Egyptian Pediatric Association Gazette

RESEARCH Open Access

Comparative efficacy of micro-erythrocyte sedimentation rate (m-ESR) and C-reactive protein (CRP) as a neonatal septic screening marker—a single-center, retrospective observational study

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Abstract

Background Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in neonatal period. Most of neonatal sepsis-related morbidity and mortality can be prevented by early diagnosis and treatment with appropriate antimicrobial agents. Micro-erythrocyte sedimentation rate (m-ESR) is a simple, inexpensive, and rapid screening test for neonatal sepsis that can be done even in resource limited setups.

Objectives To compare the efficacy of m-ESR with C-reactive protein (CRP) as a screening tool in neonatal sepsis.

Methodology A retrospective chart-based analysis was done in division of neonatology, of our tertiary care hospital over a period of 21 months. A total of 202 suspected cases of neonatal sepsis with documented CRP and micro-ESR values were included. We evaluated the role of micro-ESR as a screening tool in neonatal sepsis in comparison with CRP. The validity and reliability of micro-ESR in comparison to CRP were estimated and its sensitivity, specificity, positive, and negative predictive value to diagnose sepsis were calculated.

Results There was a significant correlation between micro-ESR and CRP with a moderate degree of agreement, especially in 'late onset sepsis' group. The overall sensitivity, specificity, positive predictive value and negative predictive value of micro-ESR were 67%, 84%, 58%, and 89% respectively.

Conclusion Micro-ESR is a simple, inexpensive test comparable to CRP in screening for neonatal sepsis.

Keywords C-reactive protein, Micro-ESR, Neonatal sepsis, Screening test

Background

Neonatal sepsis is defined as a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in neonatal period [1]. It is a global health challenge with its incidence ranging between 3.5 and 38 per 1000 live births globally [2]. Neonatal sepsis is associated with high mortality around 19 to 38% in India [3]. Most of the neonatal sepsis-related

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morbidity and mortality can be prevented by early diagnosis and treatment with appropriate antimicrobial agents.

The clinical diagnosis of neonatal sepsis is still a challenge due to non-specific signs and symptoms. This difficulty is further enhanced by the lack of 100% sensitive and specific tests for laboratory diagnosis of neonatal sepsis [4]. A positive blood culture is considered as gold standard in diagnosis of neonatal sepsis but it has its own demerits including long turn- around time of about 48–72 h, low yield (30–70%), need for expensive equipment, unavailability in rural areas and resource limited setups [5]. Other disadvantages of blood culture also include low sensitivity of this test and false negative results due to less blood collected from neonates and prior use of antibiotics [6].

Common laboratory tests currently used for neonatal sepsis screening include white blood count (WBC), differential count (DC), absolute neutrophil count (ANC), immature/total neutrophil (I/T) ratio, and C-reactive protein (CRP). However, these traditional sepsis screening markers have low sensitivity and specificity, often falsely positive in other neonatal conditions such as asphyxia, meconium aspiration, and prolonged rupture of membrane. There are many novel biomarkers proposed to predict neonatal sepsis like procalcitonin, IL 6, IL-8, procalcitonin, and CD11b, but are not routinely used due to many factors including lack of definite evidence, high cost and not freely available in most of the laboratories [7].

Micro-ESR is widely used as screening tests for neonatal sepsis and has for long been recognized as a useful investigative tool [8]. It is a simple bedside test done with heparizined capillary tube and can be done easily even in remote, resource limited and primary care setups. Traditionally, the cut off for normal micro-ESR is taken as value of day of life plus 3 mm/h for neonates aged 0–14 days; and greater than 15 mm at the end of one hour for neonates aged 15–28 days [9]. However, very minimal data is available regarding its validity in neonatal sepsis. This study was done to evaluate the role of micro-ESR as a screening tool in neonatal sepsis and to compare micro-ESR with CRP values in neonatal sepsis.

