. Likewise significant dyspnea was less common. TEE was done more commonly (90.6% vs. 57.2%) and revealed smaller vegetation. Complications were however more common with PVE especially CCF, Para valvular abscess, Renal failure, and conduction abnormalities (All $p < 0.05$). Mortality in those with PVE (40%) was significantly more than those with NVE (24.3%)

Parameter	PVE(%)	Number	NVE	Number	P value
Age (Average in years)	40.1 ±12.9 years		34.4 ± 16.7 years		
Male	58.8	(50)	65.8	(100)	0.286
Embolism	18.8	(16)	15.8	(24)	0.550
Fever >30 days	30.6	(26)	46.7	(71)	0.015
Dyspnea- 3/4	24.7	(21)	38.2	(58)	0.035
Vegetation> 10 mm	21.2	(18)	44.1	(67)	<0.01
TEE Done	90.6	(77)	57.2	(87)	<0.01
Surgery	11.8	(10)	12.5	(19)	0.868
Complication	81.2	(69)	70.4	(107)	0.069
Embolism	36.5	(31)	33.6	(51)	0.651
Refractory heart failure	44.7	38	33.6	51	0.089
Para valvularAbscess	42.4	(36)	13.8	(21)	<0.01
Sepsis	24.7	(21)	21.7	(33)	0.598
S. Creatinine>2.5 mg%	27.1	(23)	17.1	(26)	0.070
Conduction	8.2	(7)	2.6	(4)	0.049
IC Bleed	10.6	(9)	8.6	(13)	0.605
Death	40.0	(34)	24.3	(37)	0.012

Table 28

The Microbiological spectra in PVE were also significantly different in the PVE group. An organism could be isolated almost twice as often in PVE when compared to NVE. PVE was characterized by a lower culture of Streptococcus spp(9.4%)and Enterococcus Spp(8.2%) and

higher culture of Staphylococcus Spp (20%),Gram Negative Bacteria (14.1%) and higher candida(20%)

Organism	**PVE**	**Number**	**NVE**	**Number**	**P value**
Culture Negative	22.4	(19)	42.8	(65)	0.002
Streptococcus Spp	9.4	(8)	23.0	(35)	0.009
Staphylococcus Spp	20.0	(17)	9.9	(15)	0.029
Enterococcus Spp	8.2	(7)	13.2	(20)	0.253
Gram Negative Bacteria	14.1	(12)	5.9	(9)	0.033
Candida	20.0	(17)	3.9	(6)	0.000

Table 29

Discussion

This is the one of largest studies on infective endocarditis from the Indian subcontinent consisting of 237 definite cases of infective endocarditis. Other large studies from the subcontinent included 198 patients studied byGarg et al in 1992 to 2001[11], 190 patients studied by Choudhary et al from 1981 to 1991[12], and 188 patients studied from 1988 to 2001 in Pakistan by Tariq, M. et al[59]. These studies were conducted almost a decade earlier than our study (2000 to 2010). Among the international studies a large multicentric prospective cohort study of 2781 adults with definite IE who were admitted to 58 hospitals in 25 countries between 2000 and 2005 was conducted by David R Murdoch et al[32]

Table 30 shows a comparison between this study and other large studies.

Other Studies	**Garg et al.**	**Choudhary et al**	**Murdoch et al**	**Present Study**
Duration	1992-2001	1981-1991	2000 -2005	2000- 2010
Place	SGPGI India	PGI Chandigarh India	Multicentric 25 countries	SCTIMST Kerala, India
Number of patients	198	190	2781	237
Age (years)	27.6±12.7	25±1.2	57.9	36.4 ±15.6
PVE	10.4%	1.0%	21%	35.8%
RHD	46.9%	42.0%	3.30%	28.3%
Congenital	28.6%	33.0%	12%	24.5%
Culture Negative	32.3%	53.0%	9.80%	35.4%
Streptococcus Spp	23.3%	17.9%	29%	18.1%
Staphylococcus Spp	19.7%	19.5%	31.20%	13.5%

IV drug abuse	0.0%	0.5%	9.80%	0.0%
Surgery performed	23.0%	1 %	48.20%	12.2%
Mortality	21.0%	25.0%	17.70%	29.9%

Table 30

The mean age of the patients in our study was 36.4 ± 15.6 years. When compared to the Indian series the patients in our series are older by almost a decade– 27.6±12.7 years in the Garg series[11] and 25±1.2 years in the Choudhary series[12]. However they are similar in age to the study by Tariq et al[59] (34 years + 21.2 years). In contrast the average age in the contemporary series from the west have all shown a much older cohort. The mean age was 57.9 years in the large prospective study by the Murdoch et al[32]. IE in India occurs in relatively young patients' because of underlying rheumatic and congenital heart diseases. When compared to the 2 subsets of our study the age had significantly increased from group 1 (January 2000- December 2005) to group 2 (January 2006- December 2010). The sex ratio in the study was 1.72: 1, which was similar to both studies from the India or developed countries[3,4,11,12,19].

The predominant predisposing factor of our study was prosthetic valve accounting for 35.9% of all cases. All prior studies from India have shown a much lower incidence of PVE. It was only 1% in the 1980s[12] and rose to 10% in 1990s[11]. This is probably multifactorial. The surgical treatment for valvular heart disease is now increasing in India; hence the susceptible population with prosthetic valves is also increasing. Secondly not many centers do large number valve replacement surgeries in this part of the country. Hence there may be an element of referral

bias -patients with PVE may be more specifically reviewing back to this centre for follow up compared to those with NVE who might be treated elsewhere.

Rheumatic heart disease was present in 28.3% of the cohort. Other studies from India have shown RHD to be the most common predisposing factor (more than 40% of the cases)[11,12].However in the contemporary series from developed countries RHD accounted for less than 10% of all IE[2,4,5]. RHD is still widely prevalent in India and continues to be a large public health problem. Congenital anomalies accounted for 24.5 % of all cases in our study. However in Group 1 it was the most common predisposing factor (36.9%). In Group 2 the incidence had decreased to 14.9%. The absolute numbers had also decreased from 38 to 20 patients. This may be due to early surgical correction and improved post operative surgical care over the years. The incidence of degenerative heart diseases was very low in both the groups (1.9 % and 2.2% respectively). Similarly only 7 patients (3%) had structurally normal hearts. In the large prospective series by Murdoch, degenerative valve disease accounted for almost 70% of the NVE[32].

