Value of Serum Pro-adrenomedullin in Diagnosis of Neonatal Sepsis

Nashwa M. Samrah[1], Somaia M. Elgawhary[2], Wael S. Mohammed[1], Shaymaa M. Taha[3*]

1   Department of Pediatrics, Faculty of Medicine, Fayoum University, Fayoum, Egypt.
2   Department of Clinical pathology, Faculty of Medicine, Fayoum University, Fayoum, Egypt.
3   Department of Pediatrics, Beni-Suef General Hospital, Beni-suef, Egypt.
  *   Correspondence: Shaymaa M. Taha, drshaymaped@gmail.com; Tel.: (002) 01277243885

Abstract

Introduction: Neonatal sepsis is a life-threatening condition that represents one of the major causes of morbidity and mortality among term and preterm infants. Pro-adrenomedullin (Pro-ADM) is the precursor of adrenomedullin, one of the inflammatory mediators. It is a more stable molecule, and its level has been reported to correlate with other acute phase reactants, such as interleukin-6 and C-reactive protein (CRP).

Aim of the study: The study aimed to evaluate the value of serum pro-adrenomedullin measurement in the diagnosis of neonatal sepsis.

Subjects and Methods: This cross-sectional study enrolled 50 neonates admitted to the neonatal ICU at Beni-suef General Hospital in 2017 and 2018 with clinical and laboratory evidence of sepsis. Normal healthy neonates (N = 30) were recruited as the control. All participants were subjected to history taking, clinical examination, and routine lab investigations, as well as, blood culture and measurement of serum Pro-ADM (using enzyme-linked immunosorbent assay).

Results: The mean serum levels of both CRP and pro-ADM were significantly higher in the sepsis group compared to the healthy control neonates. Their diagnostic performances were found to be good with an overall accuracy of 80.4% and 91.3%, respectively. CRP and pro-ADM had comparable values for sensitivity (78% and 98%), specificity (84.4% and 81.2%), positive predictive value (88.6% and 88.9%), negative predictive value (71.1% and 96.3%), respectively.

Conclusion: Pro-ADM seems to be a good, reliable diagnostic marker in neonatal sepsis. Pro-ADM levels above 20.1 indicate a high probability of sepsis diagnosis, and it may be a better marker of neonatal sepsis than CRP because it exceeded the performance of the latter.

Keywords: Pro-adrenomedullin; Neonatal sepsis; C-reactive protein.

1. Introduction

Neonatal sepsis remains one of the leading causes of morbidity and mortality, both among term and preterm infants [1]. Early diagnosis of neonatal sepsis is possible by measuring biomarkers of inflammation. Re-liable biomarkers for sepsis help not only early diagnosis of the condition, but also guide treatment by rapid initiation of antimicrobial therapy. That could avoid the over-use of therapeutic agents and improve the patient's prognosis [2-4].

In sepsis, the released bacterial toxins activate a cascade of events that result in the stimulation of intra-cellular pathways that are responsible for producing inflammatory mediators. Adrenomedullin released from endothelial cells is one of these mediators. It has vasodilator, natriuretic, and bactericidal effects. Also, it reduces endothelial permeability, which results in the down-regulation of pro-inflammatory cytokines, and that clarifies its elevated serum levels in sepsis [5-7]. Adrenomedullin is rapidly cleared from the circulation; hence, reliable measurement of its serum level is

challenging [8]. Pro-ADM is the precursor of adrenomedullin, and it is a more stable molecule. Its level correlated with other acute phase reactants, such as interleukin-6 and C-reactive protein, and it might be used as a prognostic indicator in patients with sepsis [9]. In adults, the elevation of serum pro-ADM level has been reported in systemic inflammatory response syndrome, sepsis, and septic shock [10].

This study aimed to evaluate the value of serum pro-ADM measurement during the diagnosis of neonatal sepsis.

2. Subjects and methods

2.1. Subjects

The current cross-sectional study recruited neonates ad-mitted to the neonatal intensive care unit at Bani-suef General Hospital. The study enrolled 80 participants; 50 neonates (41 full-term and nine pre-term) with confirmed sepsis and 30 normal healthy neonates (24 full-term and six pre-term) as control.

We included neonates with clinical and laboratory evidence of sepsis presenting to the hospital in 2017 and 2018. We excluded neonates weighing less than 1000 gm, as well as, those with perinatal asphyxia, congenital anomalies, surgical emergencies, and congenital heart diseases.

2.2. Methods

All participants were subjected to complete medical history reporting, clinical examination, and other routine laboratory investigations such as, complete blood count, differential leucocytic count, and C-

reactive protein. In addition, blood culture and measurement of serum pro-ADM (using enzyme-linked immunosorbent assay) were carried out for each subject.

