Targeted Neonatal Echocardiography (TnECHO) and Increased Detection of Intracardiac Thrombi and Endocarditis in Very low Birth Weight Infants

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Citation

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Abstract

Objectives: Infective Endocarditis is a rare but potentially serious condition in very low birth weight infants and we aimed to evaluate the incidence and outcomes in this population. Study design: 203 infants <1500g were admitted to the NICU over 24 months. Routine echocardiography was introduced in the unit on all infants <1500g by a neonatologist trained in echocardiography. Echocardiography was specifically requested for persistent positive blood cultures, new onset murmur and patent ductus arteriosus evaluation. Results: Five infants were diagnosed with endocarditis giving an incidence of 2.5% compared to 0.4% in the previous 2 years. There were no cases of Congenital Heart Disease. All infants had a history of central venous or central arterial catheter use and received six weeks of antibiotic treatment. Four infants with endocarditis had persistently positive blood cultures and 2 infants received low molecular weight heparin. In all but one case, the sepsis resolved and the vegetative intracardiac lesions disappeared prior to completion of treatment.Conclusion: The diagnosis of endocarditis increased in VLBWs which coincided with institution of regular echocardiography. Thrombocytopenia, persistent positive blood cultures and a new murmur require urgent echocardiography to outrule endocarditis in VLBW infants.

INTRODUCTION

Infective endocarditis is a rare but serious condition in very low birth weight (VLBW) infants and in the absence of congenital heart disease is often associated with central venous catheters.[1] The incidence of symptomatic thrombosis is 5.1 per 100 000 live births and 2.4 per 1000 neonatal intensive care admissions.[2,3] Although central venous and arterial catheters have contributed to the improved survival of VLBW infants, they expose the infant to the risk of thrombus formation and line infection. If a catheter lies within the heart, damage to the endocardium can induce the formation of intracardiac thrombi despite a normal cardiac structure.[4] Spontaneous, non-catheter related events are relatively uncommon in the neonatal period and most commonly involve the renal vein.[5] Predisposing risk factors for infective endocarditis include central catheterization, septicaemia, osteoarthritis, gastroenteritis, ventilation, a hypercoagulable state and congenital heart disease. Persistent sepsis despite removal of the infected line and appropriate antibiotic therapy poses a particular challenge, as surgical intervention is associated with a high mortality.[3]

Infective Endocarditis has been successfully treated in extremely low birth weight infants with both low molecular weight Heparin and recombinant tissue plasminogen activator (rTPA)[4-8] in addition to prolonged courses of antibiotics. The management of VLBW infants with infective endocarditis presents a particular challenge especially in view of the paucity of literature on endocarditis in this population. Regular targeted echocardiography (TnECHO) in the neonatal unit may increase the diagnosis of infective endocarditis or intra-cardiac thrombi. During the study period, a Specialist Registrar in Paediatrics trained in functional and basic structural echocardiography performed routine echocardiography on in the neonatal unit. We hypothesised that a possible increase in the diagnosis of endocarditis in VLBW infants coincided with the increased availability of echocardiography in our unit.

METHODOLOGY

Routine targeted Neonatal Echocardiography (TnECHO) were performed on all infants < 1500g on day 1 and day 3 of life for Patent Ductus Arteriosus (PDA) assessment and in

the presence of clinical signs suggestive of intracardiac vegetations or thrombi. TnECHO was performed by a trained paediatric specialist registrar (Senior Neonatology Fellow: A.K.) and all cases were confirmed by a consultant paediatric cardiologist who also guided clinical management. All episodes of infective endocarditis diagnosed in <1500g infants during the study period were identified and defined using the modified Duke's criteria[9]. Cranial ultrasounds were carried out to assess the presence of brain abcesses in the setting of persistently positive blood cultures and intracardiac vegetations. This study was approved by the Hospital's Ethics Committee and informed consent was requested from parents within the first 24 hours of life.

Medical charts were systematically reviewed for demographic and clinical data. The diagnosis of endocarditis was based on clinical, bacteriological and echocardiographic findings[9]. Clinical details including maternal preeclampsia, histological chorioamnionitis, antepartum haemorrhage, antenatal steroid doses, Apgar score at 5 minutes, respiratory distress syndrome (RDS), and ventilation days were recorded. Echocardiographic examination was carried out by a single echocardiographer (A.K), when clinical signs suggestive of infective endocarditis were present. We used the Siemens Acuson Sequoia Ultrasound machine and a 10v4 cardiology multi-frequency probe using standard neonatal windows including apical, parasternal, subcostal, and high parasternal windows. The scans were recorded on the machine's internal hard drive for later measurements. Two dimensional, M-mode imaging, pulse and colour Doppler information were recorded. Other outcome measures including periventricular leukomalacia, necrotising enterocolitis, and death before discharge were collected[6].

