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CLINICAL STUDY ON NEONATAL SEPSIS

Ch. Sneha*, Sandhya Sree

M, Department of pharmacology, Assistant professor, Bharat institutions, Ibrahimpatnam.

Email: vatupali@gmail.com

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Abstract

Study-1

The purpose of the first study was to determine the clearance of CONS from the bloodstream 48-72h after initiation of antibiotic therapy in infants with CONS sepsis. Therefore the number of colony-forming units/ml (CFU/ml) is determined in blood samples drawn at onset of sepsis and after 48-72h of antibiotic therapy. We considered these data important for the decision on discontinuation of antibiotic therapy earlier than after the generally recommended period of 7-10 days.

Study-2:

According to our objective it was decided to design our protocol for the treatment of neonatal CONS sepsis in 2013, to discontinue anti-CONS treatment after a period of 3 days, when the diagnosis CONS sepsis is confirmed, the clinical signs of infection have disappeared within 48 hours, the value of CRP decreases and no indwelling central venous catheters (CVCs) are present. So our aim of the study was to evaluate the effect of short (3 days) treatment duration for CONS sepsis.

Study-3:

Our objective is to reduce the insertion of CVCs is an effective measure to decrease the incidence of CONS sepsis. However, this measure is not realistic in the care of VLBW infants. The continuous administration of vancomycin is an alternative measure to prevent catheter-associated sepsis. The aim of the present prospective study was to evaluate the effect of a specific anti-staphylococcal agent (cefazolin) on the prevention of CoNS sepsis after the removal of a percutaneously inserted central venous catheter (PCVC).

Key words: Sepsis, infections, syndrome, asphyxia, neonates.

Introduction

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Superficial infections like conjunctivitis and oral thrush are not usually included under neonatal sepsis.

Based on the studies from India, the following risk factors seem to be associated with an increased risk of early onset sepsis (Singh M et al; 1994, Takkar VP et al;1974):

1. Low birth weight (<2500 grams) or prematurity
2. Febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery.
3. Foul smelling and/or meconium stained liquor.
4. Rupture of membranes >24 hours.
5. Single unclean or > 3 sterile vaginal examination(s) during labor
6. Prolonged labor (sum of 1st and 2nd stage of labor > 24 hrs)
7. Perinatal asphyxia (Apgar score <4 at 1 minute)

Presence of foul smelling liquor or three of the above mentioned risk factors warrant initiation of antibiotic treatment.

Infants with two risk factors should be investigated and then treated accordingly. Neonatal sepsis can be classified into

two major categories depending up on the onset of symptoms (Singh M et al; 1994). **Early onset sepsis (EOS) and Late**

onset sepsis (LOS) (Baltimore RS et al; 1998, Wolach B et al; 1997). Since treatment should be initiated in a neonate suspected to have sepsis without any delay, only minimal and rapid investigations should be undertake (Gerdes JS et al;

1998). **Septic screen (Polinski C et al; 1996, Da Silva O et al; 1995)**, For very low birth weight infants, the reference ranges are available from Mouzinho's charts (Mouzinho A et al; 1994). However, recent reports suggest that at least 60-

70% of the gram-ve organisms are resistant to them (Upadhyay A et al; 2006, Zaidi AK et al; 2005). **Intravenous**

Immunoglobulin (IVIG): Non-specific pooled IVIG has not been found to be useful (Jenson HB et al; 1998).

Granulocyte-Macrophage colony stimulating factor (GM-CSF): This mode of treatment is still experimental (Goldman S et al; 1998). Approach in the management of septic shock.(Bierley J, Carcillo, et al; 2009). identifying and controlling the source of infection, intravenously (IV) administering fluids, and maintaining glycemic control.(Goldstein B, Giroir B, et al; 2005).

Material and Methods-

Study group and procedures:

- 72 Patients with coagulase-negative staphylococcal sepsis were participated.
- All patients were treated and followed up at the Department of paediatrics at site under the Mahatma Gandhi Memorial hospital, Warangal.

