



International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 2 Number 11 (November-2014) pp. 191-196

www.ijcrar.com



A study on role of C-reactive protein in deciding duration of antibiotic therapy in neonatal septicemia

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KEYWORDS

Neonates,
Septicemia,
C-reactive
protein

A B S T R A C T

Neonatal sepsis is one of the commonest causes of neonatal mortality in the developing world and identifying bacteriological profile is of prime importance including antibiotic sensitivity. Hence this study aims to know the role of CRP in deciding duration of antibiotic therapy in neonatal septicaemia. It was a prospective study of series of newborns admitted in the tertiary care hospital with sepsis. Data relating to history, clinical examination, investigation and treatment were entered in a specially designed Performa for the study. PROM > 12 hours and multiple vaginal examinations were significantly associated with increased CRP. Negative predictive value of serial serum CRP was 100% in deciding duration of antibiotic therapy in neonatal septicaemia up to 7 days.

Introduction

According to the WHO, young infant study group infection contributes to approximately 30 – 40% of neonatal deaths in developing countries¹; hence early diagnosis of neonatal sepsis has remained a frustrating experience even in high income countries². The inability to be certain of infection coupled with non-specific signs of the life threatening illness in neonates with blood culture positivity varying from 45.6% according to sunaina Rishi Garg³ study from Delhi has reported 56%⁹ and from Hubli 64.8%⁴, has resulted in wide spread use of antibiotics leading to the growing problem of antibiotics use and abuse in new born care.

This is resulting in the selection of increasingly resistant gram negative and gram positive bacteria⁵. Gram negative bacteria like Klebsiella can produce extended spectrum beta lactamases (ESBL) which render the Klebsiella resistant to almost all antibiotics, gram positive bacteria can carry genes conferring vancomycin resistance such as vancomycin resistant enterococci (VRE) and genes coding for methicillin resistance, such as methicillin resistant staphylococcus aureus (MRSA) and methicillin resistant staphylococcus epidermidis (MRSE). Prolonged use of broad spectrum antibiotics is also causing a rising incidence of severe fungal sepsis in

India. Systemic candidal infections, which were once discounted as being blood culture contaminants, were recognized in the 1980's as being responsible for 2% to 4% of nosocomial infections. Currently they are thought to be responsible for as many as 15% of these infections and overall morbidity and mortality for disseminated candidiasis are very high, often approaching 25% to 54% respectively^{6,7}.

Broad spectrum antibiotics are more potent selector of antibiotic resistant than narrow spectrum antibiotics. It is known that ampicillin and third generation cephalosporins select for ESBL producing gram negative organism. Most worrying is that there are exceedingly high rates of resistance of gram negative bacilli to almost all antibiotics. Resistance to aminoglycosides is about 50% foramikacin, higher for netilmicin and over 75% for gentamicin. Resistance to third generation cephalosporins is 80 % plus⁵ thus there is an increasing need for careful evaluations of indications and duration of treatment, which in turn would shorten the length and cost of hospital stay and diminish the trauma and side effects of antibiotics. Blood cultures, the gold standard for the diagnosis of septicemia, requires up to 48-72 hours before the results are known and almost half of the positive samples do not Show growth. More over if the mother has received antibiotics before delivery, proper documentation of bacterial infection may not be possible⁸. Blood culture techniques which are known to be highly sensitive and reliable, such as the Bactec or BacT Alert systems which can be positive in 95% of case according to the Mexican study⁵, such facilities are not in place in many of the institutions in India. This has prompted the evaluation of surrogate markers of inflammation as possible tools for early diagnoses of bacterial sepsis^{14,15}.

Estimations of cytokine levels and CRP levels are potentially useful in this respect. Although several studies confirm that CRP levels are usefiil in the early diagnosis of sepsis, there are reports of the contrary⁵. It is suggested that serial rather than single determinations of CRP levels may be more useful in diagnosis of sepsis¹¹.

C. reactive protein (CRP) an acute; phase reactant, is synthesized in the liver in response to inflammatory cytokines and may rise more than 1000 times during an acute phaseresponse¹². It is known to be increased in both bacterial and fungal infection but remain slow in viral infections¹³. It falls quickly after efficient elimination of microbial stimulus, due to its short half-life of 19 hours¹². Thus CRP may be used as a parameter to identify the time period when antibiotic therapy can safely be discontinued in case of suspected neonatal septicemia, which is the aim of the present study.

Methodology

Source of Data

Newborns admitted in the neonatal unit of department of Pediatrics, VIMS, Bellary, India.

