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Original Research Article

ELEVATED CENTRAL-PERIPHERAL TEMPERATURE DIFFERENCE IN EARLY DETECTION OF LATE-ONSET SEPSIS IN PRETERM LOW BIRTH WEIGHT NEW-BORN; OBSERVATIONAL PROSPECTIVE STUDY

Sujay G Patil[1], Pankaj Pradeep Panyang[2], Nabanita Das[3], Pranabjit Biswanath[4], Manab Narayan Baruah[5]

[1]Senior Resident, Department of Pediatrics, Jorhat Medical College and Hospital, Jorhat affiliated to Srimanta Sankardeva University of Health Sciences, Guwahati, Assam, India.
[2]Assistant Professor, Department of Pediatrics, Jorhat Medical College and Hospital, Jorhat affiliated to Srimanta Sankardeva University of Health Sciences, Guwahati, Assam, India.
[3]Assistant Professor, Department of Pediatrics, Jorhat Medical College and Hospital, Jorhat affiliated to Srimanta Sankardeva University of Health Sciences, Guwahati, Assam, India.
[4]Professor and Head of Department, Department of Pediatrics, Jorhat Medical College and Hospital, Jorhat affiliated to Srimanta Sankardeva University of Health Sciences, Guwahati, Assam, India.

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Corresponding Author:
Dr. Manab Narayan Baruah,
Email: drmnbaruah@gmail.com
ORCID: 0000-0002-1263-3142

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Abstract

Background: Early diagnosis of Late onset sepsis (LOS) remains a clinical challenge in preterm neonates. Clinical signs of systemic infection are non-specific and sometimes overlap with physiological characteristics. Previous studies have investigated that an increase of Central-peripheral temperature difference (c-pTd) >2°C showed high sensitivity and specificity in early diagnosis of LOS. **Aim:** To assess the role of elevated c-pTd as an early clinical marker in diagnosing LOS in Preterm Low birth weight (LBW) new-born. **Materials and Methods:** A prospective observational study conducted in the Neonatal intensive care unit (NICU) of Jorhat Medical College and Hospital (JMCH). c-pTd of all admitted neonates fulfilling inclusion criteria was recorded. In case of elevated c-pTd (>2°C) LOS evaluation was done. The diagnostic accuracy of c-pTd in early diagnosis of LOS was assessed along with sensitivity, specificity, Positive predictive value (PPV), and Negative predictive value (NPV). **Results:** 165 neonates were included in the study out of which 105 were evaluated for LOS. 60 cases were left out of the study because the neonates did not develop any signs of LOS or elevated c-pTd. c-pTd was elevated >2°C in N=79 (76.19%) cases with diagnosed LOS. Elevated c-pTd showed a sensitivity of 90.8%, specificity of 65.38%, PPV of 89.77%, NPV of 68% and diagnostic accuracy of 91.42% in early diagnosis of LOS (p-value<0.05) **Conclusion:** Based on the result of current study elevated c-pTd >2°C can be considered an early clinical marker of LOS in preterm LBW neonates.

INTRODUCTION

Sepsis is one of the common causes of neonatal morbidity and mortality; it is responsible for about 30-50% of the total neonatal mortality in low and middle-income countries.[1] Neonatal sepsis is defined as a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first 4 weeks of life.[2] It can be broadly classified based on onset into Early-Onset Sepsis (EOS) (<72 hours of life) and Late-Onset Sepsis (LOS) (>72 hours of life).[3] It comprises of various systemic infections of the new-born such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Since the early 1980s, epidemiological studies have observed a drastic reduction in EOS, may be due to advances in obstetric care.[4] Meanwhile, the incidence of LOS has increased in parallel with the improved survival of premature infants, especially in Very Low Birth Weight (VLBW), indicating the role of hospitalization and life-sustaining medical devices.[5]

Compared to the enormous number of studies establishing the usefulness of laboratory tests for early detection of LOS[6-10] only a few studies have investigated clinical signs as early markers of LOS.[11-15] Early diagnosis of LOS remains a clinical

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challenge. Clinical signs of systemic infection are non-specific and sometimes overlap the physiologic characters of a preterm neonates. Previous studies have shown a relation between thermoregulatory alterations and sepsis in new-born infants with normal temperatures. It has been observed that Central peripheral temperature difference (c-pTd) monitoring is a feasible, non-invasive, and simple tool which may be applied in everyday practice. An increase of >2°C showed high sensitivity and specificity for the diagnosis of LOS[11,12]

Therefore, the present study is done to assess the role of the elevated c-pTd in the early diagnosis of LOS and to know clinical findings consistent with LOS.