1. Number of Subjects- 72

2. Duration of study- Nov 2012 to July 2013.

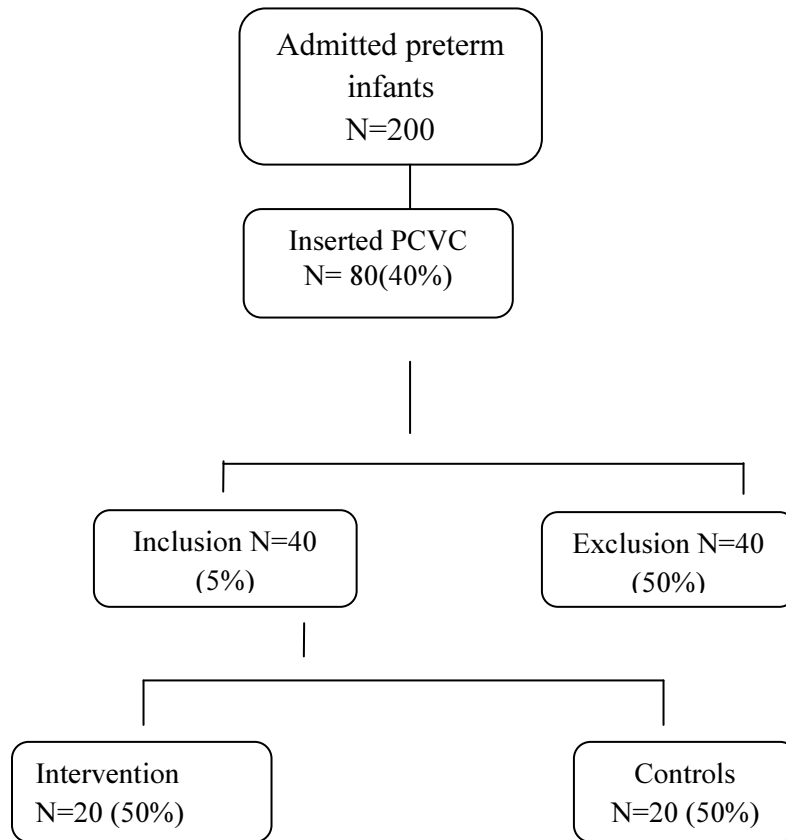
3. Place of study- Mahatma Gandhi Memorial hospital, Warangal.

4. Types of subject- Patient (infants)

5. The study was approved by the local Medical Ethical Committee. During a period of 9 month (2013-2013), infants admitted at the NICU of the Children's Hospital, with clinical signs of neonatal late-onset sepsis and matched control infants without sepsis, were enrolled in the study, after informed parental consent.

Study -1:

- Postoperative patients and patients with chromosomal abnormalities were excluded from the study. In infants with clinical signs of sepsis 1 ml of blood was obtained for blood culture, determination of the number of CFUs/ml, and CRP-value (t=0).
- The blood sample was drawn from a peripheral vein before initiation of antibiotics.
- Blood cultures were performed according to a defined protocol, using the Phoenix automated system.

Study-2:**Fig No- Study design for patient enrolment****Exclusion Criteria:**

Episodes were excluded from the analysis for the following reasons:

- The CVC remained in situ ,
- Diagnosis of NEC
- Drains remaining in situ
- Persistent thrombocytopenia
- Insufficient clinical improvement
- Lost for evaluation

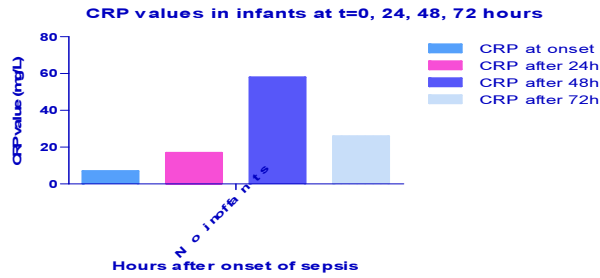
Study-3:

- After parental informed consent, infants were randomly assigned to either the intervention group (receiving cefazolin) or the control group (no antibiotics) during the removal of a PCVC. Cefazolin was administered twice, 50 mg/kg/dose, 1 hour before and 12 hours after removal of the PCVC.
- Statistical analyses were performed using Graph Pad prism, version-5. Groups were compared using ttest, chi square test, and Mann-Whitney Utest when appropriate. Statistical significance was assumed for $p < 0.05$.

