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Role of procalcitonin in diagnosis of late onset sepsis in neonates

[1]Dr. Bheemaraya Shivasharana, [2]Dr. Vasanth Kumar D. L[3]Dr.Manjunathaswamy. R, [4]Dr. Ananya U Shetty,[5]Ravindra B Patil

[1,2]Assistant Professor, Department of Paediatrics, SIMS, Shivamogga, Karnataka, India
[3]Associate Professor, Department of Paediatrics,SIMS, Shivamogga. Karnataka, India
[4]Senior Resident, Department of Paediatrics, SIMS, Shivamogga, Karnataka, India
[5]Professor& Head, Department of Paediatrics, SIMS, Shivamogga, Karnataka, India

Corresponding Author: Dr. Vasanth Kumar D. L (dr.vasanth23@gmail.com)

Abstract

Background: Neonatal sepsis refers to systemic infection of the new born. It is characterized by a constellation of non-specific symptomatology in association with bacteremia.Neonatal sepsis is the most common cause of (52%) neonatal mortality in our country, which could be reduced in large proportion by a high index of suspicion, prompt diagnosis and aggressive management of this condition. Many studies have come up regarding the usefulness of procalcitonin in the early diagnosis of neonatal sepsis and have found it to be 87-100 sensitive and also highly specific.

Methods: A prospective clinical study was conducted in Neonatal Intensive Care Unit of Shimoga Institute of Medical Sciences, Shimoga. From November 2020 to November 2021 to study role of Procalcitonin in diagnosis of LOS.All intramural neonates admitted to NICU during this period with clinically suspected Late onset sepsis were included in the study and were subjected to sepsis screen, blood culture and procalcitonin. Study population was further divided into 3 group as Proven sepsis (sepsis screen positive and blood culture positive), Probable sepsis group (sepsis screen positive, blood culture negative) and no sepsis group (sepsis screen negative and blood culture negative, with alternate diagnosis).Sensitivity, specificity of Procalcitonin at a level of 2ng/ml in diagnosis of late onset sepsis in neonates was calculated (Proven sepsis was taken as test group and No sepsis group was taken as control group).

Results: PCT was found to be >2ng/ml in 58.6% of the enrollees,our study had high PCT of 19.2ng/ml in proven sepsis,our study had sensitivity of PCT as high as 78.57% with specificity of PCT to the tune of 77.78%.

Conclusion: The procalcitonin values were higher in sepsis proven group than in probable sepsis and no sepsis group. Sensitivity, Specificity, PPV and NPV of Procalcitonin at value of.2ng/ml in diagnosis of LOS was found to be 78.57%, 77.78%, 76.74%, 78.57.

Keywords: Procalcitonin, neonate, late onset sepsis

Introduction

The first 28 days of life-the neonatal period-is the most vulnerable time for a child's survival.Children face the highest risk of dying in their first month of life at an average global rate of 17 deaths per 1,000 live births in 2019, down by 52 per cent from 38 deaths per 1,000 in 1990. In comparison, the probability of dying after the first month and before reaching age 1 was estimated at 11 deaths per 1,000 and the probability of dying after reaching age 1 and before reaching age 5 was estimated at 10 deaths per 1,000 in 2019. Globally, 2.4 million children died in the first month of life in 2019-approximately 6,700 neonatal deaths every day-with about a third of all neonatal deaths occurring within the first day after birth, and close to three-quarters occurring within the first week of life[1,2].

Advances in neonatal intensive care has led to improved survival of neonates, but neonatal

sepsis continues to be an important cause of morbidity and mortality. Neonatal infections are estimated to cause about 1.6 million deaths worldwide[3]. Neonatal sepsis is responsible for about 30-50% of the total neonatal deaths in developing countries[4]. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes[5]. Etiology of neonatal sepsis is multifactorial, but the principal sources of newborn infection are mother and nursery environment. Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition by early diagnosis, rational antimicrobial therapy and aggressive supportive care. Even though blood culture is warranted as a gold standard method in identifying sepsis, the sensitivity varies based on the volume of blood and the bacterial load and it often yield false-negative results, particularly after maternal antibiotic,false positive results because of specimen contamination and also the result is delayed upto 48 hours for bacterial growth. A sensitive and specific laboratory test that can identify sepsis at an early stage would be of great benefit in the management of neonates who are suspected of sepsis. Current study aims at identifying role of Procalcitonin in diagnosis of Late Onset Sepsis in neonates. Procalcitonin is physiologically elevated in the first 3 days of life and concentration normalizes by day 4 of life, hence it is utilized in diagnosis of late onset sepsis in neonates [6].