Aims/ Objectives

1. To assess the role of elevated c-pTd as an early clinical marker in diagnosis of LOS in Preterm, LBW new-born.
2. To assess the relationship between elevated c-pTd with clinical findings consistent with LOS.

MATERIALS AND METHODS

Study Type: A hospital-based observational prospective study.

Study Period: The study was conducted from June 2020 to May 2021 over a period of 1 year after obtaining ethical clearance from Institutional Ethics Committee.

Study Setting: In the Neonatal Intensive Care Unit (NICU), Department of Pediatrics, Jorhat Medical College and Hospital (JMCH), Jorhat.

Inclusion Criteria

All preterm new-born (Less than 37 completed weeks or 259 completed days of gestation) with Low birth weight <2500 gm admitted in the NICU of JMCH.

Exclusion Criteria

- Term new-born (>37 weeks gestation).
- Birth weight >2500 gm.
- Preterm with a congenital anomaly.
- Preterm with severe birth asphyxia.
- Preterm diagnosed with early onset sepsis.
- Preterm with risk factors for early onset sepsis.

Study Scheme

- ✓ On admission into NICU, the preterm was placed in the radiant warmer.
- ✓ Minimal handling with nesting protocols were followed.
- ✓ A servo controlled thermal probe was placed over right upper quadrant of abdomen of the infant with a piece of self-adhesive paper tape.
- ✓ The radiant warmer temperature was adjusted in real time using the minimum necessary to achieve a central temperature of 36.5°C – 37.5°C.
- ✓ The ambient room temperature of NICU was measured using a digital thermometer maintained between 25-28°C with relative humidity of 30-60 %.
- ✓ In case of ventilatory assistance, the gas supplied was heated to 37°C with a relative humidity near 100 %.
- ✓ Central and peripheral temperature of all admitted newborns fulfilling the inclusion criteria was recorded every 2 hrs on a daily chart specifically designed for this purpose until the temperature reading is constant for at least 3 mins with an accuracy of up to ± 0.1°C by the resident doctor on duty.
- ✓ Peripheral temperature was recorded using the same thermal probe used for central temperature monitoring which will be placed on the sole of infant until the temperature reading is constant for at least 3 mins.
- ✓ Temperature monitoring was done from the day of admission of the neonate till the time the neonate is evaluated for LOS.
- ✓ In case of elevated c-pTd (>2°C) at least 3 readings are taken 5 mins apart before proceeding to LOS evaluation and any associated clinical signs/symptoms are noted.

Procedures and Collection of Data

In admitted preterm LBW New-born (>72 hours age) LOS workout was performed with suspicion of sepsis, i.e.

1. Preterm with central-peripheral temperature alteration (c-pTd >2°C) and if any associated clinical signs or symptoms.
2. Preterm with at least two clinical signs or symptoms suggestive of sepsis with or without Central-peripheral temperature alteration.

Intravascular volume depletion, a major cause of circulatory symptoms in preterm infants, usually presents with prolonged Capillary Refill Time (CRT >3secs), low pulse volume and tachycardia (Heart rate >160 bpm). It was ruled out by administration of 10 ml/kg normal saline intravenously. If symptoms persist for >30 mins after volume therapy, LOS workout was done.

Neonates who did not fulfil the above criteria were not evaluated for LOS.

Initial LOS workout includes sepsis screen (TC, ANC, CRP, Micro ESR and Immature neutrophil ratio), blood culture, cerebrospinal fluid (CSF) culture in patients with hemodynamic stability, and urine culture (if urinary tract infection was suspected).

In cases with suspected LOS:

- ✓ The findings of clinical signs/symptoms, Sepsis screen parameters and C/S reports were compared with elevated c-pTd at the time of LOS evaluation.
- ✓ Two post graduate trainees established the final diagnosis of – No LOS/ Clinical-LOS/ Laboratory-proven LOS (At least two parameters of sepsis screen positive)/ Culture-proven LOS.
- ✓ **No LOS** was defined as preterm LBW new-born who were evaluated for LOS, but there were no deranged laboratory parameters, no

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growth in culture and subsequent clinical course not compatible with LOS.

- ✓ **Clinical LOS** was defined as preterm LBW new-born who were evaluated for LOS, but there were no deranged laboratory parameters, no growth in culture and subsequent clinical course compatible with LOS.
- ✓ **Laboratory-diagnosed LOS** was defined as preterm LBW new-born who were evaluated for LOS, with deranged laboratory parameters, no growth in culture.
- ✓ **Culture-proven LOS** was defined as preterm LBW new-born who were evaluated for LOS, with a positive growth in culture.