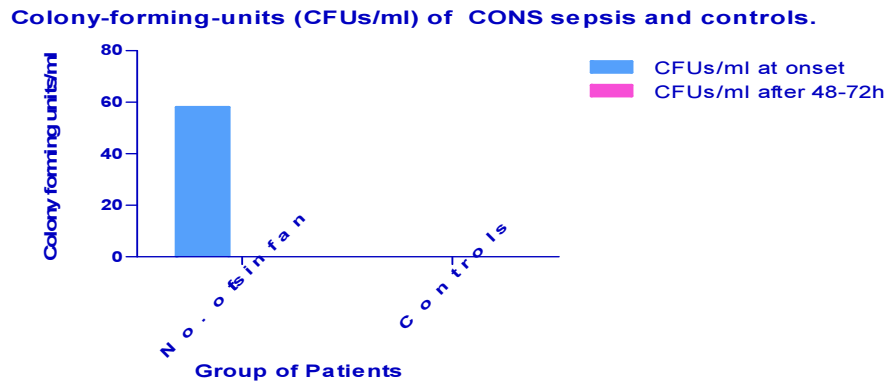
Results

Table 1: Clinical characteristics, values for C-reactive protein (CRP) and Colony-forming-units (CFUs/ml) of infants with proven CONS sepsis and controls.

	Number of infants	Controls	p-value
Number of infants	22	19	
Base line Characteristics			
GA (wks) (median, range)	31 (25-41)	30 (26-31)	NS
BW (g) (median,range)	1400 (730-3770)	1380 (690-1920)	NS
Postnatal age at onset of sepsis or day of sampling in controls (d) Median range	11 (5-20)	14 (7-25)	NS
CRP- values			
CRP at onset (t=0) (mg/L) (Median range)	7 (0-39)		
CRP after 24hrs (mg/L) (Median range)	17 (0-119)		
CRP after 48hrs (mg/L) (Median range)	58 (15-112)		
CRP after 72 hrs (mg/L) (median range)	26 (12-86)		
Colony forming units (CFUs/ml)			
CFUs/ml at t=0 (median range)	58 (1-500)	0	0.002
CFUs/ml after 48-72 hrs (t=1) (median range)	0 (0-5)	NA	



Graph No:1- C-reactive protein (CRP) of infants with proven CONS sepsis and controls.

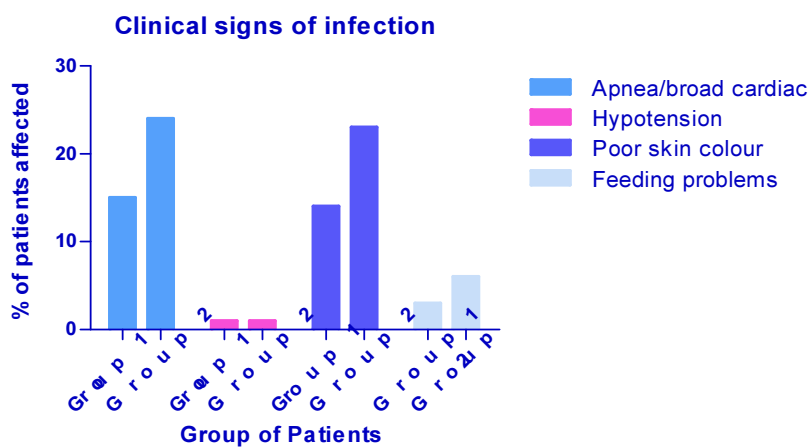


Graph No-2: Colony-forming-units (CFUs/ml) of infants with proven CONS sepsis and controls.

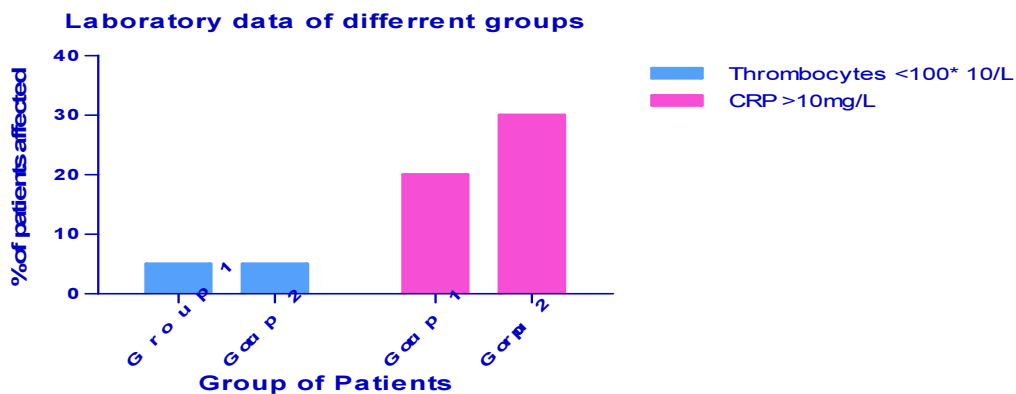
Table 2: Demographics, clinical characteristics and outcome of infants with CONS sepsis, with 7days of anti-CONS treatment (Group 1) versus 3 days (Group 2).