In our study an organism could be isolated in 64.6% of the entire group. Indian studies have always shown lower culture positivity ranging from 21- 66%[10,11,12,13].This is most likely due to prior antibiotic use. Several studies from developed countries have shown a shift in the microbiologic characteristics with staphylococcus aureus now being the most common cause of IE in much of the developed world[60,61,62.]

However the most common isolate in our study was still alpha hemolytic Streptococci (17.7%). It was followed byEnterococcus (11.4%), Candida (9.7%) and CONS in 9.3%.Staphylococcus aureus(including MRSA) was isolated in only 10 patients (4.3%). However

in the entire group the incidence of staphylococcus group(including CONS)had increased from 8.7% in Group 1 to 17.2 % in Group 2. Hence in group 2 the incidence of staphylococcus species was more than of streptococci (16.4%). This was mainly driven by an increase in incidence of CONS in PVE patients (from 5.8% in group 1 to 11.9% in group 2). The incidence of Staphylococcus aureus however remained low in both groups (2.9% and 5.2% respectively).In previously published Indian series the incidence of staphylococcal group was 13 to 19%. Increase in S. aureus in the West is due in part to the global presence of risk factors for S aureus–associated IE (intravenous drug use, health care contact, and invasive procedures). Long term domiciliary care treatment is still uncommon in our country and intravenous drug abuse is very rare. Not a single patient in this study had a history of intravenous drug abuse. Prior Indian studies have also confirmed the low incidence of IV drug abuse related IE[11,12].This could explain why the incidence of S. Aureus is low in our study. The higher frequency of candida and CONS is explained by the high incidence of PVE.

Relevant in the presenting feature of IE was the duration of fever in patients. Contemporary studies from developed countries show that most patients (77.0%) are admitted within 1 month of the initial signs of illness2[,32]. In this study only 60% had fever for less than 1 month. 18 patients had fever of more than 3 months duration before admission. This is due to several factors. Many patients in India take medicines (including antibiotics) directly from the pharmacy for fever and seek medical help only when fever persists. This skews the blood culture results and further delays diagnosis. Specialist centers with transesophageal echocardiography are also not as widespread as in developed countries.

When compared to NVE patients with PVE surprisingly had a shorter duration of fever (32.6 ± 32.4 days vs. 50.1±48.8 days),less dyspnea (Class III/IV dyspnea- 24.7 % in PVEvs.

38.2 % in NVE; p= 0.035) and smaller vegetations (p <0.01). This early presentation can be explained because of the greater awareness of IE among those with prosthetic valve, higher suspicion by the physicians and more frequent follow up and specialist referral in this group. Also TEE was performed more commonly (90.6% vs. 57.2%) in those with PVE. However this early presentation did not translate into improved outcomes, as the complications were higher in PVE. Refractory heart failure, paravalvular abscess, renal failure, and conduction abnormalities were all more common in those with PVE (p <0.05 for all). This ultimately led to a higher mortality in those with PVE (40%) than those with NVE (24.3%) [p=0.012].

Several studies have proved that surgery is potentially lifesaving[63] and is required in at least 25% to 50% of cases during acute infection[1,3,32.] Surgical intervention was performed in only 12.2% of patients in our study. No significant difference was noted between surgical intervention in PVE (11.8%) and NVE (12.5%) [p=0.868]. In the 1980 -1990 series Choudhary et al surgery was performed in 1 % of the group whereas in the study by Garg et al. surgery was performed in 23.0%. However in studies from developed countries surgery was performed in 25-40%. Again in the multicentric prospective study of 2781 adults in 25 predominantly developed countries surgery was performed in 48.2%[32]. The major reasons are the lack of availability and affordability of cardiac surgery in developing counties.

Complications rates seen in this study (74.3 % overall) included CCF in 37.6%, embolism in 34.6%, thrombocytopenia in 32.1%, paravalvular Abscess in 24.1%, MODS/Sepsis in 22.8%, valve perforation in 8%, Conduction abnormalities in 4.6%, IC Bleed in 9.3%.These are largely similar to that reported in several large series on infective endocarditis[64,65].

Mortality rates for large series of patients with NVE treated in developed countries since 1980 range from 13% to 20%[32,66]. Outcome for patients with PVE, as contrasted with NVE, has been less favorable. Even with surgical intervention, mortality rates for PVE have ranged from 14% to 36%[67,68]. The overall mortality in our study population was 30%. Patients with PVE had a significantly higher mortality (40%) than those with NVE (24.3%) (p=0.012). Although the mortality in Group 2 (27.6%) was lower than that in Group 1(33%) it was not significant (p=0.369). Mortality in patients from India varied significantly from 42% in 1970 by Kabde et al[69], 20.3% in 1981 by Agarwal et al[70] , 21% by Garg et al. in 1992-2001[11] to 25% in Choudhary et al 1981-1991[12]. Mortality has been high in developing countries due to late presentation, lesser surgical intervention and poorer resources. Surprisingly the mortality in our study (30%) was higher to both the Garg and Choudhary series. This may be explained by the fact that our Institute is a tertiary care referral center representing a skewed population of complicated cases and has a much higher incidence of PVE.

Limitations

- This was a retrospective study with data collected from case records.
- The ‘true’ microbiological spectra of our cases could not be determined because many of the patients received prior antibiotic therapy prior to diagnosis leading to higher culture negative infective endocarditis.
- Serology and polymerase chain reaction testing for fastidious organisms such as Brucella, Bartonella, Coxiella, and other rare causes of endocarditis were not performed in all patients
- Finally, being a tertiary care referral center our data may not truly represent endocarditis in the general community and may be skewed towards a sicker patient population.