RESULTS

15,812 infants were delivered in the National Maternity Hospital between September 2004-2006 (2 years) and 203 infants < 1500g were admitted to the Neonatal Intensive Care Unit. Five cases of infective endocarditis were diagnosed including four male and one female infant; two infants were outborn (Table 1). The incidence of endocarditis in VLBW infants was 0.4% over the preceeding two year period (one case out of 227 admissnios < 1500grams) and 2.5% over the study period. All infants were < 1500g with a mean gestational age of 28 + 3 weeks. All five infants were delivered by emergency caesarean section delivery following labour. Only one infant had a complete course of antenatal steroid therapy, 2 were partially treated and 2 infants had no steroids. Four of the five infants required positive pressure mechanical ventilation. Two infants had a PDA which were treated medically with ibuprofen and all infants had strucutrally normal cardiac anatomy.

Five infants had persistently positive blood cultures, antecedent thrombocytopenia. All infants had either a current or recent percutaneous central venous or umbilical arterial/venous catheter in situ. In three of five cases, the indication for echocardiogram was persistently positive blood cultures and new onset cardiac murmur. In all cases, diagnosis of intracardiac thrombosis was made on the basis of echocardiogram evaluation. In the two other cases, intracardiac thrombi were incidentally found during assessment of a PDA. In these two infants, an intracardiac thrombum was not the indiction for echocardiography, which was to assess the posibility of dutal reopening in the setting of sepsis. Two infants had left sided atrial intracardiac lesions and two infants had right sided atrial lesions. One infant was noted to have a left atrial mass extending across the patent foramen ovale into the right atrium.

Cranial ultrasounds were normal in 3 infants. One infant had a left Grade IV intraventricular haemorrhage (IVH) and a right Grade III IVH and developed ventriculomegaly and porencephaly. He also required laser therapy for retinopathy of prematurity. The remaining infant had initially normal cranial ultrasounds but developed a left thalamic infarct and bilateral white matter echogenicity suggestive of periventricular leukomalacia. There was no overt evidence of abscesses in any of the studied infants.

There was at least one attempt at central venous and or arterial access in all cases and the catheters were initially misplaced in the right atrium in three cases. All infants were commenced on six weeks of antibiotic treatment and two infants were also treated with Low Molecular Weight Heparin. In all but one case (the infant who died) sepsis resolved and the vegetative intracardiac lesions disappeared prior to completion of treatment (Table 1).The infant who died had coagulase-negative Staphylococcus species in the intracardiac vegetations, blood and CSF cultures.

Figure 1

Table 1: Clinical characteristics and management of Pretrm infants with Endocarditis:

Case	Gest (weeks)	Birth Weight (g)	APGAR Scores At 5	ANS doses	No. positive blood cultures	Positive Blood Culture DOL	Fever DOL	Plt ↓ DOL	Max CRP (mg/l & DOL)	Probable causative Organism	Antibiotics	Thrombus Resolution DOL
1	34+4	1430	9	0	S.aureus: x3 CoNS: x2	7	D8 + D14-20	3-11	72, DOL18	Staph aureus	Flucloxacillin Gentamicin	34
2	28	940	8	1	E.faecalis: x2 CoNS: x1	17	D22-26	16-23	80.5 DOL 22	E. faecalis	Ampicillin Gentamicin	70
3	28+5	530	8	0	MRSA: x4	21	D43-46	1-35	136.5 DOL 21	MRSA	Vancomycin Rifampicin	60
4	25+2	840	10	1	CoNS: x1	2	nil	11-17	6.6	?CoNS	Vancomycin	59
5	25+6	680	9	2	E.Coli: x1 CoNS: x4	6	nil	3- 13	23.5 DOL 10	CoNS	Meropenem Gentamicin Vancomycin Ambisome	RIP

Gest: gestation; EmLSCS: emergency caesarean section; ANS: antenatal steroids; Vent: positive pressure ventilation required; DOL: day of life; Plts ↓: thrombocytopenia; Max.CRP: Maximum C-reactive protein; Staph.: staphylococcus. CoNS: coagulase negative staphylococci. E. Coli: Escherichia coli. E.faecium: Enterococcus faecium. MRSA: Methicillin resistant staphylococcus aureus.

