Original Article

INFECTIVE ENDARTERITIS IN PATENT DUCTUS ARTERIOSUS

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ABSTRACT

***Background**: Once a serious complication, infective endocarditis has become extremely uncommon in patients with persistent ductus arteriosus. Early diagnosis and closure irrespective of the size of duct, has essentially made it an unheard entity in the West. The only indication of closure of a small PDA being prevention of infective endarteritis, however, is often debated.*

***Objective:** To report our experience of infective endarteritis on PDA in an ongoing study on infective endocarditis, evaluating its incidence, clinical pattern and to determine the outcome.*

***Setting:** A tertiary referral center for paediatric and adult cardiology.*

***Patients and Methods**: In an ongoing study of infective endarteritis in children admitted to a single center, all children with infective endocarditis of PDA from April 1997 to March 2003 were analyzed. The diagnosis was based on Duke's criteria, which proposed two major and six minor criteria. Minor criteria were expanded to include raised acute phase reactants and presence of newly diagnosed or increasing splenomegaly. PDA was classified as small, moderate and large by standard methods.*

***Results:** Of 2908 hospital admissions, PDA was the major underlying lesion in 368(12.6%) patients. Of all hospital admissions, 96 fulfilled the diagnostic criteria for infective endocarditis. Of these, PDA was the underlying lesion in 14 patients (14.6%). The mean age was 8.9 ± 4 years with only one patient under one year of age. Seven patients had small PDA while five had moderate and two had large. Blood cultures were positive in 6(43%) patients while vegetations on echocardiography were present in 12(86%) patients. The duration of treatment was 4-6 weeks in all but one patient, who needed 10 weeks antibiotics.Thirteen patients had subsequent uneventful closure, 8 by occlusion devices (Coils, Amplatzer device and Rashkind's umbrella) and 5 by surgical ligation without cardiopulmonary bypass.*

***Conclusions:** The proportion of infective endarteritis on PDA is small in a tertiary paediatric cardiology referral center. Majority were small PDA's and an early closure may have prevented this serious complication. All patent arterial ducts merit closure irrespective of the size.*

***Key Words:** Patent ductus arteriosus, Infective endocarditis, Children.*

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INTRODUCTION

One major factor which influences the decision as to whether or not to close an arterial duct is the cumulative risk and associated morbidity and mortality of endarteritis in the untreated duct[1-3]. Since the closure of patent arterial duct became technically feasible, there has been a trend to always close the isolated duct in childhood. This policy of duct closure has modified the natural history of disease and the risk of endocarditis is now difficult to assess.

The occurrence of endarteritis is now so rare that there has been an argument that there is no need to close a small, haemodynamically insignificant duct for the sole purpose of preventing infective endocarditis[4,5].

It is, however, tempting to say that this reduction has partly or wholly occurred as a result of the policy of universal closure in childhood[6]. The overall incidence of endarteritis has decreased in the West in the last three decades. An improvement in dental hygiene, antibiotic prophylaxis and an early diagnosis are important contributing factors towards this reduction. In the developing world, where diagnosis is often missed at early age, antibiotic prophylaxis for potential septic procedures is not a routine and late referral is common, it remains an important cause of morbidity and mortality in all age groups[7,8]. We have analyzed the incidence, clinical pat-

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tern, and outcome of endarteritis on PDA over a six-year period in an ongoing study on infective endocarditis at our center. This may answer some of these important questions on the issue of duct closure at an early age irrespective of its size.

MATERIALS AND METHODS

All patients under the age of 16 years admitted to a single tertiary referral center were included in this prospective study on infective endocarditis.

The study period was between April 1997 and March 2003.