CONCLUSION

- The epidemiology of IE in our country is also changing but in way very different from that seen in developed countries.
- While IE in India continues to affect relatively younger patients, the mean age has now increased by almost a decade to 36.4 years compared to older studies.
- Rheumatic heart disease and congenital heart disease continue to be important predisposing factors unlike the west.
- IE complicating degenerative heart diseases, mitral valve prolapse and intravenous drug abuse isvery rare in India
- Almost one third of our patients are culture negative most likely due to prior antibiotic therapy and limitation of microbiological tests.
- Changes in spectrum of organisms causing bacterial endocarditis reported by data from developed countries do not also exist in our community.
- Alpha hemolytic streptococci continue to be the most common isolate. In contrast S. Aureus was isolated in only 4.3 % of the cases. However the incidence of staphylococcus group and fungal IE has increased in the last 5 years predominately because of a higher incidence of CONS and fungal IE in the patients with PVE.
- Surgical intervention is carried out in only a small minority of the patients (Less than 15%)
- Short term hospital mortality rate in those with infective endocarditis is 30% and has not changed appreciably over the 11 year study period.Those with PVE had a significantly higher mortality than those with NVE although they presented earlier.

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Report II

A STUDY ON THE CLINICAL PROFILE OF PROSTHETIC VALVE THROMBOSIS IN A TERTIARY CARE HOSPITAL OVER 25 YEARS

Introduction

More than 100 million people are affected by valvular heart disease worldwide[1]. The estimated number of prosthetic heart valve replacements done every year worldwide is 300,000 and the total number of replacements isprojected to be 850 000 per year by 2050[2]. Prosthetic valve thrombosis (PVT) is anuncommon but serious complication of valve replacement, often encountered with mechanical prostheses.[3]Multiple causes ranging from inadequate anticoagulation to pannus formation have been identified[4]. The clinical presentation is variable and ranges from insidious dyspnea to cardiac arrest. The untreated mortality associated with this condition warrants rapid diagnostic evaluation. Cinefluoroscopy (for mechanical valves) and transesophageal echocardiography represent the main diagnostic procedures.

The different therapeutic modalities available for PVT (heparin treatment, fibrinolysis, surgery) are largely influenced by the presence of valvular obstruction, by valve location (left- or right-sided), and by clinical status. Although surgical treatment is usually preferred in cases of obstructive PVT, optimal treatment still remains controversial.

Although there are a number of studies regarding the clinical case presentation, treatment options and management of patients with prosthetic valve thrombosis there are no studies from South India.

Review of the Literature

Prosthetic valve thrombosis (PVT) is defined as any thrombus, in the absence of infection, attached to or near an operated valve, occluding part of the blood flow or interfering with valvular function[5]. In a study by Hammermeiste et al the 11-year probability of PVT was 0.01% to 0.02% for patients with either type of valve in the mitral or aortic position[6]. Non-obstructive PVT is a relatively frequent finding in the postoperative period[7]. In a large study, it was shown that 21% of cases of prosthetic valve thrombosis occurred in thefirst month after heart valve replacement[8].Two major types of prosthetic heart valves exist: mechanical and bioprosthetic. Mechanical prosthetic heart valves are more durable but also more thrombogenic than bioprosthetic valves. The advantages of bioprosthetic over mechanical valves are that they provide more physiological hemodynamics and do not need long-term anticoagulation. Thrombosis of a bioprosthetic valve is a rare occurrence when compared to mechanical prostheses[9].

PATHOLOGYPHYSIOLOGY

The pathogenesis of intracardiac thrombus formation with or without the implantation of prosthetic material is complex.[10]According to Virchow's triad, factors predisposing to thrombus formation can be divided into endothelial, hemodynamic and haemostatic factors[11]. Endothelial factors represent biocompatibility of the prosthesis itself and interaction between the prosthesis and the suture zone. Tissue cicatrisation and endothelialisation characteristically require a few weeks to be complete. Hemodynamic factors include both hemodynamic characteristics of the prosthesis, as well as overall cardiac hemodynamic status. Although the profile of new generation mechanical bileaflet valves is largely superior to that of earlier generation prostheses (and thus associated with a lower occurrence of thromboembolic complications), localised regions of turbulent flow can still develop and lead

to stasis and thrombus formation. In addition, the location of the prosthesis plays an important role in thrombogenicity. Obstruction of a tricuspid mechanical prosthesis is 20 times more frequent than left-sided PVT[12]. Similarly for hemodynamic reasons, mitral PVT is 2–3 times more frequent than thrombosis of an aortic prosthesis. Interruption of oral anticoagulant treatment for anticipated non-cardiac surgery[13] and pregnancy[14] represent high risk situations for patients with prosthetic valves.

Clinical Presentation of Prosthetic valve thrombosis

The clinical presentation of PVT is highly variable, often depending on the presence or absence of obstruction. Severe obstructive PVT is typically associated with overt heart failure, whereas non-obstructive PVT is often an incidental finding or can present as an embolic episode. Partial obstruction (for example, obstruction of one leaflet) can manifest itself with abnormal dyspnoea or systemic embolism and rarely fever. In the presence of fever, diagnostic blood cultures should be performed to rule out infectious endocarditis. When PVT is first suspected, a careful physical examination should be performed, with particular attention being paid to muffling or disappearance of prosthetic sounds and the appearance of a new regurgitant or obstructive murmur. It is prudent to instruct patients to pay attention to the quality of their valve clicks and report any change. The disappearance of formerly audible prosthetic valve clicks in a patient with valve prosthesis may be the first clue leading to the diagnosis of stuck valve. However, auscultation maybe unreliable if the obstruction is partial, as with a bileaflet valve or in the presence of another normally functioning prosthesis[15]. Previous adequacy of anticoagulation should be defined.

Contrary to the florid appearance of left-sided heart failure in patients with stuck left-sided valves, signs of right heart failure associated with stuck tricuspid valve may be quite

subtle. Bedside physical examination can be diagnostic or at least raise clues to the diagnosis of stuck valve. Useful findings include muffled or absent valve clicks, alterations in jugular venous pulse (tall systolic waves, slow Y descent), and diastolic murmur augmented during the inspiratory phase[16,17].