Methods

This retrospective chart-based analysis was done in the division of neonatology, of our tertiary care hospital over a period of 21 months from August 2017 to May 2019. Institute ethical committee clearance was obtained before commencement. All suspected cases of neonatal sepsis with documented CRP and micro-ESR value in the case sheet were included for analysis. Cases with additional co-morbidities like preterm babies (Gestational age < 37 weeks), anemia (Hb < 10 gm%), polycythemia (Hb > 20 gm%), heart disease, major anomalies were excluded. Basic demographic and clinical details of the included cases like gestational age, birth weight, Apgar score, and mode of delivery were documented. All suspected cases were classified as either 'early onset neonatal sepsis' (EOS) or 'late onset neonatal sepsis' (LOS) based on the cut off of 72 h for clinical presentation [8]. All suspected cases of sepsis underwent blood sampling for micro-ESR and CRP estimation done at the same time.

Micro-ESR estimation method

A pre-heparinized capillary tube was used to measure micro-ESR. Blood was allowed to fill three-fourth of the length of capillary tube. One end was sealed and the capillary tube was then mounted on the wall with the sealed end down. The capillary tube is then allowed to stand for one hour. The fall of red cell column in noted down in millimeters (Fig. 1). Any value of more than age in days + 3 or > 15 at the end of one hour during neonatal period regardless of postnatal days is considered positive [4]. CRP level was estimated using particle-enhanced turbidimetric immunoassay method. A value of more than 10 mg/L was taken as positive.

Statistical analysis

Data was analyzed by SPSS version-26. The continuous variables were summarized as frequency and proportion. The association between categorical and continuous variables was assessed using independent *t* test and association between categorical variables was assessed using Chi-square test. The validity and reliability of micro-ESR was expressed as sensitivity, specificity, PPV, NNP. The agreement between CRP and micro-ESR was analyzed using Kappa statistics. The p value of < 0.05 were considered as statistically significant.

Results

A total of 202 case records were included for analysis after excluding the records with incomplete data and those who fulfilled exclusion criteria. Out of the 202 study participants 49 (24.2%) were CRP positive as shown in Table 1. A total of 23% of study participants had low birth weight. More than 80% of study participants had no distress at birth and 3.4% had severe distress. Assisted delivery/LSCS was mode of delivery in 50% of study participants. The median (IQR) age of study participants was 1 day (1–2 days) and 83% were early onset. The mean (SD) micro-ESR of CRP positive and CPR negative study participants are 5.4 (4.1) and 3.5 (3.1) mm at the end of one hour. Independent *t* test showed this difference in micro-ESR was statistically significant (p value < 0.001).