For diagnosis of infective endocarditis, we used the Dukes[9] criteria proposed by Durack et al in 1994 with inclusion of two additional minor criteria. As proposed in Dukes criteria, three diagnostic categories were defined by combining these criteria. In addition to the criteria proposed by Durack, we included two more minor criteria: newly diagnosed or increasing splenomegaly and raised acute phase reactants. Presence of splenomegaly is a non-specific finding and may be present in upto 5% of normal children in a country like Pakistan where malaria is endemic. It was taken as minor criteria only if it was not known to be palpable before the episode or an increase in size was clearly documented clinically and on abdominal ultrasound. A rise in acute phase reactants like erythrocyte sedimentation rate or C-reactive protein is again non-specific. ESR may be falsely low in the presence of heart failure. Absence of a rise in ESR or CRP has a negative predictive value in diagnosis of infective endocarditis. Raised ESR and CRP were taken as minor criteria in the absence of an extra cardiac infection.

All patients had three to five sets of blood cultures. In patients receiving antibiotics before arrival, antibiotics were stopped for at least forty-eight hours before they were re-cultured. In very sick patients presenting acutely, blood cultures were taken at admission and antibiotics started. Bloods tests were also done routinely for hemoglobin estimation with hematocrit and peripheral blood picture, total and differential white cell count, acute phase reactants like ESR and CRP, electrolytes, renal function tests like urea and creatinine, Rheumatoid factor and liver functions. Serology was done where necessary. Urine tests for microscopic hematuria and chest X-rays were done routinely.

Three operators experienced in paediatric echocardiography performed echocardiography. Vegetations were defined as typical if a mobile echo-dense mass was found attached to valves or their supporting structures or in path of turbulent jet of blood passing through PDA. The number and nature of antibiotics used, their dosage and duration were carefully recorded. The outcome of medical treatment and any complications were also recorded.

PDA was classified as small, moderate and large by standard methods. In 5 patients the family knew the diagnosis of PDA while another 3 were known to have a heart murmur although exact diagnosis was not made. Endarteritis was the first presentation in the remaining 6 patients, as diagnosis had not been made in the past.

On completion of antibiotic course, all children underwent PDA closure with timing and mode of closure dependent upon hospital resources and the presence or absence of vegetation at the end of antibiotic treatment and choice of the family.

RESULTS

A total of 2908 children under 16 years of age were admitted in the paediatric cardiology unit over the six-year study period. These also included patients admitted electively for surgery. Of these all, 96 fulfilled the diagnostic criteria for infective endocarditis giving an incidence of 33 patients per thousand hospital admissions. Of 2908 hospital admissions, PDA was the major underlying lesion in 368(12.6%) patients. Of all patients with infective endocarditis, PDA was the underlying lesion in 14(14.6%) patients. There were 4 boys and 10 girls. The age at diagnosis ranged from 9 months to 16 years (mean 8.9 years ± 4 years). Of these 14 patients treated for endarteritis on PDA, 12 had clinically definite diagnosis while 2 had possible infective endocarditis.

Table 1 Clinical findings -Symptoms

Clinical Symptom	Number	Percentage
Fever	14	100
Cough	6	43
Arthralgia	2	14
Chest Pain	2	14
Abdominal Pain	2	14
Shortness of breath	6	43
Poor appetite/malaise	8	57

Table 2 Clinical findings –Signs

Sign	Number	Percentage
Heart Murmur	14	100
Marked Pallor	7	50
Heart Failure	3	21
Splenomegally	6	40
Clubbing	1	7
Embolism	1	7
Pericarditis	0	0
Petichae	1	7

As regards symptoms, fever was the presenting symptom in all patients (Table 1). The mean duration of fever prior to diagnosis was 13 days suggesting late presentation. Heart murmur was present in all patients. Pallor was another common sign and so was splenomegaly >40% patients. Other classical signs like clubbing, Osler's nodes, Janeways lesions, Roth spots and splinter hemorrhages were extremely rare (Table 2).

Cross-sectional echocardiography was able to detect vegetations in 12(85.7%) patients. The pulmonary artery side of the PDA was the site of vegetation in all patients (Figure 1). Vegetations were present on both PDA and pulmonary valve in 2 patients; one of them had moderate pulmonary stenosis as well. Blood cultures were positive in just under 50% of the patients. Streptococcus viridans was the chief isolate in 3 of 6 (50%) culture positive patients, followed by Staphylococcus aureus in 2(33%) patients (Table 3).