Diagnosis of prosthetic valve thrombosis

Establishing the diagnosis can be quite difficult, and some series have reported the diagnosis as being made at postmortem examination in up to 50% of cases[18]. Fluoroscopy in the proper projection may be considered for initial screening of mechanical bileaflet valve motion. Cinefluoroscopy assesses restriction of leaflet motion and opening and closing angles,but is limitedto radiopaque disc or bileaflet valves[19]. Also, this technique will not be helpful in identifying non-obstructive PVT or differentiating pannus from thrombus. Hence, additional diagnostic procedures are often necessary[20]

Transesophageal Doppler echocardiography (TEE) has been reported to be the diagnostic technique of choice for selecting and monitoring candidates for safe and efficacious thrombolytic treatment of mitral PVT[21,22,23].TEE may visualize restricted prosthetic valve leaflet motion.In most cases, an echogenic mass is observed on the prosthetic valve surface at the site of the stenosis[24]. It images thrombus on the atrial but rarely on ventricularsurface of mitral prosthetic valves[35].Differentiation from pannus may be possible with TEE. In prosthetic thrombosis, the movement of the disc is always abnormal, whereas in 40% of patients with obstruction due to pannus the mobility of the disc is normal. The visualization of an echogenic mass is almost universal in thrombosis, but only appears in 70% of obstructions caused by pannus. The echogenic characteristics of the mass are more important: it has an appearance of soft tissue (thrombotic material) in thrombosis, while it appears as hard tissue (fibrotic material) in the case of pannus. A thrombotic mass is usually

larger than pannus. In mitral prosthetic thrombosis the mass frequently extends into the atrial endocardial surface, a feature rarely seen in obstruction caused by pannus. The international PRO-TEE[25] registry identified a previous cerebrovascular event and a thrombus size .0.8 cm2 as the major risk factors for complications of lytic treatment

Measurement of Doppler echocardiographic hemodynamicvariables is essential for assessment of obstructive PVT bymeasurement of gradients and valve area. Aflow-dependent Doppler gradient is insufficient for diagnosis,unless the gradient is very high.For mitral prostheses, a mean gradient 8 mm Hg and an effective area <1.3 cm2 is indicative of PVT. For aortic prostheses, criteria for PVT are a mean gradient 45 mm Hg. These findings must be interpreted with certain caution since all prostheses are intrinsically stenotic, often demonstrating a considerable gradient despite normal function. A Doppler gradient maysignificantly overestimate the hemodynamic situation in theaortic position, particularly with small prostheses and with St.Jude valves[26]. To avoid misinterpretation of patient or prosthesishemodynamic variables, most investigators now recommendbaseline postoperative and pre discharge Doppler measurements[27].

Management

The New York Heart Association (NYHA) has classified dyspnea in functional classes I to IV. Those presenting with NYHA class I or II are nonobstructive forms, usually incidental echocardiographic findings in patients with evidence of thromboembolic stroke or peripheral arterial embolism. Those classified in NYHA functional classes III or IV correspond to obstructive forms with obvious hemodynamic repercussions, sometimes including cardiogenic shock, often associated with cerebral or peripheral embolism[28,29]. The benefit and risk of the many factors of the individual patient must be balanced against the expertise and experience at each center to arrive at a decision for thrombolysis or operation.

Valve types (all may thrombose) or the suspected duration of valve thrombosis does not influence the choice of, or indications for, treatment[30,31].

Surgical treatment

Surgical intervention has been the traditionaltreatment for PVT. Replacement of the prosthesis is the most widely used approach but often simple removal of the thrombus (thrombectomy), in a normally functioning prosthesis is also possible[32]. The replacement of an obstructed valve offers the advantage that structural dysfunction of the prosthesis or fibrous tissuein-growth can be reliably identified. Mechanical de-clotting was introduced in 1973 by Björkand Henze to reduce the total cardiopulmonary bypass time[33]. Hospital mortality with this approach, however, is not significantly lower than that with conventional valve replacement and the incidence of recurrent thrombosis appears to be higher[34]. Overall, reported operative mortalityrates range between 0% and 69%, largely depending on clinical functional class[35,36].Recurrent episodes of PVT should probably be treated surgically[37].

Fibrinolytic therapy

Fibrinolytic therapy is an alternative to surgical treatment[38,39,40].It is considered the treatment of choice for tricuspid PVT[41,42]. However, because of the high risk of cerebral thromboembolism duringthrombolysis for left-sided PVT, its use is reserved for high risksurgical candidates[43,44,45] .In a review of 200 reported cases of left-sided PHVT treated with thrombolysis, Lengyel et al. reported an initial success rate of 82% and a mortality of 6%. In this study the incidence of complications was 12% for any kind of thromboembolism, 5% for cerebrovascular accidents and 5% for haemorrhage[22].A meta-analysis including 515 cases reported an initial success rate of 84%, a mortality of 5%, bleeding complications in 3% and systemic embolism in 9%[46]. A thrombus area of less than 0.8 cm2 was associated with a low risk of complications from thrombolysis, regardless of the NYHA Functional Class

Group[25]. Improvement in hemodynamics may not occur until 24 to 48 hours after commencement of fibrinolytic drug infusions[22].