2.3. Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) version 17. Numerical data were summarized using median and ranges. Categorical data were summarized as per-centages. Comparisons between cases and controls concerning normally distributed numeric variables were done using the t-tests. Ordinal variables were compared by the Mann-Whitney test. To measure the strength of the association between pro-ADM and other factors, Pearson's correlation coefficients were used. All P-values are two-sided. *P-values<0.05* were considered significant. The Receiver operator characteristic (ROC) curve was used to display the relationship between sensitivity and specificity.

3. Results

The current study reported premature rupture of membranes in a significantly higher percentage of mothers of the sepsis group than in the control group.

The analysis of the complete blood picture revealed a significantly lower platelets count, but a significantly higher mean total leukocytic count (TLC) in the sepsis group than in the control group (Tables 1 &2).

Table 3 shows that there is significant difference between the studied groups, regards CRP and Pro-ADM.

Table 1: Maternal history of neonates of cases and controls.

Variable		Cases (n=50)	Controls (n=30)	*P-value*
Premature rupture of membrane	Yes	15 (30)	3 (10%)	0.028
	No	35 (70%)	27 (90%)	

Table 2: Differences in blood indices between cases and controls.

Variable		Min-Max	Mean±SD	*P-value*
Platelets ($\times 10^9$/L)	Cases	30-352	141.94±97.96	<0.0001
	Controls	260-550	355.47±75.11	
TLC ($\times 10^3$/mm^3)	Cases	3.9-29	14.69±6.98	0.002
	Controls	4-12	7.49±2.44	

Table 3: Comparison between cases and controls regarding inflammatory parameters.

Variable		Min-Max	Mean±SD	*P-value*
Pro-ADM (nmol/L)	Cases	18.6-63.6	35.09±13.51	<0.0001
	Controls		10.58±3.17	
CRP (mg/L)	Cases	12-192	72.24±59.66	<0.0001
	Controls		1.47±1.11	

The diagnostic performance of pro-ADM was found to be good as the area under the ROC curve was 0.892 with an overall accuracy of 91.3%. At an optimal cutoff value of 20.1, pro-ADM exhibited a sensitivity of 98%, a specificity of 81.2%, a positive predictive value of 88.9%, and a negative predictive value of 96.3% (Figure 1). The results of the present study revealed the presence of a significant strong positive

correlation between serum Pro-ADM levels and C-reactive protein. Table (4) shows the

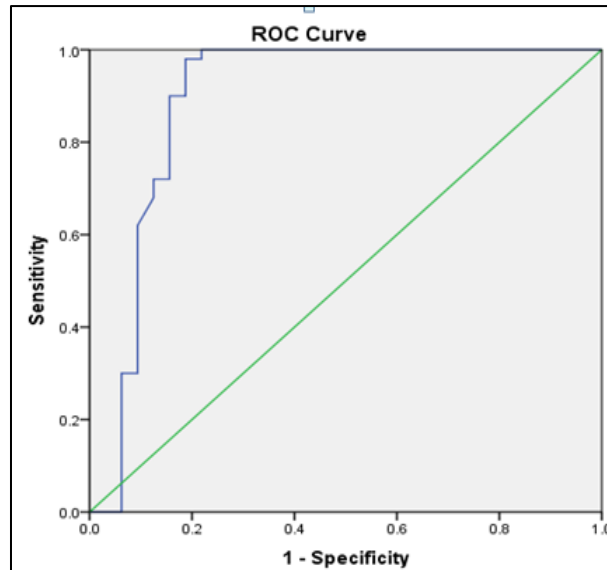strong positive correlation of Pro-ADM with C-reactive protein.

Figure 1: ROC analysis of pro-ADM.

Table 4: Correlations of pro-ADM with C-reactive protein.

Variable		Pro-ADM
CRP	r	0.869
	P-value	<0.0001

4. Discussion

Comparison of the gestational age, birth weight, sex, and mode of delivery between the sepsis and the

control groups did not reveal any significant difference in the present study, which was following the results of Oncel *et al.,* (2012), Hagag *et al.,* (2011), and Abd-Elmouttaleb *et al.,* (2016) [11-13]. These findings are partially agreed with Fahmey *et al.,* (2018), who reported no significant differences in gestational age, sex, or mode

of delivery, but found a significantly lower mean body weight in the sepsis group [14].

Analysis of serum pro-ADM levels in the present study revealed that the sepsis group had a significantly higher mean pro-ADM level compared with the control group (mean=35.09 versus 10.58, respectively; *P<0.001*). This result is in agreement with earlier studies, which reported higher levels of pro-ADM in neonates diagnosed with bacterial infection [11-12, 15-16].