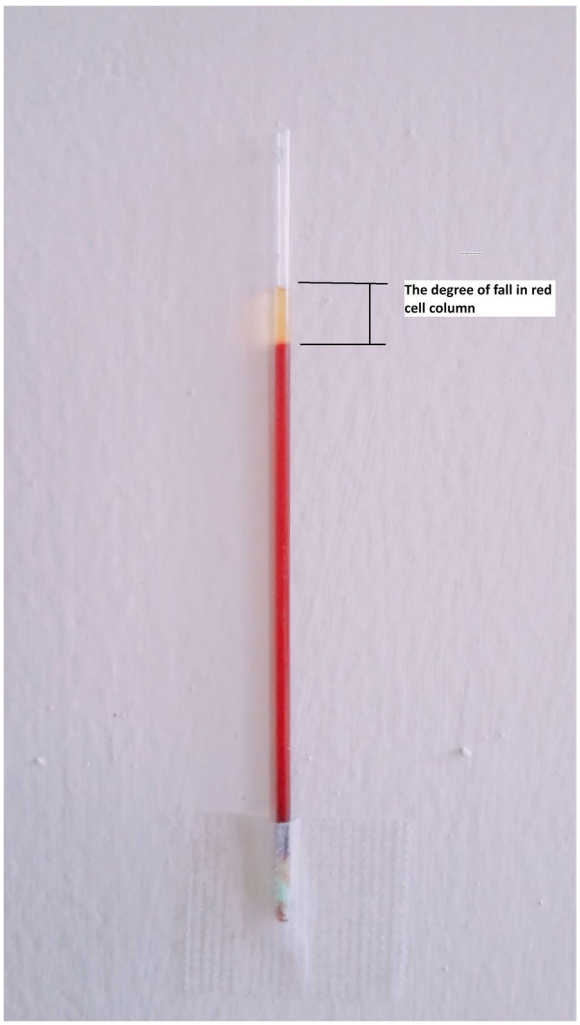

Fig. 1 A capillary tube mounted with anticoagulated blood for checking micro-ESR

Micro-ESR values more than 'age in days plus 3' was considered as positive. The comparison of micro-ESR values with CRP values is shown on Table 2. Among 153 CRP negative cases 24 (15.7%) showed elevated micro-ESR. The percent agreement between micro-ESR values with CRP values was 79.2%. Table 3 shows the comparison of micro-ESR values with CRP values among early and late onset sepsis group. The percent agreement between micro-ESR values with CRP values among early onset sepsis was 76.6% where among late onset sepsis percent agreement was 91%.

The overall sensitivity, specificity, positive predictive value, and negative predictive value for comparing micro-ESR with CRP was around 67%, 84%, 58%, and 89% respectively (Table 4). The overall accuracy of micro-ESR in diagnosing elevated CRP was 80%.

Table 1 Distribution of clinical parameters of the study participants

Parameter	Sub-groups	Frequency n (%) *N* = 202
Sepsis screening	CPR positive	49(24.2)
	CPR negative	153(75.7)
Birth weight	Low birth weight (< 2.5 kg)	47(23.2)
	Normal weight (≥ 2.5 kg)	155(76.7)
Apgar score 1	9≥	167(82.6)
	6–8	28(13.8)
	≤5	7(3.4)
Apgar score 5	9≥	194(96.0)
	6–8	8(4.0)
Mode of delivery	Spontaneous vaginal delivery	100(49.5)
	Assisted/LSCS delivery	102(50.5)
Sepsis	Early onset sepsis	167(82.6)
	Late onset sepsis	35(17.3)

Table 2 Comparison of micro-ESR values with CRP values

	CRP positive n(%)	CRP negative n(%)	Total n(%)
Micro ESR positive	33(56.1)	24(43.9)	57(28.2)
Micro ESR negative	16(11.7)	129(88.3)	145(71.8)
Total	49(24.7)	153(75.3)	202(100)

The overall kappa value was 0.48 this shows moderate agreement based on Landis and Koch interpretation of kappa value. The sensitivity and specificity of micro-ESR among the study participants with late onset sepsis (75%, 96%) was higher than early onset sepsis group (66%, 81%). The accuracy of micro-ESR is about 77% in early onset sepsis whereas the accuracy among late onset sepsis group increased to 94%. The kappa value was higher for study participants with late onset sepsis (0.72) compared to the study participants with early onset sepsis (0.44).

Discussion

Though neonatal sepsis is a common cause of morbidity and mortality among neonates, there is no single gold standard rapid screening test for diagnosing sepsis. Most of the available screening tests have limitations in terms of low sensitivity, specificity and positive predictive value. Micro-ESR is a simple, inexpensive screening test for neonatal sepsis that can be easily performed even in resource limited settings.

In our study, there was a moderate degree of agreement between micro-ESR and CRP in our study overall, but in LOS group, this agreement was strong. The overall sensitivity, specificity, positive predictive value and negative

Table 3 Comparison of micro-ESR values with CRP values among early and late onset group

	Early onset sepsis			Late onset sepsis		
	CRP positive n(%)	CRP negative n(%)	Total	CRP positive n(%)	CRP negative n(%)	Total n(%)
Micro-ESR positive	30(56.6)	23(43.4)	53(31.7)	3(75)	1(25)	4(11.4)
Micro-ESR negative	15(14.0)	99(86.0)	114(68.2)	1(3.2)	30(96.8)	31(88.6)
Total	45(27.5)	122(72.5)	167(100)	4(11.4)	31(88.6)	35(100)