Variables	Group 1 (7days) N=20	Group 2 (3days) N=30	P-value
GA (wks) (median, range)	30(26-41)	30(25-42)	0.548
BW (g) (median, range)	1325(770-5000)	1150(660-4500)	0.0555
Male (n. %)	11(53)	14(48)	0.499
Age at onset of sepsis (d) (median, range)	9(5-26)	10(4-107)	0.292
Clinical signs of infection			
Apnea/broad cardiac (n,	15(76)	24(79)	0.677

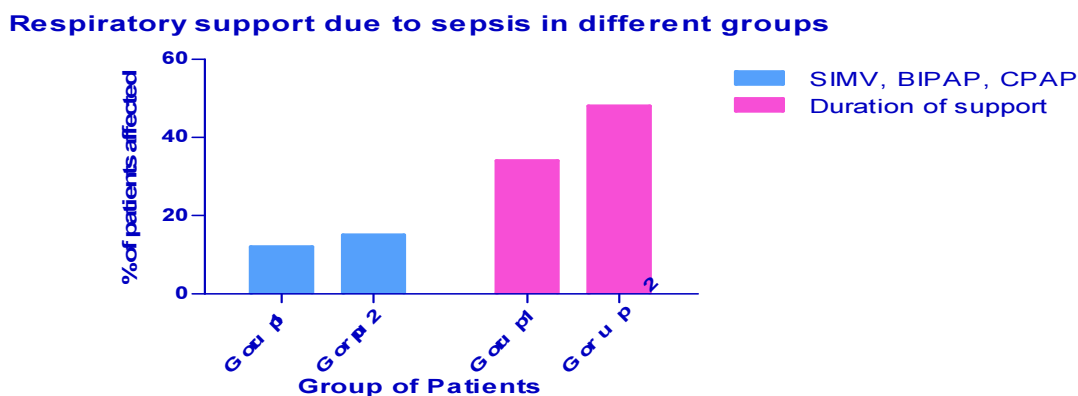
(%)			
Hypotension (n, %)	1(5)	1(3)	0.715
Poor skin colour(n,%)	14(69)	23(76)	0.357
Feeding problems(n,%)	3(16)	6(19)	0.684
Laboratory data			
Thrombocytes < 100* 10/L (n,%)	5(23)	5(15)	0.261
C-reactive protein >10mg/L (n,%)	20(100)	30(100)	-
Respiratory support due to sepsis			
SIMV,BIPAP,CPAP (N,%)	12(61)	15(51)	0.232
Duration of support (h)(median,range)	34 (5-72)	48(24-72)	0.349
Relapse of CONS sepsis	0	0	-



Graph N0-3: Clinical signs of infants with CONS sepsis, with 7 days of anti-CONS treatment (Group 1) versus 3 days (Group 2).



Graph N0-4: Laboratory data of infants with CONS sepsis, with 7 days of anti-CONS treatment (Group 1) versus 3 days (Group 2).



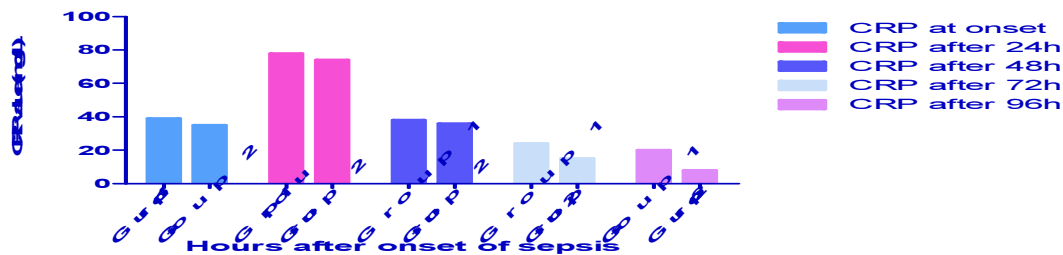
Graph N0-5: Respiratory support with CONS sepsis, with 7 days of anti-CONS treatment (Group 1) versus 3 days (Group 2).