Table 3 Organism Cultured and Outcome

Organism	Number (%)	Cured	LAMA
Streptococcus viridans	3(21)	3	0
Staphylococcus Aureus	2(14)	2	0
Pseudomonas Aeurginosa	1(7)	1	0
Culture Negative	8(57)	7	1
Total	14	13	1

LAMA:Left against medical advice

On routine investigations, anemia was seen in 8 (57%) patients while 3 had haemoglobin below 7gm/dl. An elevated erythrocyte sedimentation rate above 20 or C-reactive protein above 6 was present in all patients. Haematuria on laboratory testing was present in 3(21%) patients. Blood urea and serum creatinine was raised in 1(7%) patient. Rheumatoid factor was also raised in only 1(7%) patient.

On admission antibiotics were started considering the duration of infection and available epidemiological clues. Combination of benzyl penicillin and gentamycin was started in essentially all patients after blood cultures were taken. Where organism was suspected or proved to be staphylococcus aureus, oral Rifampicin was added. Vancomycin was added in two patients. No patient needed anti-fungal treatment. The decision to change antibiotics or add a new one was based on reports following culture or failure to respond to earlier combination. The duration of treatment was between 4 and 6 weeks in 13 patients. In 1 patient it was prolonged to 10 weeks. In another patient, the duration of treatment was less than 4 weeks as family left against medical advice after three weeks of treatment. Emergency surgery was not required in any of the patients.

Complications included phlebitis of peripheral veins, which was the most common complication in initial patients (5 patients). All patients had a central line in subsequent period. Heart failure was the presenting feature in 2 patients and one child had pulmonary embolism in the course of treatment. There were no deaths. One patient left against medical advice once improved clinically but his final outcome is not known (table 4).

Table 4 Complications

Complication	Number	Percentage
Heart failure	3	21
Pulmonary embolism	1	7
Renal Impairment	1	7
Phlebitis	5	35

Of 14 patients, 13 had duct closed subsequently. Eight patients underwent occlusion in cath lab while five underwent surgery without cardiopulmonary bypass (Table 5).

Table 5 Definitive treatment following antibiotic course

Pt. #	Age	Size of PDA	Antibiotic Course	Definitive Treatment
1.	16 Yrs	< 2mm	6 weeks	Coil Occlusion (previous surgical ligation)
2.	2 Yrs	2.5mm	5 weeks	Rashkind's Umbrella device
3.	8 Yrs	3.5mm	6weeks	Rashkind's' Umbrella device
4.	6 Yrs	< 2mm	3 weeks	Left against medical advise
5.	08 months	3mm	6 weeks	Surgical Ligation
6.	11 Yrs	4 mm	6 weeks	Amplatzer duct Occluder
7.	03 Yrs	< 2mm	4 weeks	Coil Occlusion
8.	15 Yrs	5 mm	4 weeks	Amplatzer duct Occluder
9.	02 Yrs	2mm	5 weeks	Surgical ligation
10.	07 Yrs	2mm	6 weeks	Surgical ligation
11.	04 Yrs	3.5mm	6 weeks	Surgical ligation
12.	08 Yrs	< 2mm	4 weeks	Coil Occlusion
13.	12 Yrs	5.5 mm	6 weeks	Amplatzer duct Occluder
14.	14 Yrs	3.5mm	5 weeks	Surgical ligation