Statistical Analysis

- ✓ Data was entered into MS excel. Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Chi-square test has been used to find the significance (p-value) of study parameters on categorical scale between two or more groups.
- ✓ The diagnostic accuracy of thermal gradient alteration for Clinical LOS, Laboratory-diagnosed LOS and Culture-proven LOS was assessed by the sensitivity, specificity, PPV and NPV.

Ethics Committee

IRB name: Institutional Ethics Committee (IEC) of Jorhat medical college and hospital
IRB no: 5256

RESULTS

Table I: Relation between elevated c-pTd and LOS (N=105)

c-pTd	No. of cases		P-value	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
	LOS +	LOS -						
>2°C	79	9	<0.05	90.8%	65.38%	89.77%	68%	91.42%
	75.23%	8.57%						
<2°C	8	17						
	7.61%	16.19%						

Table II: Clinical signs/symptoms during the time of evaluation for LOS (N=105)

Clinical features	No. of cases		P-value
	c-pTd +	c-pTd -	
CRT>3 secs	23	4	>0.05
	21.9%	3.8%	
Tachycardia (HR>160 bpm)	34	7	>0.05
	32.38%	6.66%	
Bradycardia (HR<100 bpm)	13	5	>0.05
	12.38%	4.76%	
Tachypnoea (RR>60/min)	27	8	**<0.05**
	25.71%	7.61%	
Lethargy	23	16	**<0.05**
	21.9%	15.23%	
Apnoea	10	1	>0.05
	9.52%	0.95%	
Seizure	8	0	>0.05
	7.61%	0%	
Feed intolerance	19	12	**<0.05**
	18.09%	11.42%	
Mottling	5	1	>0.05
	4.76%	0.95%	
Vomiting	6	4	>0.05
	5.7%	3.8%	

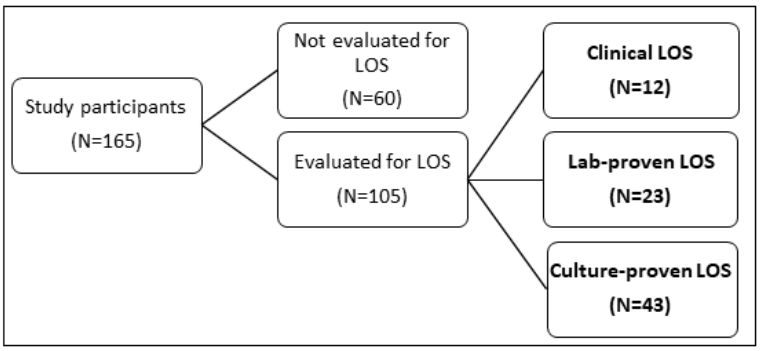

Figure 1

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As per Figure No. I, 165 Preterm LBW neonates were included in the study over a study period of one year from June 2020 to May 2021, out of which 105 were evaluated for LOS. 60 cases were left out of the study because the neonates did not develop any signs of LOS or elevated c-pTd (>2℃) during their NICU stay. The mean gestational age was 33.24 ± 1.431 (28 wks -36 wks) and mean birth weight was 1.5871 ± 0.25134 (1kg -2.1 kg). The mean duration of NICU stay was 13.23 ± 8.02 days (4 to 41). c-pTd was elevated >2℃ in 79 (76.19%) cases and was <2℃ in 26 (23.8%) cases at the time of evaluation of LOS. In the present study population, final diagnosis for cases evaluated for LOS include No-LOS (N=27) (25.7%), Clinical-LOS (N=12) (11.4%), Laboratory-diagnosed LOS (N=23) (21.9%) and Culture-proven LOS (N=43) (41%). Incidence of LOS was more in males N=44 (41.9%) compared to females N=35 (33.33%) as mentioned in Figure No. I.

Blood culture was positive in a total of 43 cases in the present study population with Klebsiella pneumonia (N=15) being the most common isolated pathogen accounting for 34.88%, followed by Staphylococcus aureus (N=12), Non-albicans candida (N=10) and Escherichia coli (N=6) with an overall culture positivity rate of 40.95%. The overall outcome of the study shows that, 98 cases (93.33%) were discharged, 6 cases (5.7%) died and 1 case (0.95%) was referred and hence a case fatality rate of 5.7% was observed.

Analysis of c-pTd and LOS as final diagnosis show that 79 cases (75.23%) diagnosed with LOS had an elevated c-pTd and 8 cases (7.61%) diagnosed with LOS did not have an elevated c-pTd. Overall, c-pTd has a sensitivity of 90.8%, specificity of 65.38%, PPV of 89.77%, NPV of 68% and a diagnostic accuracy of 91.42% with p-value of <0.05 which is statistically significant as mentioned in Table No. I.

