International Journal of Research in Medical Sciences
Pessar SA. Int J Res Med Sci. 2016 Nov;4(11):4938-4944
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20163795

Original Research Article

Evaluation of polymorphonuclear leukocyte elastase levels in neonatal sepsis

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Received: 02 September 2016
Accepted: 28 September 2016

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ABSTRACT

Background: Sepsis is an important cause of neonatal morbidity and mortality. In Egypt, A multi-center study reported that 45.9% of the neonates admitted to neonatal intensive care units (NICUs) were due to suspected neonatal sepsis. Proper management is not guaranteed due to nonspecific symptoms and signs especially at the onset of disease, delay of culture results and high rate of false negative results. Attempts have been made to use hematologic parameters, acute phase reactants and cytokine profiles for early and accurate diagnosis of neonatal sepsis; however, none was adequately sensitive or specific. Polymorphonuclear elastase (PMN-E) is a serine protease secreted during inflammatory diseases. The aim of the current study was to explore the reliability of PMN-E level for the diagnosis of neonatal sepsis and assess response to treatment in comparison to hematological parameters and C - reactive protein (CRP).
Methods: The study comprised 30 neonates with proven sepsis, 30 neonates as control group. Both groups were subjected to calculation of hematologic sepsis score (HSS), CRP measurement, blood culture and serum PMN-E levels, the latter was measured both at diagnosis and 6 days after treatment in sepsis group.
Results: Serum PMN-E levels were significantly higher in sepsis group (118.4±21.8) than in control group (57.9±27.9) and the best cut-off value was at 85 ng/ml with 97% sensitivity and 81% specificity, PMN-E levels also decreased significantly with response to treatment.
Conclusions: Raised PMN-E level was found to be a diagnostic and prognostic marker in neonates with sepsis comparable with CRP and HSS.

Keywords: CRP, I/T ratio, Neonatal sepsis, Hematologic scoring system, PMN elastase

INTRODUCTION

About four million deaths were estimated among neonates worldwide per year, of which 36% are due to infections and 40% of these deaths, caused by infections, occur in developing countries which make sepsis an important cause of morbidity and mortality between neonates in these countries.[1] Consequently, caregivers should maintain high suspicion for possibility of sepsis in neonates.[2]

Neonatal sepsis is categorized into early-onset sepsis (EOS) usually within 72 hours due to trans-placental or trans-cervical infection and late-onset sepsis (LOS) within 4-90 days due to acquisition of microorganisms from the surrounding environment.[3] Both microbial and host factors such as maternal, environmental, immunologic and genetic factors are involved in the pathogenesis of sepsis.[4]

In 2005, Neonatal sepsis was defined as a "systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection" by the International Pediatric Sepsis Consensus Conference. Sepsis is suspected when at least two of four criteria including fever, heart rate, respiratory rate and leukocytic

count is observed, one of the two being fever or leukocyte count.[5] In 2010, a list of seven clinical and six laboratory parameters defining neonatal sepsis were suggested by a group of European experts. However, it showed unacceptable predictive value, which together with low prevalence of the classic diagnostic criteria necessitates development and validation of a more reliable list of criteria for diagnosis of neonatal sepsis which should not only include clinical data but also laboratory parameters.[6-8]

Many laboratory parameters were used to predict sepsis in neonates and even formulated into a scoring system like that of Rodwell et al, who incorporated hematological parameters based on automated and differential counts.[9] Polymorphonuclear granulocytes are crucial components of the innate immune response during sepsis, contributing directly to antimicrobial killing via production of a range of antimicrobial peptides, proteases, oxidants and extrusion of neutrophil extracellular traps (NETs).[10]

NETs are complex structures composed of nuclear chromatin, histones, a variety of granular antimicrobial proteins and some cytoplasmic proteins.[11]

NETs are formed upon exposure of neutrophils to septic plasma, as well as direct contact with microbial pathogens.[12,13] Polymorphonuclear elastase (PMN-E) is released from azurophilic granules of polymorphs, assisting the formation of NETs via decondensation of nuclear chromatin, and it also resides within NETs along with other serine proteases that have antimicrobial properties.[14]

It plays also an important physiological function in degrading phagocytosed substances and facilitating diapedesis. Excessive amounts of free unbound elastase may result in degradation of the essential elements of the interstitium (elastin, collagen, proteoglycans) and decomposition of plasma proteins, proteinase inhibitors, blood coagulation factors, immunoglobulins, the basal membrane of renal glomeruli and the ciliary epithelium of the respiratory tract.[15-20] The aim of this study was to evaluate performance of PMN elastase in neonatal sepsis diagnosis and response to treatment.