Methodology

Type of study: Prospective observational study.

Place of study: NICU, SIMS, Shimoga.

Duration of study: November 2020-November 2021.

Inclusion criteria

All inborn babies delivered by vaginal/caesarean delivery admitted in NICU from November 2020-November 2021 with at least 3 symptoms and signs of LOS.

Exclusion criteria

- Babies with clinical features of sepsis before 72 hours of life.
- HIE stage III.
- Neonate with surgical problem.
- Babies with life threatening congenital anomalies.
- Extramural babies.
- Not consenting.

Sample size

Study conducted by Athiraman N *et al*. showed that the sensitivity of PCT was found to be 68%and that of CRP was 56%. Expecting similar results at 10%precision sample sizes of 95 was calculated for PCT using master software v 2.0 developed by CMC Vellore. Therefore a minimum sample of 95 neonates of suspected late onset neonatal sepsis were recruited consecutively for the study with minimum 30 blood culture proven sepsis.

Method of collection of data

A written and informed consent was obtained in a language well understood by the parents/legal guardian before submitting a neonate to investigations.

A detailed history, general physical examination and systemic examination findings at the time of diagnosis of clinically suspected sepsis, was recorded on a proforma.

Appropriate investigations,including sepsis screen and Procalcitonin was carried out, as per our NICU protocol and was followed up and results recorded on the proforma.

Sample collection

1) Screening Hemogram-0.5 ml of blood.
2) Blood culture-0.5 ml blood collected by sterile methods and sent for blood culture.
3) CRP-0.5 ml of venous blood collected from the peripheral vein and CRP is determined by immunonephelometric method.
4) Procalcitonin-2 ml blood drawn from peripheral vein and centrifuged within 30 minutes of collection and serum stored at-20 degree before analysis. Procalcitonin is measured by quantitative Chemiluminescence method.

Results

Table 1: Sepsis screen

Sepsis screen	No of respondents	% of respondents
Positive	83	64.84
Negative	45	35.16
Total	128	100.00

Of 128 clinically suspected late onset sepsis, 83 (64.84%) were septic screen positive, while 45 (35.16%) were screen negative.

Table 2: Sepsis types

Status of sepsis	No of respondents	% of respondents
Proven sepsis	42	32.81
Probable sepsis	41	32.03
No Sepsis	45	35.16
Total	128	100.00

Of 128 clinically suspected late onset sepsis, 42 (32.81%) had proven sepsis, 41 (32.03%) had probable sepsis and 45 (35.16%) had no sepsis.

Table 3: Procalcitonin levels

Procalcitonin	No of respondents	% of respondents
Positive (>=2.0 ng/ml)	75	58.59
Negative (<2.0 ng/ml)	53	41.41
Total	128	100.00

Of 128 clinically suspected late onset sepsis, 75 (58.59%) had PCT >2ng/mL, while 53 (41.4%) had PCT <2ng/mL.

Table 4: Mean Procalcitonin levels in sepsis groups

Status of sepsis	Mean	Std.Dev.	Sum of ranks
Proven sepsis	19.20	25.54	3383.5
Probable sepsis	13.34	16.50	3192
No sepsis	1.71	3.48	1680.5
Total	11.18	18.85	
P-value	0.0001*		

Mean procalcitonin levels was 19.2 ng/ml, 13.34 ng/ml and 1.71 ng/ml in proven sepsis, probable sepsis and no sepsis group respectively.

Table 5: Association between Procalcitonin and shock

Pro-calcitonin	Without shock	%	With Shock	%	Total	%
Positive (>=2.0ng/ml)	55	73.33	20	26.67	75	58.59
Negative (<2.0ng/ml)	46	86.79	7	13.21	53	41.41
Total	101	78.91	27	21.09	128	100.00
Chi-square= 3.3801 P = 0.0662						

Among 75 neonates with PCT > 2ng/ml, 20 (26.67%) had shock while 55 (73.33%) did not have shock.
Among 53 neonates with PCT < 2ng/ml, 7 (13.21%) had shock and 46 (86.79%) did not have shock.
The association between Procalcitonin and presence of shock is not significant as p value is >0.05.