Indications for Thrombolysis

Thrombolytic treatment of left-sided PVT has been accepted for critically ill patients in functional class III or IV in whom surgical intervention carries high risk or in patients with contraindication to operation[47]. The reasoning against thrombolysis in patients in functional class I or II is based on the relatively low surgical mortality in this group as opposed to the embolic risk of 12% to 17% caused by thrombolysis[48,49] .Patients with mitral or aortic PVT documented by TEE with Doppler flow obstruction and functional class III or IV symptoms should be treated with fibrinolysis if the surgical risk is high and there is no contraindication. Surgical therapy is an alternative for patients in functional class III or IV not at high surgical risk. In addition, obstruction due to endocarditis with abscess formation and usually very large thrombi with obstruction or mobile masses are indications for operation. If longer periods of subtherapeutic oral anticoagulation can clearly be identified, thrombus formation is more likely to be the sole reason for valve obstruction and thrombolysis should be considered first line therapy[50]

Contraindications to Thrombolysis

Absolute contraindications include active internal bleeding, history of hemorrhagic stroke, recent cranial trauma or neoplasm, blood pressure >200/120 mm Hg. Relative contraindications include recent (within 10 days) gastrointestinal bleeding, recent (within 10 days) puncture of noncompressible vessels, recent (within 2 mo) non hemorrhagic stroke ,Infective endocarditis, uncontrolled severe hypertension, large thrombus in left atrium or on prosthesis, recent (within 2 wk) major operation or trauma, known bleeding diathesis. Although pregnancy is generally considered a relative contraindication, when there is great

danger to the patient, the advantages and disadvantages of fibrinolysis should be considered. There have been at least four reported cases in which fibrinolysis was successfully used during pregnancy, with no harm to the fetus[51]. Left-sided intracardiac thrombus has generally been considered a relative contraindication to thrombolysis. Patients with large thrombotic material attached to the prosthetic valve or in the left atrium are probably at increased risk of major embolism and stroke when treated with thrombolytic therapy[52]. Although a few reports of successful thrombolysis of left atrial (LA) clots have been published[53], a large LA thrombus should be ruled out by TEE before the start of thrombolytic treatment.

Conservative management

Nonobstructive PVT in patients presenting in functional class I or II may be treated with intravenous heparin by continuous infusion for 48 h. If patients remain hemodynamically stable and thrombus is not dissolved (not unusual), intravenous infusion can be converted to subcutaneous injection (overlap infusion for 2 h after injection, average dose from five studies is 17,000 U subcutaneously every 12 h)[54]. With complete or nearly complete resolution of thrombus, the need for operation may be avoided.The experience with heparin treatment of nonobstructive PVT has been reported in one study with a 63% success rate and 5% of fatal stroke[55]. An alternative approach used successfully by some investigators in functional class I or II patients with a large amount of thrombus takes advantage of the different antithrombotic actions of heparin and warfarin and their enhancement of longer term endogenous lysis. The use of subcutaneous heparin (every 12 h, aPTT 55 to 80 s) plus warfarin (INR 2.5 to 3.5) for 3 months usually dissolves moderate amounts of residual thrombosis

Management of complications

In case of Cerebral embolism thrombolytic treatment should be discontinued if neurologic symptoms of stroke develop. A CT scan of the brain should be urgently obtained to rule out hemorrhage. If the stroke is non-hemorrhagic, anticoagulant treatment may be administered. If the second CT scan performed 36 to 48 h after the stroke still rules out brain hemorrhage, operation may beperformed 72 h after the stroke[22]. The efficacy of early thrombolytic treatment of acute stroke for improvement at 3 months has been established for patients not receiving anticoagulant therapy, with no bleeding and no or only minor early signs of infarction on the initial CT scan. They are treated with short-term (1 h) rt-PA therapy within 3 h of onset[56]. In case of peripheral embolism thrombolytic and then antithrombotic therapy should be continued, irrespective of the hemodynamic results, to dissolve the peripheral embolus. Severe peripheral embolism with persistent symptoms despite lysis should be treated by embolectomy.

Recurrent PVT

A major disadvantage of thrombolytic therapy is the relatively high incidence of recurrent thrombosis during follow-up. According to a meta-analysis by D. Hering et al., recurrent thrombosis was observed in 20% after thrombolysis as compared with 3% after valve re-replacement ($P < 0{\cdot}01$) and 8% after thrombectomy[57]

Indian Experience

Accurate data on the incidence of left-sided PVT in developing countries are lacking. In a retrospective analysis from a large tertiary-care hospital in India, left-sided PVT occurred in 6.1% of patients within 6 months of valve replacement[58], a rate far higher than that seen in developed countries. Similarly in a recent study from All India Institute of Medical Sciences,

New Delhi in 2007, the incidence of Prosthetic valve thrombosis almost 10%[59]. The incidence of peripheral embolism is consistently higher (18%–22%) in western series compared to Indian ones (2.8% in a series by Reddy et al.,[60] 12% in the series by Vasan et al.,[61]). In a recent study by Karthikeyan et al.,[59]from the All India Institute of Medical Sciencesthe success rate with fibrinolytic therapy was low overall (59%) and very low in patients in New York Heart Association functional class III/IV (24%).The relatively low success rate occurred despite the inclusion of a high proportion of patients in NYHA functional class I/II (69%). 72% of the patients had inadequate anticoagulation at presentation.

Thus thrombolysis and reoperation (valvular re-replacement or de-clotting) are widely accepted options for treatment of prosthetic valvular thrombosis. Immediate success rate, major adverse events and peri-procedural mortality are comparable. Reoperation constitutes a more definitive treatment, with complete and thorough removal of thrombotic material. Thrombolysis serves to avoid a second operation, although this may still be necessary if thrombolysis fails. Treatment with intravenous heparin for 48 h, followed by a combination of subcutaneous heparin and oral anticoagulation on an outpatient basis, should be restricted to patients with non-obstructive thrombosis and a stable clinical condition.

Aims & Objective:

- To study the clinical presentation, diagnostic features,treatment strategies, complications and outcome of Prosthetic valve thrombosis treated in SCTIMST during January 1985 through May 2011 (over a period of 25 years).
- To compare the data with literature from both developed countries and India and analyze the differences seen in our population

Materials and Methods

All patients who presented with prosthetic valve thrombosis from June 1985 through May 2011 were included in the study.Data were collected on a retrospective basis from the clinical records of these patients. Preoperative clinical data, initial valve procedure, diagnosticfeatures of valve thrombosis, and management before, during,and after the treatment, complications and follow up were recorded.

All patients underwent routine blood investigations, electrocardiogram, transthoracic echocardiogram. TEE and fluoroscopy were done based on the clinical indication. The decision to either thrombolyse or undergo surgery was made after analysing the risks and merits in each case. It was based on a consensus agreement involving the cardiologist, cardiac surgeon and the patients' relatives.