DISCUSSION

Neonatal mortality associated with infective endocarditis is high and the first survivor was reported in 1983[11,12]. The incidence of endocarditis was 0.4% over the preceding two year period and 2.5% over the study period. Symchych[13] et a1 reported an incidence of 3% in neonatal post-mortems in one year although other reports are lower[14,15]. Non-bacterial endocarditis forms an important focus for subsequent bacterial infection and the precipitating event may be endocardial damage at central venous catheter insertion[16-18]. Infective endocarditis in the absence of congenital heart disease is often associated with central venous catheters in neonates[3,19]. Although coagulase negative Staphylococci (CONs) are less commonly associated with endocarditis in patients without prosthetic valves recent literature suggests the incidence is increasing[20]. Preterm neonates are particularly susceptible to CONs sepsis and these organisms have been implicated in endocarditis in several case series in this population [21-23].

Diagnosis of infective endocarditis versus intra-atrial thombus is difficult as infection may be difficult to confirm in an infant partially treated with antibiotics. Therefore consensus on definitions of infective endocarditis, endocarditis of unknown aetiology and intra-cardiac thrombus is required. The increased availability of echocardiography by trained neonatologists under paediatric cardiology supervision has raised awareness of neonatal cardiac problems. In addition more infants with intracardiac lesions will be found incidentally raising dilemmas about their management. This report highlights the importance of TnECHO in the neonatal unit as using clinical judgment alone in these situations may result in withholding or inapproriately commencing therapeutic interventions. The importance of echocardiography in the neonatal unit by trained neonatologists has been recently highlighted.[24] The focus of these studies should be on functional assessment which include study of the patent ductus arteiosus, myocardial function, and pulmonary haemodynamics. The routine use of echocardiography in our unit may have facilitated early treatment of these infants. In addition, these infants were more readily monitored for treatment response. However, the role of paediatric cardiologists in assisting in the development of echocardiography in the neonatal unit is essential in confirming a suspected diagnosis, elaborating on the findings, and aiding in management strategies.

In VLBW the use of low molecular weight heparin may increase the chance of haemorrhage and surgery is difficult as their low weight may preclude the use of cardiac bypass. Longterm cardiac outcome in preterm infants is unknown and has not been described in this group. However neonatal cardiac repair and the presence of haematopoietic stem cells may mean that early treatment may prevent any sequelae in either childhood or adulthood.

There was an increase in diagnosis of endocarditis in infants <1500g which coincided with institution of regular echocardiography in the NICU allowing for early detection. Thrombocytopenia, persistent positive blood cultures and a new murmur require urgent investigation with echocardiography and should alert the clinician to a possible diagnosis of endocarditis in VLBW infants[25,26]. Based on out findings, we recommend an echocardioram looking for vegetations or intracardiac thrombi in any infant with a central catheter and persistent thrombocytopenia, positive blood cultures, and a fever. Infants with isolated thrombocytopenia and a central catheter without overt signs of sepsis also warrant assessment. Weekly echos should be done to assess treatment response and thrombus resolution.

Echos should be done more frequently in infants showing signs of clinincal deterioration.