Method of Collection of Data

It is a prospective study of a series of newborns admitted with neonatal sepsis for a period of one year from April 2004 to March 2005. Data relating to history, clinical examination, investigations and treatment are entered in a specially designed proforma for the study. Fifty consecutive neonates up to 4 weeks of age with birth weight more than 1500g and suspected septicemia were studied prospectively.

Inclusion criteria for the study

Septicemia was suspected with “Sepsis score” which included following signs and symptoms such as refusal for feeds, abdominal distension, vomiting, lethargy, jaundice, poor cry, seizures, diarrhea, apnea, tachypnea, poor capillary refill, hypothermia, fever and umbilical discharge. If baby had three or more than three of above signs and symptoms septicemia was suspected and those with at least three of following risk factors were present.

- a) Febrile illness in the mother during or within two weeks of delivery.
- b) Foul smelling liquor amnii.
- c) Prolonged rupture of membranes (>12 hrs)
- d) Prolonged and difficult delivery.
- e) Pathological evidence of funisitis or presence of polymorphs in the gastric aspirate.

Exclusion criteria

1. Neonates who had undergone surgery
2. Neonates with meningitis were excluded from the study because they require longer duration of treatment regimes.

Micro ESR, buffy coat smear, blood culture and sensitivity was done in all the cases along with other investigations such as hemogram, X ray chest, swabs for culture and sensitivity as and when required. CRP valve was estimated by latex agglutination method with CRP kit manufactured by SPAN diagnostics ltd. as per instructions in the manual provided by the company. The CRP valve of more than 6 mg% was taken as abnormal. Serum CRP was estimated again 48 hours after initiation of therapy. If it was less than 6 mg%, antibiotics were stopped and patients were assigned to group 1. Neonates with CRP more than 6 mg%

were assigned to group 2. Group 2 was further sub divided into 2a and 2b depending upon whether CRP was done every other alternative day (2a) or only on the 7th day after commencing of antibiotic therapy (2b). Antibiotics were stopped when CRP levels returned to normal (<6 g%). After stopping the treatment babies were observed for 48 hours in the hospital and followed up to 4 weeks for any relapse.

Result and Discussion

Fifty consecutive neonates up to 4 weeks of age with birth weight more than 1500 grams and suspected septicemia were studied out of 352 neonatal cases admitted during the study period. Most of the cases (72%) occurred after 72 hours of birth, only 28% of cases occurred before 72 hours of birth. Vaginal mode of delivery accounted for 80% of the total deliveries.

Blood culture revealed that the commonest gram positive organism was staphylococcus coagulase and the commonest gram negative organism was Klebsiella. Out of 9 blood culture positive cases showing gram positive organisms, buffy coat smear was positive in 6 cases. Out of 13 blood culture positive cases of gram negative organisms, buffy coat smear was positive in 6 cases. Buffy coat smear positivity was not significantly associated more frequently with gram positive or negative organism.

Out of 50 cases of suspected septicemia, CRP was negative after 48 hours in 42% (21) cases and antibiotics were stopped, no relapse was observed within 4 weeks (group 1). In remaining 58% (29) cases where CRP was raised after 48 hours antibiotics were stopped on the 5th day in 4% (2) and continued for more than 7 days in 28% (14) cases as CRP was raised even on the 7th day (group 2a).

Table.1 Common maternal risk factors associated with increased CRP levels

Risk factors	Cases	CRP + at admission	CRP + at 24 hrs	P value
PROM>12 hours	12	12	10	0.04
Prolonged/difficult labour	07	07	05	0.44
Multiple vaginal examinations	11	11	10	0.01
Chorioamnionitis	03	03	02	0.75
Maternal fever	03	03	01	0.37
Meconium liquor	08	08	04	0.60

PROM>12 hours and multiple vaginal examinations were significantly associated with increased CRP at 24 hours after admission

Table.2 Buffy coat smear positive, CRP positive at 7th day and positive blood culture

Organism	Blood culture+	Buffy coat smear+	CRP+ on 7 th day
Gram positive	09	06	09
Gram negative	13	06	13

Table.3 CRP guided distribution of treatment, relapse rate in various groups and correlation with blood culture

CRP value	Groups	Duration of treatment	Blood culture positive	Relapse
<6 mg%	Group 1 (21)	< 3days	Nil	Nil
>6 mg%	Group 2 (29)	Group 2a (16)	5 days (2)	Nil
			7 days (14)	12
	Group 2b (13)	7 days (2)	Nil	Nil

In group 2b, antibiotics were stopped in 4% (2) on 7th day and in 22% (11) continued for more than 7 days. CRP was not done beyond 7 days in any group. The antibiotics were required for more than 7 days in all neonates with raised CRP and positive blood culture. There was no relapse in each group after stopping antibiotics following normalization of CRP with negative predictive value of 100% in each group.