The hospital follows a system of income classification for every patient which is analysed using several parameters principally income and education.

Category	**Income**
Category A	Below poverty line
Category B1	Low income group
Category B	Mid Income group
Category C	High income group
Category D	Affluent/ Insured patients

Statistical analysis

All statistical analysis was done using SPSS 14 (SPSS Inc, Chicago, Illinois). Data were expressed as mean ± SD. Comparison between Group 1 and Group 2 as well comparison between NVE and PVE were made using students paired T Test. A p value <0.05 was considered to be statistically significant

RESULTS

A total of 54 patients with prosthetic valve thrombosis were identified and analyzed.

Age:

Age ranged from 16 years to 65 years. The mean age was 35.5 (±11.0) years. Majority were in the age group of 30 to 49 years. (Refer Table 1)

Age	Number	Percentage
0 to 19	5	9.3
20-29	5	9.3
30-39	24	44.4
40-49	12	22.2
50-59	7	13.0
60-65	1	1.9

Table 1

Sex

Of the total 54 patients majority (61.1%) were women with a sex ratio of 0.6: 1.

Type of Prosthetic valve

Mitral prosthesis was most commonly involved (66.7%) followed by Aortic (18.5%) and Tricuspid prosthesis (5.6 %). 5 patients had had double valve replacement. However in these patients either mitral or aortic prosthesis was only involved (Refer Table 2)

PV Position	Number	Percentage
Mitral	36	66.7

Aortic	10	18.5
Tricuspid	3	5.6
DVR - Mitral	3	5.6
DVR - Aortic	2	3.7

Table 2

The most common type of prosthesis was the single leaflet type.

PV type	**Number**	**Percentage**
Caged Ball	7	13.0
Bileaflet	14	25.9
Single leaflet	33	61.1

Table 3

The Predisposing factor leading to valve replacement was rheumatic heart disease in majority (70.4%) of the patients. (Refer Table 4)

Type	**Number**	**Percentage**
Rheumatic heart disease	38	70.4
Bicuspid Aortic valve	5	9.3
Mitral valve prolapse	1	1.9
Endomyocardial fibrosis	5	9.3
Ebstein's anomaly	2	3.7

Table 4

Recurrent Prosthetic valve thrombosis

20.4 % (11 patients) had a prior history of Prosthetic valve thrombosis. Two patients had 2 prior episodes. (Refer Table 5)

Prior thrombosis	Number	Percentage
Never	43	79.6
Once	9	16.7
Twice	2	3.7

Table 5

Oral Anticoagulant Usage

Warfarin was the most commonly prescribed anticoagulant, followed by Phenindione and Acenocoumarol. In 4 patients were anticoagulants interrupted by the cardiologist in view of temporary medical contraindication (Pregnancy/ Intracranial bleed). (Refer Table 6)

Anticoagulant	Number	Percentage
Acenocoumarol	9	16.6
Warfarin	24	44.4
Phenindione	16	29.6
None	4	7.4

Table 6

However 32.1% had discontinued oral anticoagulants. More patients in economically underprivileged groups had discontinued when compared to those who were a better socioeconomic group. (Refer Table 7)

Discontinued OAC	Number	Percentage

Below poverty line	10 (of 24)	41.7
Low income group	5 (of 21)	23.8
Mid Income group	2 (of 5)	40.0
High income group	0 (of 4)	0.0
Affluent/Insured	17 (of 54)	32.1

Table 7

37.7% had stopped monitoring prothrombin time. As seen in the tables, below all the patients in Category D were monitoring PT/INR compared to only 50% in those belonging to Category A. (Refer Table 8)

Regular PT Monitoring	**Number**	**Percentage**
Below Poverty Line	12 (of 24)	50.0
Low income group	15 (of 21)	71.4
Mid Income Group	2 (of 5)	40.0
High Income group	4 (of 4)	100.0
Affluent/Insured	33 (of 54)	62.3

Table 8

The mean INR of the cohort was 1.8 (SD ± 1.0). Majority of the patients (68.5%) had an INR <2. Aspirin (in addition to oral anticoagulants) was prescribed in only 7.4% of the cohort. Even among the 11 patients with prior prosthetic valve thrombosis the use of aspirin was only 36.4 %. (Refer Table 9/10)

INR	**Number**	**Percentage**
<2	37	68.5
2 to 3	13	24.1

>3	4	7.4

Table 9

Aspirin	**Number**	**Percentage**
Yes	4	7.4
No	50	92.6
Among prior Thrombosis (n=11)	4	36.4

Table 10

Clinical Presentation

Almost all patients presented with symptoms. However in 2 patients the diagnosis was made on routine follow up Echocardiogram. (Refer Table 11)

Symptoms	**Number**	**Percentage**
Yes	52	96.3
No	2	3.7

Table 11

The duration of the symptoms was short with 74 % presenting with less than one week history. 11 patients (20.4%) had been symptomatic for more than 2 weeks.

Duration	**Percentage**	**Number**
1 day	18.5	10
2 days	11.1	6
3-7 days	44.4	24
8-14 days	5.6	3

>14 days	20.4	11

Table 12

At admission only 7 patients were in Class I or Class II. Others had at least Class III dyspnea and a quarter of the patients were actually in pulmonary edema. (Refer Table 13)

NYHA Class	**Percentage**	**Number**
Class 1	1.9	1
Class 2	11.1	6
Class 3	44.4	24
Class 4	16.7	9
Pulmonary Edema	25.9	14

Table 13

24.1% (13 patients) had AF at presentation. Of this in 4 patients the AF was documented to be new. (Refer Table 14)

Atrial fibrillation	**Percentage**	**Number**
No	75.9	41
Yes New	7.4	4
Yes old	16.7	9

Table 14

Comorbidities

A significant minority of patients had associated comorbidities. 5 patients in the cohort had were either pregnant or were in the post partum state. 2 patients had deranged kidney function and 2 had a recent stroke. (Refer Table 15)