References

1. Saiman L, Prince A, Gersony WM. Pediatric infective endocarditis in the modern era. J Pediatr 1993;122:847-53
2. Nowak-Gottl U, von Kries R, Gobel U. Neonatal symptomatic thromboembolism in Germany: two year survey. Arch Dis Child Fetal Neonatal Ed 1997;76:F163–7
3. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. Pediatrics 1995;96:939–43
4. Giuffre B, Compagnoni G, Farina C, Mosca F. Successful use of tissue plasminogen activator (t-PA) in catheter-related intracardiac thrombi of two premature infants. Acta Paediatr. 1998;87:695-698
5. Chalmers A. Neonatal thrombosis. J. Clin. Pathol., June 1, 2000; 53(6): 419 – 423
6. Marks KA, Zucker N, Kapelushnik J, Karplus M and Levitas A. Infective Endocarditis successfully treated in Extremely Low Birth Weight Infants With Recombinant Tissue Plasminogen Activator. Pediatrics 2002;109;153-158
7. Michaels LA, Gurian M, Hegyi T and Drachtman RA. Low Molecular Weight Heparin in the Treatment of Venous and Arterial Thromboses in the Premature Infant. Pediatrics 2004;114;703-707
8. Hauslerl M, Hubner D, Hornchen H, Muhler EG, Merzl U. Successful Thrombolysis of Inferior Vena Cava Thrombosis in a Preterm Neonate. Clinical Pediatrics, February 1, 2001; 40(2): 105 - 108.
9. Tissières P, Gervaix A, Beghetti M, Jaeggi ET. Value and limitations of the von Reyn, Duke, and modified Duke criteria for the diagnosis of infective endocarditis in children. Pediatrics. 2003 Dec;112(6 Pt 1):e467.
10. El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. Arch Dis Child Fetal Neonatal Ed 2005 Sep;90(5):F419-F422.
11. Wheeler JG, Weesner KM. Staphylococcus aureus endocarditis and pericarditis in an infant with a central venous catheter. Clin Pediatr 1984;23:46-7.
12. Oelburg DG, Fisher DJ, Gross DM, Denson SE, Adcock EW.Endocarditis in high risk neonates. Pediatrics 1983;71:392-9.
13. Symchych PS, Krauss AN, Winchester P. Endocarditis following intracardiac placement of umbilical venous catheters in neonates. J Pediatr 1977;90:287-9.
14. McGuinness GA, Schiekan RM, Maguire GF. Endocarditis in the newborn. Am J Dis Child 1980;134:577-80.
15. Johnson DH, Rosenthal A, Nadas AJ. Bacterial endocarditis in children under two years of age. Am J Dis Child 1975;129:183-6.
16. Butler-O'Hara M, Buzzard CJ, Reubens L, McDermott MP, DiGrazio W, and D'Angio CT. A Randomized Trial Comparing Long-term and Short-term Use of Umbilical Venous Catheters in Premature Infants With Birth Weights of Less Than 1251 Grams. Pediatrics, July 1, 2006; 118(1): e25 - e35.
17. Coleman MM, Spear ML, Finkelstein M, Leef KH, Pearlman SH, Chien C, Taylor SM, McKenzie SE. Short-Term Use of Umbilical Artery Catheters May Not Be Associated With Increased Risk for Thrombosis. Pediatrics, April 1, 2004; 113(4): 770 - 774.
18. Male C, Chait P, Andrew M, Hanna K, Julian L, Mitchell L. Central venous line-related thrombosis in children: association with central venous line location and insertion technique. Blood, June 1, 2003; 101(11): 4273 - 4278.
19. Kenny D, Tsai-Goodman B. Neonatal arterial thrombus mimicking congenital heart disease. Arch. Dis. Child. Fetal Neonatal Ed., January 1, 2007; 92(1): F59 - F61.
20. Chu VH, Woods CW, Miro JM, Hoen B, Cabell CH, Pappas PA, Federspiel J, Athan E, Stryjewski ME, Nacinovich F, Marco F, Levine DP, Elliott TS, Fortes CQ, Tornos P, Gordon DL, Utili R, Delahaye F, Corey GR, Fowler VG Jr; International Collaboration on Endocarditis-Prospective Cohort Study Group. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis Clin Infect Dis. 2008 Jan 15;46(2):232-42
21. Pearlman SA, Higgins S, Eppes S, Bhat AM, Klein JD. Infective endocarditis in the premature neonate Clin Pediatr (Phila). 1998 Dec;37(12):741-6
22. Verhoef J, Fleer A. Staphylococcus epidermidis endocarditis and Staphylococcus epidermidis infection in an intensive care unit Scand J Infect Dis Suppl. 1983;41:56-64
23. Noel GJ, O'Loughlin JE, Edelson PJ. Neonatal Staphylococcus epidermidis right-sided endocarditis: description of five catheterized infantsPediatrics. 1988 Aug;82(2):234-9
24. Sehgal A, McNamara PJ. Does Point-of-Care echocardiography enhance cardiovascular care in the NICU? J Perinatol. 2008;28,729-735.
25. O'Callaghan C, McDougall P. Infective endocarditis in neonates Arch Dis Child. 1988 Jan;63(1):53-7
26. Armstrong D, Battin MR, Knight D, Skinner J. Staphylococcus aureus endocarditis in preterm neonates. Am J Perinatol. 2002 Jul;19(5):247-51.

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