METHODS

This case control study was performed on sixty neonates admitted to neonatal intensive care unit (NICU) of Ain Shams University Maternity Hospital.

Thirty neonates were admitted for suspected neonatal sepsis and thirty neonates for non-infectious causes (e.g. neonatal jaundice, hemorrhagic disease of newborn, infant of diabetic mother, prematurity without sepsis, congenital heart disease, intrauterine growth retardation and respiratory distress syndrome) to serve as control group. Informed consent was obtained from their parents.

Upon admission to the NICU, all neonates were subjected to:

1. History taking (to detect risk factors for sepsis) including obstetric, prenatal, natal, postnatal and thorough clinical examination.
2. Complete blood counts (CBC) using Sysmex XS-800i five part differential hematology analyzer, Sysmex Europe GmbH, Norderstedt, Germany with calculation of hematologic sepsis score (HSS) according to Rodwell et al.[9] All leishman stained blood films were reviewed by a clinical pathology specialist blinded to the infection status of the infants for differential counts, correction for nucleated red blood cells and screening for degenerative morphologic changes.

Hematologic scoring system of Rodwell et al includes the following:[9]

- White blood cell and platelet counts.
- White blood cell differential count including immature neutrophils.
- Nucleated red blood cell count (to correct WBC count).
- Assessment of neutrophil morphology for degenerative changes including vacuolization, toxic granulations, and Dohle bodies.

Toxic granulation was graded in neutophils were graded 0 to 4+ according to Zipursky et al.[21]

3. CRP using latex agglutination test Rapitex CRP kit for semi quantitative estimation of C - reactive protein in human serum. CRP levels ≤6 mg/L was accepted as normal.
4. Blood culture: specimens of blood were obtained by a sterile technique and inoculated into commercially-prepared BD Bactec™ Peds Plus™/F blood culture Medium (Becton Dickinson Diagnostics, Sparks, MD). Growth of organisms were detected by chemical sensors and then identified based on gram staining, growth on agar media and biochemical reactions. If no growth was detected, the bottles were incubated up to 10 days with further subcultures every other day on solid media. If no growth appeared after 10 days of incubation, blood culture was considered negative.
5. Ancillary tests (whenever indicated): Routine chemistry (electrolyte level, renal and liver function tests), coagulation studies, chest x-ray, other cultures (CSF, urine, pleural...).
6. Polymorphonuclear leukocyte elastase levels were measured at the time of diagnosis in both sepsis and control groups and 6 days after starting treatment for sepsis group using an enzyme linked immunosorbent assay (ELISA) with Human PMN-Elastase Platinum ELISA Kit from eBioscience, Inc, San Diego, USA.

The diagnosis of sepsis was made when:

- Positive findings on blood culture (or)
- Strong maternal and fetal risk factors for infection (and)
- Suggestive clinical picture including (fever, respiratory dysfunction, cardiac dysfunction, perfusion abnormality, hypotonia, seizures and altered mental status) (or)
- Laboratory findings including (CBC, CRP, liver and kidney function) with clinical sepsis score ≥10 according to Töllner.[22]

Statistical methods: Descriptive statistics were expressed as percentage (%), mean X and standard deviation (SD). Analytic statistics: Chi-square (X^2) test was used for comparison between qualitative variables in different groups and Student t-test was used for comparison between quantitative variables in different groups. P-value is considered significant if <0.05.

The sensitivity and specificity for PMN-E level and the proposed cut-off level were calculated according to construct the receiver operator characteristic curves. The sensitivity and specificity for hematological parameters of HSS and CRP were calculated from number of true positives (TP), false positives (FP), true negatives (TN), false negatives (FN).

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the guardians of the involved neonates.

RESULTS

In this case control study, 30 neonates with sepsis (Sepsis Group) and 30 neonates with noninfectious disorders (Control Group) were investigated. Demographic characteristics of the participants are shown in Table 1.

There were no significant differences in age, sex and gestational status between the two groups (P>0.05). The age of onset of sepsis ranged from day 1 to day 15. Early onset sepsis (72 hours of age) 24/30 (75%), late onset sepsis (presented at >72 hours of age) 6/30 (25%).

Table 1: Demographic characteristics of both sepsis and control groups.