Total culture positive cases were 22 (44%). A study by Marina thomas et al¹⁴ showed culture positivity in 40% of cases, culture positivity rates in other studies ranged from

56% to 75%. The commonest organism for early onset septicemia was *Klebsiella*, *E.coli* and late onset septicemia was *Staphylococcus* coagulase positive and *Klebsiella*. In our study 40.9% were gram positive and 59.0% were gram negative almost similar finding was seen by RS. Jaswal et al in 2003¹² i.e. 47.62% were gram positive and 52.48% gram negative. A study by A.S.M. Nawshad Uddin Ahmed et al in 2002¹⁵ showed *E coli* and *Klebsiella* being the commonest organism in Eo8 and *E. coli* and *Klebsiella pneumoniae* being the commonest organism in late onset sepsis.

In our study PROM > 12 hrs, prolonged / difficult labour and multiple vaginal examinations, chorio amnionitis, maternal fever and meconium liquor were commonly seen with increased CRP levels among these, PROM > 12 hrs and multiple vaginal examinations were significantly associated with increased CRP at 24 hrs after admission. A study by Elizabeth mathai et al in 2004¹⁶ revealed. At 24 hours, elevation in CRP levels was significantly associated with primi parity, more than three vaginal examinations after rupture of membranes, meconium staining of amniotic fluid and amnio infusion.

In our study 22 cases were blood culture positive, out of 9 blood culture positive cases showing gram positive organisms, buffy coat smear was positive in 6 cases. Out of 13 blood culture positive cases of gram negative organisms, buffy coat smear was positive in 6 cases. Buffy coat smear positivity was not significantly associated more frequently with gram +ve gram negative organism.

Out of 50 cases of suspected septicemia, CRP was negative after 48 hours in 42% (21) cases and antibiotics were stopped, no relapse was observed within 4 weeks (Group 1). In remaining 58% (29) cases where CRP was raised after 48 hours antibiotics were stopped on the 5th day is 4% (n = 2) and continued for more than 7 days in 28% (n=14) cases as CRP was raised even on the 7th day (Group 2a). In group 2b antibiotics were stopped in 4% (n = 2) on 7th day and in 22% (n = 11) continued for more than 7 days. CRP was not done beyond 7 days in any group. The antibiotics were required for more than 7 days in all neonates with raised CRP and positive blood culture. There was no relapse in each group after stopping antibiotics following normalisation

of CRP with negative predictive value of 100% in each group.

A study by RS.Jaswal in 2003¹² showed .CRP was positive in all culture positive cases similar to our finding, 87.5% cases that required longer duration of antibiotics therapy (> 7 days) had positive blood culture suggesting that, those with positive blood culture and raised CRP needed longer duration of antibiotic therapy, a finding similar to our study. There was no relapse in any of the cases in which antibiotics were stopped following normalisation of CRP giving a negative predictive value of 100%, which is similar to our study and other studies like stephen et al.

Another study by Stephen Ehl et al in 1997¹⁷ concluded that CRP could be a key parameter for individually guiding the duration of antibiotic treatment in a major subgroup of newborns with suspected bacterial infection. This approach would allow considerably shorter courses of antibiotic therapy. Within the 4 weeks follow up period, one infant in group 1 and no infant in group 2a received a second course of antibiotics for bacterial infection. CRP levels of less than 10 mg / L determined later than 24 hours after beginning the antibiotic treatment thus correctly identified 120 of 121 infants as not needing further antibiotics. This corresponds to a negative predictive value with respect to further treatment of 99%. The mean treatment duration was 3.7 days in the CRP guided group and 5.5 days in the at least 5 day study group. In the latter group, one infant was treated for a likely relapse. The low relapse rates in both treatment groups are a preliminary indication that relapses may not occur more frequently if patients are treated until CRP is negative rather than for a 5 day of longer treatment period.

In conclusion, a CRP level of < 6mg / L at 24 hrs has a good negative predictive value for neonatal sepsis. Serial CRP levels are useful in diagnosis of early onset sepsis. PROM > 12 hrs and multiple vaginal examinations were significantly associated with increased CRP at 24 hrs after admission.

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