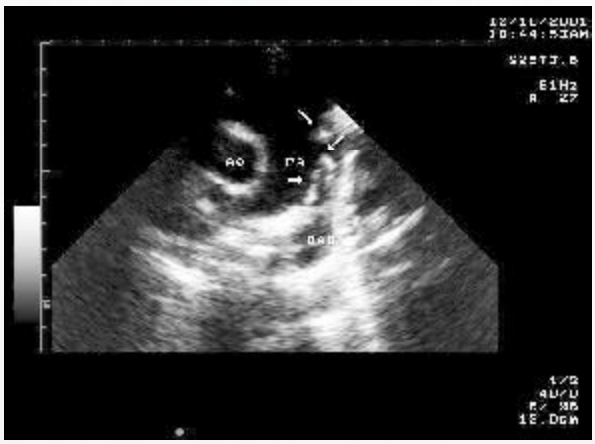

Figure 1. Two-dimensional echocardiographic left parasternal short axis view of an 11-year old girl with large PDA showing multiple vegetations (arrows) attached to the pulmonary artery end of the PDA and hanging into the pulmonary artery.
Ao = Aorta, DAO = Descending aorta, PA = Pulmonary artery.

DISCUSSION

There is a widespread general agreement that isolated patent arterial duct should always be closed in childhood. In children with moderate ducts where there is haemodynamic disturbance in the form of left ventricular volume overload but no pulmonary hypertension, closure is justified to prevent heart failure in later life. In patients with small arterial ducts and no haemodynamic disturbances, the only argument for duct closure is the prevention of infective endarteritis.

The risk of endarteritis is however, difficult to assess, as the extent to which a policy of duct closure has modified the natural history of the disease is not clear. In the pre-antibiotic era[2,3] practically every case of bacterial endocarditis proved fatal and it was the commonest cause of death (45%) in these patients followed by heart failure (30%). Introduction of antibiotics showed a large reduction in the deaths from bacterial endocarditis[9] but unless the duct is closed, they will still be exposed to further attacks of endarteritis and to the risk of heart failure, the risk of which increases sharply with age.In many of these incidence, studies are based on poorly defined populations and biased by selection of interesting or unusual cases[3]. Campbell in 1968[1] described the natural history of persistent ductus arteriosus by collecting data from several studies and estimated that the incidence of endarteritis in the patent arterial duct was between 0.45 and 1.0 percent per annum.

Our study shows that infective endarteritis on PDA is still an important cause of hospital admission with a much higher incidence of 4.8 patients per 1000 hospital admissions in children under 16 years of age admitted to a paediatric cardiology referral center. Such high incidence has never been reported in the literature in the recent times[5-7,10-13]. Huggons and Qureshi reported personal communications from 31 European cardiologists with a combined experience of over 10 years of around 5500 new cases of patent arterial duct in children and 300 in adults. It revealed only four cases of endarteritis in children (all older than 10 years of age) and one in an adult[6]. Thilen and Astrom-Olsson described an incidence of endarteritis in a defined population from their region and reported no case of duct endarteritis from 1980 to 1994[5]. This high incidence in our study may partly be due to the fact that our data is from a purely cardiac hospital as opposed to the data generated in the literature, which was based on population studies, or general paediatric hospitals. Of 2908 hospital admissions, PDA was the major underlying lesion in 368(12.6%) patients and of all patients with infective endocarditis (96); PDA was the underlying lesion in 14(14.6%) patients. The other reasons for such high incidence may be referral to a single tertiary center for paediatric cardiology for a large population of over 40 million, non-existent mechanisms of prevention, delay in seeking treatment due to poor financial status, lack of proper health delivery system and poor knowledge among medical professionals in terms of how to treat fever in patients with underlying heart disease[8].

The size of the duct is one of the important risk factors as not every patient with a duct carries the same risk for endarteritis. Scharader and Kadel[4] debated the closure of a small duct with insignificant left to right shunt as in a series of 100 adults with patent arterial ducts, all six with endarteritis had haemodynamically significant moderate or large ducts. They rightly debated that these patients would have warranted closure on haemodynamic grounds alone. Similarly study by Latson et al[14] showed that large native ducts or ducts with significant residual flow after attempted closure in animals are at increased risk of endarteritis than ducts with small amounts of residual flow after attempted occlusion. In our study, however, majority of the children (8 out of 14) had small, haemodynamically insignificant arterial duct. One of these was a 16-year old boy who initially had a large duct and underwent surgical ligation. He developed endarteritis 6 weeks following ligation and was found to have a small residual leak. Our data supports that all ducts irrespective of the size need closure to avoid risk of endocarditis. Endarteritis has also been reported on a clinically silent duct in the literature[15]. Finding of a silent

duct as an incidental finding on a routine colour Doppler is not uncommon and routine closure in these, however, cannot be justified as a policy.