	Sepsis group		Control group		t	P
	Mean	**SD**	**Mean**	**SD**		
Age	2.9	3.2	3	3.5	-0.14	0.887
	Sepsis group		**Control group**			
	n	**%**	**n**	**%**	**X^2**	**P**
Sex	F: 17 M: 13	56.7% 43.3%	F:16 M: 14	53.3% 46.7%	0.00	0.961
Gestational status	Full term 12 Preterm 18	40.0% 60.0%	Full term 19 Preterm 11	63.3% 36.7%	0.22	0.643

Table 2: causative organisms encountered in culture positive neonates.

Causative organism	N=19	Frequency (63.3%)
Coagulase negative *Staphylococcus*	5	26.2%
Klebsiella pneumoniae	3	15.8%
Enterococcus fecalis	3	15.8%
E. coli	2	10.5%
Citrobacter	2	10.5%
Acinetobacter	1	5.3%
Serratia Spp.	1	5.3%
Candida	1	5.3%
Micrococci	1	5.3%

Nineteen patients had positive blood culture in the neonatal sepsis group (n=19/30, 63.3%) Table 2 shows the causative organisms in decreasing order of frequency. When both groups compared regarding hematological parameters of the hematologic scoring system and PMN elastase levels, We found that means of total leukocytic count (TLC), total neutrophil count, immature neutrophil count, immature neutrophil/Total neutrophil (I/T) ratio,

immature neutrophil/mature neutrophil (I/M) ratio and PMN-E levels are significantly higher in sepsis group than control group while mean platelet count is significantly lower in sepsis group than in control group (Student's t-test; P<0.05) Table 3. Serum values of PMN elastase before treatment and 6 days after treatment are shown in Table 4. After treatment, serum PMN elastase levels were significantly lower than levels before treatment indicating a significant recovery parallel to CRP reversion to lower or even normal values. Table 5 show performance of hematological parameters for sepsis and CRP regarding sensitivity, specificity, positive predictive value and negative predictive value.

Table 3: Comparison of hematological parameters and PMN-E between sepsis group and control group.

	Sepsis group		Control group		t	p
	Mean	SD	Mean	SD		
TLC (10^3/µL)	19.20	11.06	10.87	6.09	3.09	0.0044
Total Neutrophil (10^3/ µL)	13.72	8.43	6.74	4.46	3.60	0.0012
Immature Neutrophil (10^3/ µL)	4.44	2.55	0.64	0.42	7.97	<0.0001
I/T ratio	0.38	0.15	0.14	0.14	6.13	<0.0001
I/M ratio	0.73	0.51	0.22	0.43	3.91	0.0005
Hb (g/dL)	12.34	2.44	13.64	3.00	-2.00	0.0548
Platelet (10^3/µL)	149.4	95.5	242.5	140.1	-3.04	0.0049
PMN elastase (ng/mL)	118.4	21.8	57.9	27.9	9.35	<0.0001

Table 4: Comparison between PMN-E levels before and 6 days after treatment.

	Before treatment		Sixth day		t	P
	Mean	SD	Mean	SD		
PMN elastase	118.4	21.8	97.6	24.2	6.41	<0.0001

Table 5: Performance characteristics for common sepsis markers were identified after calculation of TP, TN, FP, FN.

	Sensitivity	Specificity	PPV	NPV
TLC	53%	73%	66.7%	61.1%
I/T ratio	93.3%	80%	82.4%	92.3%
I/M ratio	86.7%	86.7%	86.7%	86.7%
Platelet count	66.7%	86.7%	83.3%	72.2%
Total neutrophil	73.3%	33.3%	52.4%	55.6%
Immature neutrophil	86.7%	83.3%	83.9%	86.2%
CRP	93.3%	76.7%	80%	92%

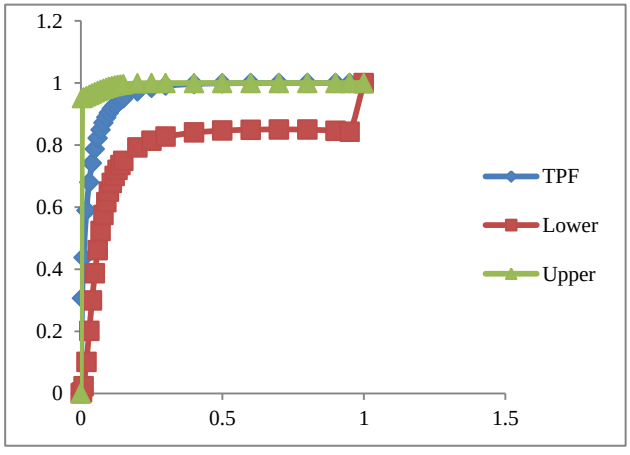

Figure 1: ROC curve for PMN- elastase performance.