Comorbidity	Number	Percentage
Pregnancy	3	5.6
Recent CVA	2	3.7
Post Partum	2	3.7
S. creatinine	2	3.7
None	44	81.5

Table 15

Diagnosis

All patients in the cohort underwent 2D and Doppler echocardiography. Majority of them also underwent fluoroscopy to confirm the diagnosis (81.5%). Of note Chitra Heart Valve Prosthesis has radiolucent leaflets- hence fluoroscopy was not contributory in this group. (Refer Table 16)

Fluoroscopy	Number	Percentage
Used	44	81.5
Not used	10	18.5

Table 16

Transesophageal echocardiogram was used in 37% of the cohort, principally in those in whom the diagnosis was not clear by fluoroscopy. (Refer Table 17)

TEE	Number	Percentage
Used	20	37
Not used	34	63

Table 17

Treatment

In all cases the decision to thrombolyse, operate or continue conservative management was taken by a combined decision by the team of senior cardiologists and cardiac surgeons taking into consideration the hemodynamic stability and functional class of each patient. The treatment options were also discussed with the patients and their relatives. (A few patients in the cohort had refused for repeat surgery)

Thrombolysis was the initial treatment in 28 patients (52.8%); Surgery in 21 (39.6%) and only heparin in 5(9.2%). 3 patients underwent surgery after failed thrombolysis. (Refer Table 18)

Treatment	**Number**	**Percentage**
Thrombolysis Alone	25	47.2
Heparin Alone	5	9.4
SurgeryAlone	21	39.6
Thrombolysis & Surgery	3	5.7

Table 18

Streptokinase was the most commonly used agent to thrombolyse(82.1%). The remaining 17.9% were treated with Urokinase. (Refer Table 19)

Lytic Agent	**Number**	**%**
Streptokinase	23	82.1
Urokinase	5	17.9

Table 19

Both Streptokinase and urokinase were given as bolus followed by infusion. The duration of infusion was based on the clinical response and complications. The most commonly used regimen in this study was a 5 lakh unit bolus of streptokinase, followed by 1 lakh unit per hour infusion till clinical response. Infusion was stopped if there was no response to treatment after a variable period of 24 to 36 hours. The mean total dose in the streptokinase group was 20.92 lakh units. (Refer Table 20)

Thrombolytic Agent	**Urokinase**	**Streptokinase**
Bolus dose (x 10^5 units)	1.6 ± 0.2	4.7 ± 2.4
Infusion Dose (x 10^5units)	1.6 ± 0.2	0.97 ± 0.1
Hours (hours)	16.2 ± 7.8	16.7 ± 11.3
Total Infusion (x 10^5units)	26.9	20.92

Table 20

Outcome to thrombolysis

Of the 28 patients who underwent thrombolysis complete response as defined as *"decrease in Prosthetic valve gradient to baseline and normal PV movement in the absence of complications, need for surgery or death"* was achieved in only 57.1% of the patients. Mortality in the thrombolysis cohort was 10.7%. Embolism occurred in 21.4% of the group and major bleed in 7.1%. 3 patients had to undergo redo valve surgery after failure to establish normal PV movement. (Refer Table 21)

OUTCOMES	**Urokinase**	**Streptokinase**	**Overall (N=28)**
Success	3 (60%)	13 (56.5%)	16(57.1%)
Embolism	1(20%)	5 (21.7%)	6(21.4%)
Bleed	0(0%)	2 (8.7%)	2(7.1%)

Died	2(40%)	1 (4.3%)	3(10.7%)

Table 21

Surgery

A total of 24 patients (45.3%) underwent surgery in this study. This includes 21 patients who underwent surgery as the first treatment option and the 3 patients with failed thrombolysis. Among these 19 patients (79.2%) had a redo valve replacement and the remaining 5 patients underwent thrombectomy(20.8%). Among the surgical group there were 6 major embolic manifestations (25%), 2 major bleeds (8.3%) and 1 death (4.2%). (Refer Table 22)

Outcome	**Number**	**Percentage**
Bleed	2	8.3
Embolism	6	25.0
Died	1	4.2

Table 22

Complications

The most common complication in the cohort was embolism followed by bleeding manifestations. Most of the embolic manifestation resulted in a CVA. One patient developed massive anterior wall MI after a successful reduction of gradients. (Refer Table 23/24)

Embolism	**Number**	**Percentage**
None	43	79.6
CVA	7	13.0

Peripheral	3	5.6
Coronary	1	1.9

Table 23

Bleed	**Number**	**Percentage**
None	46	85.2
Intracranial	2	3.7
GI Bleed	1	1.9
Minor	5	9.3

Table 24

Mortality

Overall the mortality in the entire cohort was 11.1%. Only 1 patient died in the surgical group. 2 of the five patients who underwent conservative management died.

Died	**Number**	**Percentage**
Overall (54)	6	11.1
Thrombolysis (28)*	3	10.7
Surgery (24) *	1	4.2
Conservative(5)	2	40%

Table 25 (*3 patients underwent thrombolysis & surgery)

Follow up and Long-term Survival

3 patients lost to follow up. The average follow up of those discharged alive was 7.04 years (range 0 days to 22.7 years).

Discussion

Thrombosis is a serious complication of prosthetic heart valve replacement and incurs high mortality. Early diagnosis and appropriate management is paramount in reducing mortality. In this study we report here the single-center experience of 54 instances of PHVT treated over a 25-year period fromJune 1985 through May 2011.

In our study the mean age was 35.5 (±11.0) years and majority of the patients (66.6%) were between 30 and 49 years of age. PVT was more common in women with 61.1% in this study. While many studies have shown that women are more predisposed to PVT[8,35]in most studies from India men were more frequently involved[4,29].

In our study mitral prosthesis was most commonly involved (66.7%) followed by Aortic (18.5%) and Tricuspid prosthesis (5.6 %). In the study byGupta et al, 87.3% of the PVT episodes occurred in the mitral position[62]. Similarly several studies have confirmed that mitral PVT is 2–3 times more frequent than thrombosis of an aortic prosthesis[8,17,19].