In the present study population, clinical signs and symptoms of Tachycardia (32.38%), tachypnoea (25.71%), lethargy (21.9%), CRT>3secs (21.9%), feed intolerance (18.09%), bradycardia (12.38%), seizure (7.61%), vomiting (5.7%) and mottling (4.76%) were noted with elevated c-pTd at the time of LOS evaluation. Only features of **tachypnoea, lethargy and feed intolerance** (p-value- **<0.05**) were statistically significant as mentioned in Table No. II.

DISCUSSION

Table III: Comparative analysis of elevated c-pTd and LOS

	Jos é Luis Leante-Castellanos *et al* [12] **(2012) (N=31)**		**Ussat M *et al.* (2015)** [11] **(N=67)**		**Present study (N=105)**		
Temperature measurement							
Central	Axillary		Chest/ Back bed surface		Upper right quadrant of abdomen		
Peripheral	Sole		Peripheral limb		Sole		
Diagnosed LOS	13		39		79		
	Prov- LOS	Clin- LOS	Prov- LOS	Clin- LOS	Prov- LOS	Clin- LOS	Lab-prov LOS
	11	2	20	19	43	12	23
c-pTd value in Septicemia (Mean)	3.6℃		>2℃		2.812 ± 0.8889 ℃ (1℃-5℃)		
c-pTd sensitivity	90.9%		Prov-LOS*	84%	90.8%*		
			Clin-LOS*	65%			
c-pTd specificity	90%		Prov-LOS*	86%	65.38%*		
			Clin-LOS*	86%			
c-pTd PPV	83.3%		-		89.77%*		
c-pTd NPV	94.7%		-		68%*		
Diagnostic accuracy	-		-		91.42%*		
*Statistically significant (p-value <0.05)							

Table IV: Comparative analysis of associated signs/symptoms with elevated c-pTd

	Jos é Luis Leante-Castellanos *et al* (2012) [12]		**Ussat M *et al.* (2015)** [11]			**Present study**	
Associated clinical signs/symptoms	Apnoea	N=6 (54.5%)	Pallor	Clin-LOS	N=19 (95%)	Tachycardia	N=34 (32.38%)
				Prov-LOS	N=18 (95%)		
	Pallor	N=3 (27.3%)	CRT> 2 secs*	Clin-LOS	N=12 (60%)	Tachypnoea*	N=27 (25.71%)
	Lethargy and hypotonia	N=3 (27.3%)		Prov-LOS	N=12 (63%)		
	Feed intolerance	N=1 (9.1%)	Lethargy	Clin-LOS	N=17 (85%)	Lethargy*	N=23 (21.9%)
				Prov-LOS	N=13 (68%)		
	Hyperglycaemia	N=1 (9.1%)	Tachycardia*	Clin-LOS	N=7 (35%)	CRT>3 secs	N=23 (21.9%)
				Prov-LOS	N=13 (68%)		
* Statistically significant (p-value <0.05)							

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Table V: Comparative analysis of individual diagnose

Elevated c-pTd and LOS	P-value	No. of cases with elevated c-pTd	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Clinical LOS	<0.05	11	91.6%	65.38%	55%	94.44%	73.68%
Laboratory proven LOS	<0.05	20	86.95%	65.38%	68.96%	85%	75.51%
Culture proven LOS	<0.05	40	93.02%	65.38%	81.63%	85%	82.6%

Late-Onset neonatal sepsis (LOS) is a common complication of prolonged admission to the NICU following preterm birth. The risk of nosocomial or healthcare-associated infections (HAI's) is high, due to intrinsic risk factors of the premature neonate such as the fragility of the skin which is thin and delicate (provide minimal protection), use of invasive monitoring, prolonged NICU stay and need for ventilator support, in addition to a poorly developed immune system.

Early diagnosis of LOS remains a clinical challenge. Clinical signs of systemic infection are non-specific and sometimes overlap the physiologic characters of a premature neonate. An association between neonatal sepsis and an increase in a central-peripheral temperature gradient has been observed in four studies previously.[11-14] However, the value of this clinical sign for early diagnosis of late-onset neonatal sepsis has not been previously assessed in prospective studies with a large number of study participants. In the present study, monitoring of the c-pTd was possible in all participants and was easy to perform and interpret.