Table 4 Validity and reliability indicators of micro-ESR values

Parameters	Overall percent (95% CI)	Early onset sepsis percent (95% CI)	Late onset sepsis percent (95% CI)
Sensitivity	67.3(53.4–78.8)	66.7(51.1–80.0)	75.0(19.4–99.3)
Specificity	84.3 (77.7–89.2)	81.2(73.1–87.5)	96.7(83.3–99.9)
Positive predictive value	57.9(44.9–69.8)	56.6(46.1–66.5)	75.0(28.68–95.7)
Negative predictive value	88.9(82.8–93.1)	86.8(81.2–90.9)	96.7(84.6–99.4)
Accuracy	80.2(74.0–85.4)	77.3(70.1–83.3)	94.3(80.8–99.3)
Kappa value	0.48(0.35–0.62)	0.44(0.28–0.59)	0.72(0.34–1)

predictive value of micro-ESR was 67%, 84%, 58%, and 89% respectively. The sensitivity and specificity of micro-ESR among the study participants with late onset was higher than early onset sepsis group. The overall accuracy of micro-ESR was about 80% and was observed to be higher in late onset group. Youden's index, the maximum potential effectiveness of a biomarker, is a common summary measure of the ROC curve, shows that micro-ESR can qualify as a good diagnostic test to detect or rule out neonatal sepsis.

A study of 50 cases of neonatal sepsis showed that CRP was positive in 58% of cases and another study showed elevated CRP in 47.14% of cases which was higher than our study [10–12]. CRP is an acute phase reactant whose serum levels are low in normal infants with a rapid rise after 12–24 h of infection and an immense increase as long as inflammation persists. This will be followed by immediate fall in serum levels of CRP as soon as inflammation subsides [13]. Its low sensitivity during early phases of neonatal sepsis is due to its delayed synthesis during inflammation and thus fails to be used as a screening test in early phases of neonatal sepsis [14]. Further, CRP was also found to be directly affected by the gestational age. It was found to lower in preterm newborns compared to the term neonates [14]. CRP values are also affected by non-infectious states like meconium aspiration, intraventricular hemorrhage, pneumothorax and necrotizing enterocolitis [13]. All these could affect the diagnosis of neonatal sepsis by using CRP as a screening test.

Micro-ESR can be compared to conventional ESR and its values are not affected by gestational age, birth weight except hematocrit values. It is negligibly elevated in non-infectious conditions unlike CRP. It is elevated within 24 h of infection and is not affected by the use of antibiotics [13]. Studies have showed that micro-ESR was elevated in 38.06% and 48% of EOS [15, 16]. In our study too micro-ESR was elevated in 23 cases of EOS who were CRP negative. The sensitivity and specificity of micro-ESR in one of the studies was 63.3% and 60% respectively [17]. A study showed that micro-ESR alone yielded a sensitivity of 96.9%, specificity of 90%, predictive value of 94% and proved to be a valuable screening test for sepsis in neonates [18]. In our study we found micro-ESR was highly specific but less sensitive. It was highly accurate in LOS compared to EOS. Thus, micro-ESR can be used as a screening test to rule out neonatal sepsis, especially the LOS. It is a cheap, simple test which can be useful in less developed countries where CRP can be performed.

Conclusion

Neonatal sepsis is often a diagnostic challenge and none of the single markers can confirm sepsis. Micro-ESR is a simple inexpensive test which can be used to rule out neonatal sepsis. Micro-ESR is comparable with CRP in diagnosing neonatal sepsis, especially in LOS and can be used as a screening test like CRP. Large-scale studies are needed to confirm our study findings before it can be recommended for routine screening of neonatal sepsis, especially in rural and resource limited setups.

Acknowledgements
None

Author's contributions
TA, AS, and VV conceived the study. TA, AS, VV, VS, and VKK collected data and performed statistical analysis. AS, VV, VS and VKK reviewed the literature and drafted the initial version of the manuscript which was critically reviewed by TA. All authors contributed to drafting of the manuscript and approved the final version of the manuscript. TA shall act as guarantor of the paper. The author(s) read and approved the final manuscript.

Funding
None.

Availability of data and materials
Yes.

Declarations

Ethics approval and consent to participate
Institute Ethics Committee of IGMCRI, Puducherry. (No. 26/IEC/IGMCRI/F-7/2019) Institutional Ethical Clearance approval–obtained. The need to obtain written informed consent was waived in view of retrospective design.

Consent for publication
Written informed consent was waived in view of retrospective design.

Competing interests
The authors declare that they have no competing interests.