Table 6: Association between Procalcitonin and Mechanical ventilation

Pro-calcitonin 2 test	Without MV	%	With MV	%	Total	%
Positive (>=2.0 ng/ml)	58	77.33	17	22.67	75	58.59
Negative (<2.0 ng/ml)	49	92.45	4	7.55	53	41.41
Total	107	83.59	21	16.41	128	100.00
Chi-square= 5.1762 P = 0.0230						

Among 75 neonates with PCT > 2ng/ml, 17 (22.67%) were mechanically ventilated, while 58 (77.33%) did not require mechanical ventilation.
Among 53 neonates with PCT < 2ng/ml, 49 (7.55%) were mechanically ventilated and 46 (92.45%) did not require mechanical ventilation.
The association between Procalcitonin and need for mechanical ventilation is not significant as p value is >0.05.

Table 7: Association between Procalcitonin and mortality

Pro-calcitonin	Survived	%	Death	%	Total	%
Positive (>=2.0)	60	80.00	15	20.00	75	58.59
Negative (<2.0)	50	94.34	3	5.66	53	41.41
Total	110	85.94	18	14.06	128	100.00
Chi-square= 5.2841 P = 0.0220*						

Out of 75 babies with PCT >2ng/ml, 80% survived while 20% expired Out of 53 babies with PCT <2ng/ml, 94.34% survived and 5.66% expired the association between Procalcitonin and mortality is significant.

Table 8: Sensitivity, Specificity, PPV and NPV of Procalcitonin

	Value	95% CI
Sensitivity	78.57%	63.19% to 89.70%
Specificity	77.78%	62.91% to 88.80%
Positive predictive value	76.74%	65.13% to 85.36%
Negative predictive value	79.55%	68.10% to 87.63%

Discussion

Of 42 babies with culture positivity, 76.19% of babies were born <37 weeks, while only 23.8% of babies were more than 37weeks. This result has confirmed well known observations the prematurity and low birth are important risk factors for sepsis.
This finding is comparable with studies by Tallur*et al*. and Raghavan *et al*. While in other studies higher incidence of sepsis in term babies was attributed to population characteristics.
The study also showed that male neonates are at increased risk of sepsis and sepsis related mortality. Of 42 culture positive babies 57.14% of neonates were males and 42.85% of neonates were females. This finding is comparable with other studies. The male preponderance in neonatal septicaemia may be linked to the X linked immunoregulatory gene resulting in hosts susceptibility to the infection in males.
The most common clinical presentation were apnea, shock, bleeding tendencies (petechiae,

altered NG aspirates), poor feeding, irritability. In babies with shock and scleremarate mortality was high (significant association with $p<0.05$).
LOS can have varied presentations.

Table 9: Comparative studies of Procalcitonin in evaluation of neonatal sepsis

Sl.No.	Author	Parameters studied	Sensitivity	Specificity	PPV	NPV
1.	Gendrel*et al.*(1996)[7]	PCT CRP	86% 46%	100% 97%		
2.	Blommendahl*et al.*(2002)[8]	PCT CRP	77% 58%	84% 64%		
3.	Cheisa*et al.*(2003)[9]	CRP PCT	89% 74%	87% 89%		
4.	Monneret*et al.* [10]	IL-6 PCT CRP	79% 86% 46%	95% 100% 97%		
5.	Lapillone*et al.*(1998)[11]	PCT CRP	84% 28%	91% 97%		
6.	Enguix*et al.*(2001)[12]	PCT CRP	99% 96%	89% 84%		
	Present study	PCT	78.57%	77.78%	76.74%	79.55%

Sensitivity, specificity, Positive and negative predictive value of PCT in disgnosis of LOS at cut off value of 2ng/ml was 78.57%, 77.78%, 76.74%, 79.55% respectively.

Conclusion

Neonatal sepsis is a common disease of newborn with non-specific Symptomatology and difficulty in the diagnosis. Early and prompt detection and appropriate treatment of neonatal sepsis can significantly reduce the mortality and morbidity. Blood culture is the gold standard for diagnosing neonatal sepsis but requires 48-72hrs in obtaining results. Currently available investigations diagnosing neonatal sepsis require long time in obtaining results hence there is a dire need of early marker of neonatal sepsis. Procalcitonin can be detected 6-12 hours after the infectious insult and its levels also correlates with the degree of insult. It can also thus be used to prognosticate the neonate. It has a high sensitivity which is related to its rapid response time which is much faster than that of CRP and should thus help to gain time for diagnosis. The amount of blood required for determination of PCT is very small and the results can be available within 1 hour. This approach should result in earlier recognition of sepsis and initiation of adequate antibiotic therapy in all neonates with sepsis and thus improve their outcome and prognosis. More larger multicentric studies are required for further studies of these markers which will reduce the rate of unnecessary antibiotic therapy.

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