11 patients (20.4 %) in our study had a prior history of prosthetic valve thrombosis. 2 patients had 2 prior PVT episodes. Studies have shown an episode of PVT identifies a high-risk group of patients prone to recurrences[63,64].In our study 2 of the 3 patients who had failed thrombolysis had recurrent PVT. Balasundaram et al[37] have shown thrombolysis for a recurrent episode of PVT is not as efficacious as it is for the first episode and causes more adverse events. They have concluded that recurrent episodes of PVT should probably be treated surgically.

In our study overall 32.1% had discontinued oral anticoagulants and 37.7% had stopped monitoring prothrombin time. In a recent study by Karthikeyan et al., 72% (79/110) of the patients had inadequate anticoagulation at presentation[59]. Our study shows that this was

stronglyassociatedto the patients' socioeconomic status. Among those in the lowest socioeconomic group [category A] 41.7% had discontinued medications and half did not monitor their INRs, whereas no patient in the higher socioeconomic group [category D] had discontinued their drugs and all monitored their INRs regularly. This highlights the problems of valve replacement in a developing country such as India where majority of the population is economically underprivileged.

Most of the patients with PVT in our study presented within one week of symptom onset. One fourth of the patients actually presented in acute pulmonary edema. At admission only 7 patients were in Class I or Class II. In the study by Karthikeyan et al[59] a high proportion of patients were in NYHA functional class I/II (69%). Thus our cohorts of patients were relatively more ill. PVT is an acute medical emergency. If patients cannot reach a treatment centre in time the mortality can be substantial.

Almost a quarter of the cohort (24.1%) had atrial fibrillation (AF) at presentation. Of this in 4 patients the AF was documented to be new. Some studies have suggested that AF is associated with recurrent PVT. In our study also 4 patients had AF among the 11 with recurrent PVT (36.3%).

5 patients in the cohort had were either pregnant or were in the post partum state. The hypercoagulable state during pregnancy increases the incidence of valve thrombosis. The incidence of thromboembolism during pregnancy is estimated from 7 to 23% and about half of these cases are PVT[65]. In a study by Tong et al[25] in pregnant women with PVT, lytic therapy was associated with 85% success rate, overall complication rate of 18%, and mortality rate of 5.6%.

Diagnosis of PVT was made in majority with underwent fluoroscopy (81.5%). Of note patients with Chitra heart valve prosthesis had radiolucent leaflets- hence fluoroscopy

was not contributory in this group[66].Transesophageal echocardiogram was used in only in 37% of the cohort, principally in those in whom the diagnosis was not clear by fluoroscopy.

Of the 54 patients in the cohort, thrombolytic treatment was given in 28 patients (52.8%); Surgery in 21 (39.6%) and only heparin in 5(9.2%). 3 patients underwent surgery after failed thrombolysis.

Streptokinase was the most commonly used agent to thrombolyse (82.1%). The remaining 17.9% were treated with Urokinase. Successful thrombolysis as satisfying the strict criteria of *"decrease in Prosthetic valve gradient to baseline**with**normal PV movement **and**in the absence of complications, need for surgery or death"* was achieved in only 57.1% of the patients. Embolism occurred in 21.4% of the group and major bleed in 7.1%. 3 patients had to undergo redo valve surgery after failure to establish normal PV movement. Mortality in the thrombolysis cohort was 10.7%.However in a review of 200 patients, Lengyel et al.[67]reported an initial success rate of 82% and a mortality of 6%. Similarly consensus statements on the treatment of PVT and recent systematic reviews, suggest that the success rate with fibrinolytic therapy is at least 80%[68,69,70]. The lower response of our study are however similar to that by a recent study by Karthikeyan et al. from the All India Institute of Medical Sciences[59]. They reported the overall response rate of only 59% (70 of 119) with fibrinolytic therapy. The lower success rate in our may be because of the higher proportion of patients in NYHA class III and Class IV dyspnea.

Embolism occurred in 21.4% of those who were thrombolysed and among 25% among those who underwent surgery. Other studies have shown an embolic risk of 12% to 17% caused by thrombolysis[48,49]. Again the higher incidence in our study may be due to higher patients with NYHA class III/IV which is indicative of large thrombus burden.

45.3% (24 patients) underwent surgery in this study. Among these 79.2% (19 patients) had a redo valve replacement and the remaining 20.8% (5 patients) underwent thrombectomy. Among the surgical group there were 6 major embolic manifestations (25%), 2 major bleeds (8.3%) and 1 death (4.2%). Studies have shown that the mortality rate of surgery vary with functional class from 4% to those in NYHA class I to as high as 69%in patients with NYHA class IV symptoms[34,71].

In our study 2 of the 5 patients who underwent conservative strategy died (Mortality rate 40%). This reinforces the dictum that conservative strategy must be used only in asymptomatic patients with non obstructive PVT with an overall minor clot burden.

In summary, the patients in our study presented in a more advanced state with one quarter presenting with acute pulmonary edema. This resulted in a largely unfavourable outcome from thrombolysis. The results from surgery were however more encouraging.

Limitations

- It was a retrospective single centre study with data collected from case records.
- Transesophageal echocardiogram was used in only 37% of the cohort. Had TEE been performed in all cases of Suspected PVT, then the incidence of non obstructed PVT may have been higher.
- The number of patients in the study was small

Conclusions

1. Patients with PVT usually present with acute onset of severe dyspnea with large majority in Class III/IV dyspnea or frank pulmonary edema.
2. TEE is under utilized in the evaluation of patients with suspected PVT. Hence patients with nonobstructive PVT are likely to be under represented.
3. Thrombolysis is associated with a much lower response rate (57%) compared to data from western countries (~80%)
4. Surgical intervention has a much lower mortality (~5%) than thrombolysis (~10%) but comparable embolic rate (25%).
5. Heparin alone should not be used in the treatment of patients with obstructive PVT because of its higher mortality rate.
6. Most cases of PVT are due to inadequate anticoagulation and poor monitoringmainly in patients belonging to the lower socioeconomic group.

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