Received: 7 March 2023 Accepted: 26 May 2023
Published online: 03 July 2023

References

1. Sankar MJ, Agarwal R, Deorari AK, Paul VK (2008) Sepsis in the newborn. Indian J Pediatr 75(3):67–72
2. Jasani B, Kannan S, Nanavati R, Gogtay NJ, Thatte U (2016) An audit of colistin use in neonatal sepsis from a tertiary care centre of a resource-limited country. Indian J Med Res 144(3):433–439. https://doi.org/10.4103/0971-5916.198682
3. Kolhe S, Mahajan P, Siddiqui S, Sharma A, Rai R (2017) Evaluation of efficacy of septic screen in diagnosis of early onset sepsis. Indian J Child Health 4(3):405–408
4. Kafle R, Yadav J, Gupta BK, Gupta BK (2019) Role of micro ESR in the evaluation of neonatal sepsis. J Universal Coll Med Sci 7(2):25–29. https://doi.org/10.3126/jucms.v7i2.27131
5. Bhat YR, Rao A (2010) The performance of haematological screening parameters and CRP in early onset neonatal infections. J Clin Diagn Res 4:3331–3336
6. Zakariya BP, Bhat BV, Harish BN, Arun Babu T, Joseph NM (2012) Risk factors and predictors of mortality in culture proven neonatal sepsis. Indian J Pediatr 79(3):358–361
7. Mally P, Xu J, Hendricks-Muñoz K (2014) Biomarkers for neonatal sepsis: recent developments. Res Rep Neonatology 4:157–168
8. Zakariya BP, Bhat V, Harish BN, ArunBabu T, Joseph NM (2011) Neonatal sepsis in a tertiary care hospital in South India: bacteriological profile and antibiotic sensitivity pattern. Indian J Pediatr 78(4):413–417. https://doi.org/10.1007/s12098-010-0314-8
9. West BA, Tabansi PN, Ugwu RO, Eneh AU (2012) The predictive value of micro-erythrocyte sedimentation rate in neonatal sepsis in a low resource country. Pediatr Therapeut S 2:002. https://doi.org/10.4172/2161-0665.S2-002
10. Khurram MSA, Naseem A, Prasad CND (2016) A comparative study of CBP, CRP, Micro ESR and blood culture in the diagnosis of neonatal septicemia. Int J Pediatr Res 3(7):529–535. https://doi.org/10.17511/ijpr.2016.i07.12
11. Mustafa S, Farooqui S, Waheed S and Mahmood K: Evaluation of Creactive protein as early indicator of blood culture positivity in neonates: Pak Journal Medical Science: January-March 2005; 21(1): 69-73.
12. Ghotaslou R, Ghorashi Z, Nahaei MR (2007) Klebsiella pneumonia in neonatal sepsis: A 3-year-study in the pediatric hospital of Tabriz, Iran: Jpn. J Infect Dis 60:126–128
13. Desai PP, Shah AN, Pandya T, Desai P, Pandya T (2014) C-reactive protein, immature to total neutrophil ratio and micro ESR in early diagnosis of neonatal sepsis. Int J Biomed Adv Res 5(8):364–366
14. Hofer N, Zacharias E, Müller W, Resch B (2012) An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology 102:25–36. https://doi.org/10.1159/000336629
15. Mudey GD, Tankhiwale NS, Mudey A (2011) Clinical profile and haematological indices of clinically diagnosed early neonatal septicaemia: a study conducted in teaching institute attached to rural hospital of Wardha district. Int J Curr Res Rev 3:04–10
16. Jaswal RS, Kaushal RK, Goel A, Pathania K. Role of C-reactive protein in deciding duration of antibiotic therapy in neonatal septicaemia: Indian Pediatrics 2003; 40: Page 880–883.
17. Walliullah SM, Islam MN, Siddika M, Hossain MA, Chowdhury AK (2009) Role of micro-ESR and I/T ratio in the early diagnosis of neonatal sepsis. Mymensingh Med J 18(1):56–61
18. Okolo AA, Scott-Emuakpor AB, Omene JA (1988) The diagnostic value of leukocyte indices and micro-erythrocyte sedimentation rate in neonatal infections. Trop Geogr Med 40(4):304–308

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