ROC curve analysis (Area under curve: 0.964, Std. Error: 0.0226, Asymptotic 95% Confidence Interval; 0.920-1.008) was constructed for various PMN-E cut off levels with their respective sensitivity and specificity values. The cut off showing the best specificity while preserving >97% sensitivity was achieved at point equivalent to 85 ng/ml with 81% specificity (area under curve, 0.964; 95% CI, (0.524-0.978) Figure 1.

DISCUSSION

Neonatal sepsis is a common cause of neonatal morbidity and mortality with rapid onset in premature neonate which necessitates early and effective management. Early diagnosis is not easy due to subtle and nonspecific presentations which cannot help differentiating infectious

from noninfectious causes.[3] Also, abnormal hematological counts, acute-phase reactants, and inflammatory cytokines are neither sensitive nor specific, especially at the onset of illness. Blood culture results despite being the gold standard for the diagnosis of sepsis are available only after 48-72 hours, they frequently give false negative results.[23] Thus, attempts have been made to develop a rapid and specific marker for diagnosis of neonatal sepsis.

PMN-E is a serine protease secreted during inflammation and plays an important physiological function in combating infection in septic conditions. This study aimed at evaluation of the performance of PMN elastase level as a diagnostic and prognostic marker for neonatal sepsis. Thirty neonates admitted to NICU with sepsis were studied in comparison to age and sex matched control group of thirty neonates admitted to NICU for noninfectious causes. Both groups were evaluated for plasma levels of PMN elastase levels along with other markers of sepsis i.e. CRP and HSS.

In the current study, early onset sepsis constituted about 75% of the cases while late onset sepsis constituted about 25% of the cases in contrast to a study conducted by Shehab El-Din et al in Mansoura City included three intensive care units in which sepsis was recognized as EOS in 44.2% of cases and as LOS in 55.8% of cases according to infant age at the onset of symptoms.[24]

According to Rodwell et al culture positivity rates range from 8% to 73% similar to current study in which 63.3% of the septic group showed microbial growth on cultures.[20]

Coagulase negative Staphylococcus was the most encountered organism followed by Klebsiella pneumoniae and enterococcus fecalis then Escherichia coli and Citrobacter followed by Acinetobacter, Candida, Micrococci and Serratia spp in agreement with Shehab El-Din et al who also found Coagulase negative staphylococci to be the most frequent isolated pathogens in sepsis cases in three NICUs in Mansoura city, followed by Klebsiella pneumoniae and Serratia marcescens.[24]

On the other hand, El-Nemer et al found that Pseudomonas was the most frequent followed by *Klebseilla, E.coli, Staph aureus*, and lastly *Enterobacter* in suspected sepsis group and found that *Klebseilla* was the most frequent followed by *Staph aureus* then *E.coli* then Pseudomonas, and lastly Staph.[25] *Epidermidis* in proven sepsis group in NICU of Menoufyia University Hospital.

Similar to that results found by Abdel-Hady and Zaki in the NICU of Mansoura University Children's Hospital, Badrawi et al in NICU of El Kasr El-Aini Maternity Hospital and Boseila et al in Abou El-Reish Pediatric Hospital who reported that Klebseilla dominated the organisms isolated from the blood cultures, followed in the latter study by Pseudomonas, Coagulase Negative *Staphylococci*, Group B *Streptococci*, *Staph. Aureus* and *Enterobacter*.[26-28]

Khair et al evaluated performance of various hematological parameters (TLC, total neutrophil count, I/T ratio (>0.2), I/M ratio (≥0.3), total immature PMNs count and platelet count) and concluded that they have optimal sensitivities and negative predictive values except for TLC and platelet count which is similar to our results; the parameters incorporating immature polymorphs (I/T ratio (>0.2), I/M ratio (≥0.3), total immature PMNs count) achieved high sensitivity with good specificity values), total neutrophil count had fair sensitivity with poor specificity and both TLC and platelet counts had poor overall performance for the former and poor sensitivity for the latter.