Overall, the present study showed that temperature difference as defined in the protocol was strongly associated with the imminent occurrence of LOS. c-pTd has a Sensitivity of 90.8%, Specificity of 65.38%, PPV of 89.77%, NPV of 68% and an overall diagnostic accuracy of 91.42% in early detection of LOS in Preterm Low Birth Weight New-born with statistical significance (p-value <0.05).

These study findings are closely comparable to the studies conducted by Jos é Luis Leante-Castellanos *et al.* (2012)[12] and Ussat M *et al.* (2015).[11]

Leante-Castellanos *et al.*[12] observed sensitivity of 90.9%, specificity of 90%, PPV of 83.3% and NPV of 94.7%. However statistical significance was not known.

Ussat M *et al.*[11] analyzed 67 infants with 83 episodes of suspected infection. Clin-LOS was diagnosed in 20 of 83 (24%) episodes and Prov-LOS group included 19 episodes (23%). For Clin-LOS, the optimal discrimination point was 2.05 °C, with a sensitivity of 65% and specificity of 86% and for Prov-LOS, the optimal discrimination point was again 2.05 °C, with a sensitivity of 84% and specificity of 86%. The data was statistically significant as mentioned in the Table No. III.

Jos é Luis Leante-Castellanos *et al.*[12] observed that clinical signs and symptoms, excluding thermal gradient alteration were apnoeic episodes in six (54.5 %) cases, pale or greyish skin in three (27.3 %), lethargy and hypotonia in three (27.3 %), feed intolerance in one (9.1 %), and hyperglycaemia in one (9.1 %).

Ussat M *et al.*[11] observed that elevated c-pTd had statistical significance in both Clin-LOS (N=15) and Prov-LOS (N=16) and even prolonged CRT had p-value <0.05 in both Clin-LOS (N=12) and Prov-LOS (N=12). In addition, Tachycardia had a statistical significance in Prov-LOS (N=13) as mentioned in Table No. IV.

Culture proven sepsis had better sensitivity, specificity, PPV, NPV and diagnostic accuracy followed by Clinical LOS and Laboratory diagnosed LOS as mentioned in Table No. V.

CONCLUSION

This observational prospective study titled: "***Elevated Central-Peripheral Temperature Difference in early detection of Late-Onset Sepsis in Preterm Low Birth Weight New-born"*** was done to know the diagnostic value of Central peripheral temperature difference (c-pTd) in early diagnosis of Late-Onset Sepsis (LOS) in Preterm Low Birth Weight newborns and also for the assessment of clinical markers and deranged laboratory parameters that may contribute to early diagnosis.

The present study was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Jorhat Medical College and Hospital (JMCH), Jorhat during a study period of 1 year from June 2020 to May 2021. In the present study population, c-pTd was elevated >2°C in 79 (76.19%) cases and was <2°C in 26 (23.8%) cases at the time of evaluation of LOS. Final diagnosis for cases evaluated for LOS were No LOS (N=27) (25.7%), Clinical LOS (N=12) (11.4%), Laboratory diagnosed LOS (N=23) (21.9%) and Culture proven LOS (N=43) (41%). Culture proven sepsis had better sensitivity, specificity, PPV, NPV, diagnostic accuracy followed by Clinical LOS and Laboratory diagnosed LOS associated with elevated c-pTd. Statistical significance was established in all diagnose. Clinical signs and symptoms of tachypnoea, lethargy and feed intolerance were statistically significant. Blood culture positivity rate was 40.95% with Klebsiella pneumoniae being the most common isolated pathogen.

The overall, outcome of the study includes, 98 cases (93.33%) being discharged, 6 cases (5.7%) died and 1 case (0.95%) referred. And hence a case fatality rate of 5.7% was noted in the present study.

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Clinical diagnosis of sepsis is difficult, since, symptoms and signs are not specific and dramatic worsening of clinical conditions can supervene quickly long before blood cultures results are available even in asymptomatic new-born infants. Early recognition and appropriate goal-directed therapy remain the foundations for successful treatment.

Based on the results of the present study, it can be concluded that elevated central-peripheral temperature gradient >2℃ can be considered as an early clinical marker of Late-Onset neonatal sepsis in preterm Low Birth Weight neonates. It has a sensitivity of 90.8%, specificity of 65.38%, PPV of 89.77%, NPV of 68% and overall diagnostic accuracy of 91.42%.

LIMITATIONS OF THE STUDY

- The sample size is small
- Correlation of elevated cpT-d with laboratory findings is inconsistent with previous studies.
- Previous studies were conducted in incubators with constant monitoring of air temperature and humidity which is limited when the new-born is cared under radiant warmers.
- All non-invasive measurements have limitations as to their accuracy and interpretability, and c-pTd is no exception.

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