Spontaneous closure of arterial duct is well recognized throughout life although less so after first year of life. Campbell measured the patient years as number of patients multiplied by the average number of years they were under observation. Taking all series together, 11 examples in 1842 patient-years gave an annual spontaneous closure rate of 0.6 percent per annum. Campbell calculated that 15% would have closed by 30 years of life and 20±3 percent by the age of 60. It has been observed that majority of patients reported in the literature with endarteritis are older children or adults[3,4]. Of 4 children with endarteritis reported through personal communication by Huggon and Qureshi[6] all were older than 10 years of age. Atheromatous changes in relation to the duct and differences in oral bacterial flora have been suggested as possible reasons for this susceptibility[3]. This overall low incidence in the recent past may be partly or wholly due the fact that majority of ducts are closed in the very young age irrespective of their size. Catheter closure of PDA was done at mean age of 2.4 years by using Gianturco coils[16] and median age was 3.96 years in the European Registry using Rashkind's device[17]. In our study 7 (50%) children were under the age of 7 years, one being 6 month old. This shows that, however rare endarteritis may be, no age is immune from it.

The complications of endarteritis include heart failure, septic emboli causing pulmonary embolism and lung abscess, mycotic aneurysms and very rarely death. In our study three children presented with heart failure and one child developed pulmonary embolism leading to lung abscess and required ten weeks of antibiotics. In pre-antibiotic era every case of endarteritis proved fatal. Now death will be extremely rare but hospital admission and intravenous antibiotics for 4 to 6 weeks with potential complications justifies treatment of arterial duct, which carries minimal morbidity and almost zero mortality.

It has been reported that ductus region becomes fragile following endarteritis and it may be difficult controlling haemorrhage in such patients[18]. Endopulmonary approach using full cardiopulmonary bypass has been recommended for these patients and those where ductus is associated with other cardiac malformations[19]. We delayed closure of arterial duct by a minimum of three months following the completion of antibiotic treatment and all closures were uneventful. In three patients where vegetations did not disappear completely, we empirically waited longer, 6 months or more and these three had surgical ligation rather than occlusion minimizing risk of possible dislodgement of the healed vegetation.

In a disease requiring long-term antibiotic therapy there are serious cost implications in a developing country where there is no medical insurance and state cannot provide free medical treatment. We used penicillin and gentamycin combination, which is fairly cheap and also recommended[20]. Although we were not carrying out minimal inhibitory concentrations on any organism, streptococcus viridans responded to standard antibiotic regimens in almost all patients. Rifampicin is an excellent antistaphylococcal drug when given in combination with other drugs. Its use in general is avoided to discourage drug resistance considering a large population with tuberculosis. We used oral Rifampicin as the third drug in patients with culture positive staphylococcus aureus or those not responding to the above-mentioned combination. Its use is quite justified in these selected patients requiring a six-week treatment. This was a major factor, which kept the cost of treatment low.

While improvement in overall socioeconomic status of the community and improvements in health delivery system as a whole may avoid delays in diagnosis and treatment, infective endocarditis remains an important disease with a high hospital incidence in our set up. This study clearly shows that endarteritis remains an important complication in children with patent arterial duct. No size and age are immune to the development of this important complication. Treatment with intravenous antibiotics is successful in almost all patients. Ductus can be closed 3 to 6 months after medical treatment by cardiac catheterisation or surgery without cardiopulmonary bypass. All patent arterial ducts (except truly silent duct) should be closed irrespective of their size and age of the patient.

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