Also, Payasli et al, Krediet et al and Wojsyk et al concluded that WBC count is of limited value in identifying infected newborns.[29-32]

In present study, I/T ratio had the best performance over the other hematological parameters with sensitivity 93.3%, specificity 80%, PPV 82.4% NPV 92.3% in agreement with Chirico et al who found I/T ratio may reach a sensitivity of 90% and negative predictive value of 98%.[33] In contrast to Payasli et al who found that I/T ratio failed to reach an appropriate sensitivity and NPV in neonatal sepsis and Wojsyk et al who reported poor sensitivity for I/T ratio in the early diagnosis of neonatal sepsis (59%).[30,32]

In the current study, HSS ≥3 achieved 100% sensitivity and 93.3% specificity similar to myuga and isleta who reported that a score of 3 had 100% sensitivity and 91.3% specificity. In contrast to Khair et al who concluded that a score >4 has a sensitivity of 100%, specificity of 60%, with PPV 26% and NPV 100 %.[29,34]

CRP has been routinely investigated and used for the diagnosis and follow up of neonatal sepsis. However, Elevated CRP levels are present in infections, noninfectious inflammatory diseases, trauma, surgery, recent vaccination, various perinatal problems, burns and malignancies which may cause false positive result. Also, it is reduced in severe progressive infection which together with slow increase in CRP levels may cause false negative results.

In the current study, the semi-quantitative CRP method used had 93.3% sensitivity, 76.7% specificity, 80% PPV, 92% NPV which is comparable to its performance in variable studies in which the range of reported statistical outcomes was as follows: sensitivity 70% to 93%; specificity 41% to 98%; positive predictive accuracy 6% to 83%; and negative predictive accuracy 97% to 99%.[35] In contrast to Wojsyk et al who reported poor sensitivity (60%) and better specificity (86%) of CRP in the early diagnosis of neonatal sepsis. However, CRP still remains

the preferred index of sepsis in most NICUs.[32,33] In the current study, serum PMN-E levels were evaluated along with hematological parameters and CRP levels in both sepsis and control groups and found to be significantly higher in sepsis group (X,SD: 118.4, 21.8) than in control group (X, SD: 57.9, 27.9).

This was in agreement with other studies evaluated serum elastase levels in newborns; Payasli et al.(30) found a significantly higher in sepsis group (X,SD: 145.07, 34.67) than control group (X,SD: 75.5, 9.81), Tsaka et al showed that septic newborns had significantly increased PMN elastase levels at the time of recognition of infection (X,SD: 231, 137 µg/L), Jensen et al who assessed PMN elastase in capillary plasma by repeated heel prick samples and Wojsyk et al who found that PMN elastase is higher in septic than in nonseptic newborns with the mean values of 38.85 ng/ml in non-infected, and 184.12 ng/ml in infected neonates for the latter study. Lawskoska et al also concluded that cord blood neutrophil elastase is a good marker of infection in full-term neonates.[32,36-38]

A good marker for neonatal sepsis should not be only diagnostic but also prognostic as the case with CRP. In this study, it was found that PMN elastase levels were statistically decreased in newborns after 6th day of therapy compared to newborns at the time of diagnosis parallel to reversion of CRP. Similar results have been obtained by payasli et al (before: 145.07±34.67, After: 99.15±25.45) and Tsaka et al who reported that normalisation of PMN-elastase was observed only after definite recovery of the patients.[31,36]

In this study, A ROC derived cut off ≥85 ng/mL for PMN elastase was proposed as it yielded the highest specificity (81%) while maintaining sensitivity >97% which is comparable performance to that of hematological markers and CRP with even higher sensitivity, which is desirable for the ideal diagnostic tests for diseases with high mortality and mandatory early diagnosis to be of maximal sensitivity and negative predictive value. Also, to minimize the unnecessary use of antibiotics in false-positive cases, a diagnostic marker also needs to have reasonably high specificity and a good PPV.

Similar results obtained by payasli et al who estimated the sensitivity of PMN elastase in the diagnosis of neonatal sepsis to be 91.2%, specificity 96.3% and Tsaka et al who reported the sensitivity of an elevated PMN-elastase test result at 100% and the specificity to 86.8%, PPV 78.6% , and the NPV 100% at a cut off 65 ng/ml.[30,36] Contrarily, Wojsky et al reported that the sensitivity and a specifity of serum PMN elastase in the early diagnosis of neonatal sepsis were 76%, 81%.[30]

CONCLUSION

Our findings suggest that PMN elastase level is candidate to be both diagnostic and prognostic marker which is more sensitive and specific than semiquantitative CRP and comparable to performance of HSS in the diagnosis of neonatal sepsis. However, lack of age specific reference ranges may influence its performance as a marker for infection.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Pessar SA. Evaluation of polymorphonuclear leukocyte elastase levels in neonatal sepsis. Int J Res Med Sci 2016;4:4938-44.