5. Conclusion

In conclusion, pro-adrenomedullin seems to be a good, reliable diagnostic marker in neonatal sepsis, as it exceeded the performance of CRP. Moreover, pro-adrenomedullin levels above 20.1 indicate a high probability of sepsis diagnosis.

Despite of some limitations (such as small sample size and measurement of pro-adrenomedullin levels only once), the current study had prominent points of strength including the enrollment of only patients with proven sepsis. That was confirmed by positive blood cultures and the accurate assessment of diagnostic performance of pro-adrenomedullin with identification of an optimal cutoff point.

References

1. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013 Apr;60(2):367-89. doi: 10.1016/j.pcl.2012.12.003.
2. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am. 2004 Aug;51(4):939-59, viii-ix. doi: 10.1016/j.pcl.2004.03.009.
3. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005 Jan;6(1):2-8. doi: 10.1097/01.PCC.0000149131.72248.E6.
4. Osrin D, Vergnano S, Costello A. Serious bacterial infections in newborn infants in developing countries. Curr Opin Infect Dis. 2004 Jun;17(3):217-24. doi: 10.1097/00001432-200406000-00008.
5. Allaker RP, Grosvenor PW, McAnerney DC, Sheehan BE, Srikanta BH, Pell K, Kapas S. Mechanisms of adrenomedullin antimicrobial action. Peptides. 2006 Apr;27(4):661-6. doi: 10.1016/j.peptides.2005.09.003.
6. Kaplan JM, Wong HR. Biomarker discovery and development in pediatric critical care medicine. Pediatr Crit Care Med. 2011 Mar;12(2):165-73. doi: 10.1097/PCC.0b013e3181e28876.
7. Temmesfeld-Wollbrück B, Brell B, Dávid I, Dorenberg M, Adolphs J, Schmeck B, Suttorp N, Hippenstiel S. Adrenomedullin reduces vascular hyperpermeability and improves survival in rat septic shock. Intensive Care Med. 2007 Apr;33(4):703-10. doi: 10.1007/s00134-007-0561-y.

8. Kato J, Tsuruda T, Kita T, Kitamura K, Eto T. Adrenomedullin: a protective factor for blood vessels. Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2480-7. doi: 10.1161/01.ATV.0000184759.91369.f8.

9. Khassawneh M, Hayajneh WA, Kofahi H, Khader Y, Amarin Z, Daoud A. Diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6 and immunoglobulin M. Scand J Immunol. 2007 Feb;65(2):171-5. doi: 10.1111/j.1365-3083.2006.01878.x.

10. Angeletti S, Spoto S, Fogolari M, Cortigiani M, Fioravanti M, De Florio L, Curcio B, Cavalieri D, Costantino S, Dicuonzo G. Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections. APMIS. 2015 Sep;123(9):740-8. doi: 10.1111/apm.12406.

11. Oncel MY, Dilmen U, Erdeve O, Ozdemir R, Calisici E, Yurttutan S, Canpolat FE, Oguz SS, Uras N. Proadrenomedullin as a prognostic marker in neonatal sepsis. Pediatr Res. 2012 Nov;72(5):507-12. doi: 10.1038/pr.2012.106.

12. Hagag AA, Elmahdy HS, Ezzat AA. Prognostic value of plasma pro-adrenomedullin and antithrombin levels in neonatal sepsis. Indian Pediatr. 2011 Jun;48(6):471-3. doi: 10.1007/s13312-011-0074-1.

13. Abd-Elmouttaleb AT, Aly HA, Bayomy EM, Abdelhamed MR, and Esmael NF. Plasma Procalcitonin and Proadrenomedullin Concentrations as Predictive Markers for Early Onset Neonatal Sepsis. American Journal of Biochemistry. 2016;6: 6-15.

14. Fahmey SS, Mostafa H, Elhafeez NA, Hussain H. Diagnostic and prognostic value of proadrenomedullin in neonatal sepsis. Korean J Pediatr. 2018 May;61(5):156-159. doi: 10.3345/kjp.2018.61.5.156.

15. Cao Y, Xia Q, Chen C, Yang Y. Precursors of adrenomedullin, endothelin and atrial natriuretic peptide as diagnostic markers of neonatal infection. Acta Paediatr. 2012 Mar;101(3):242-6. doi: 10.1111/j.1651-2227.2011.02511.x.

16. Kannan R, Rao SS, Mithra P, Dhanashree B, Baliga S, Bhat KG. Diagnostic and Prognostic Validity of Proadrenomedullin among Neonates with Sepsis in Tertiary Care Hospitals of Southern India. Int J Pediatr. 2018 Aug 1;2018:7908148. doi: 10.1155/2018/7908148.