Table No:3- Estimation of CRP based on the two antibiotic course

CRP Value	Groups	
	Group 1 (7 days) N=20	Group 2 (3 days) N=30
CRP at onset (t=0) (mg/l) (median, range)	39	35
CRP after 24h (mg/l) (median, range)	78	74
CRP after 48h (mg/l) (median, range)	38	36

CRP after 72h (mg/l) (median, range)	24	15
CRP after 96h (mg/l) (median, range)	20	8

CRP values in infants at t=0, 24, 48, 72, 96 hours



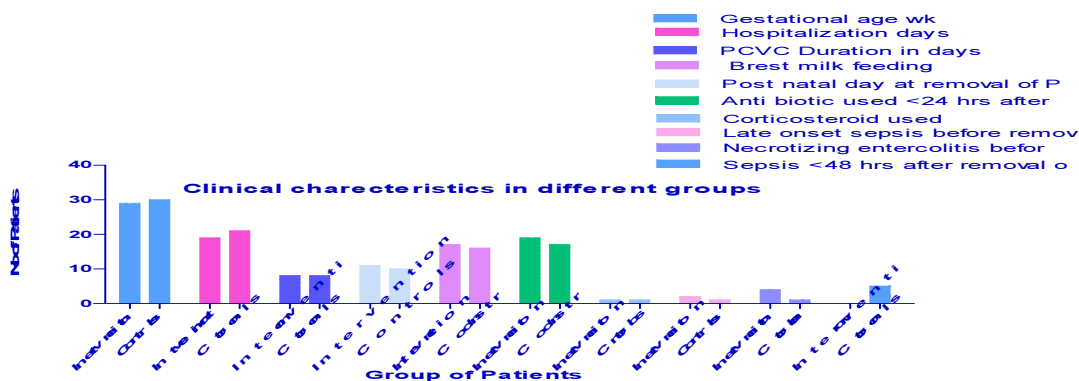
Graph No: 6 -Estimation of CRP based on the two antibiotic course

Table 4: Clinical characteristics of the intervention group receiving cefazolin during removal of the precutaneously inserted central venous catheter and the control group receiving no anti-microbial agents:

	Intervention N=20	Controls N=20	P-value
Clinical data			
Gestational age wk median (range)	29 (25-36)	30 (25-35)	0.648
Birth weight, g, median (range)	1200 (750-3240)	1170 (660-2390)	0.110
Male (%)	66	46	0.053
Hospitalization days, median (range)	19 (8-106)	21 (7-73)	0.664
PCVC Duration in days median (range)	8 (3-28)	8 (3-17)	0.395
Post natal day at	11 (5-	10 (6-30)	0.329

removal of PCVC median (range)	65)		
Ventilation days median (range)	0 (0-23)	0 (0-13)	0.726
Brest milk feeding, n (%)	17 (84)	16 (80)	0.580
Anti biotic used <24 hrs after birth, n (%)	19 (96)	17 (86)	0.138
Corticosteroid used, n (%)	1 (7)	1 (4)	0.306
Late onset sepsis before removal, n (%)	2 (11)	1 (5)	0.237
Necrotizing entercolitis before removal of PCVC, n (%)	4 (21)	1 (7)	0.062
Sepsis <48 hrs after removal of PCVC	0	5	0.021

PCVC percutaneously inserted central venous catheter



Graph No-7: Clinical characteristics of intervention group receiving Cefazoline

Conclusion

Study-1:

Coagulase-negative staphylococci (CONS) are the most common cause of late-onset sepsis in neonatal intensive care units. Infants with CoNS sepsis recover rapidly after the start of antibiotic treatment. The recommended duration of antimicrobial treatment is 7 to 10 days. Antibiotic treatment duration may be terminated earlier, when clinical signs of sepsis have disappeared and CRP is decreasing. In 22 preterm infants with CONS sepsis, the number of colony-forming units/ml (CFU/ml) was determined in blood samples drawn at onset of sepsis and after 48-72 hours of antimicrobial treatment with cefazolin.

Study-2:

The incidence of coagulase-negative staphylococcal (CONS) sepsis is high in neonatal intensive care units (NICUs) and treatment significantly adds to the antibiotic pressure, increasing the threat of resistance. Because infants recover within 24-48 hours, blood cultures are negative within 48 hours and CRP normalizes within 72 hours, we reduced anti-CONS treatment from 7 to 3 days in infants with uncomplicated CONS sepsis.

Study-3:

Central venous catheters are the most important risk factors for the development of sepsis attributable to coagulase-negative staphylococci among preterm infants admitted to neonatal intensive care units. In addition, removal of a central venous catheter may also cause CoNS sepsis, which may be prevented by the short-term administration of an anti-staphylococcal agent during the procedure of removal. The administration of a specific anti-staphylococcal agent (cefazolin) was evaluated for the prevention of central venous catheter removal-associated coagulase-negative staphylococci sepsis.

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Corresponding Author:

Sandhya Sree*,

Email: yatupali@gmail.com