IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Diagnostic Role of Serum Haptoglobin level in Early Onset Neonatal Sepsis

Seiedmohsen Emami*[1], Majid Kalani[2], Gholam Ali Mohaddes[2]

1. Pediatrician, Department of neonatology and pediatrics, school of medicine, Sabzevar, University of Medical Sciences ,Sabzevar, Iran .
2. Department of neonatology Akbarabadi Hospital, Faculty of Medicine, Iran University of Medical Science, Tehran, Iran.

ABSTRACT

***Background*:** Introduction: Searching for an ideal marker for diagnosing neonatal infection is still an important concern in every country. There are many biomarkers reported for neonatal sepsis. Haptoglobin is an acute phase reactants which rise in response to infection and injuries. In this report we discussed the efficacy of serum haptoglobin level in different cut off levels in early onset neonatal sepsis.

Material and methods: Total of 84 neonates divided in to a sepsis (43 neonates) and control group (41 neonates) and enrolled in this case-control study. Sepsis was defined base on both clinical and laboratory criteria. Serum haptoglobin level was evaluated in both groups. Sensitivity and specificity of haptoglobin in different cut off points was evaluated and study data was analyzed by SPSS 18 software.

Results: Neonates in both groups didn't have significant relation in term of gender, gestational age at birth and birth weight. Serum level of haptoglobin in sepsis group was significantly higher than control group (P=0.0001). Also there was significant relation between haptoglobin and positive blood cultures (p=0.0001). Cut of point of 25mg/dl had sensitivity of 67%, specificity of 95%, accuracy of 80% and positive predictive value of 93% and considered as preferable cut off point in early neonatal sepsis.

Conclusion: Serum plasma haptoglobin can be a specific diagnostic factor in diagnosing early neonatal sepsis in keeping with other diagnostic tests for sepsis.

Keywords: Sepsis; Infant; Haptoglobins.

Introduction

Neonatal infections as a single large cause of neonatal death are still a big concern for many countries(1). Currently about 40% under-five mortality rate occur in neonate group(1). Successful reduction of neonatal deaths from infection depends on in-time diagnosis and appropriate treatment(2). As well as most of other diseases, diagnosis is based on both clinical and laboratory findings. Unlike the clinical part, finding preferable and cost effective laboratory tests are still under research(3). Blood culture is the gold standard for diagnosis of sepsis (3). While blood culture is a time-consuming method and could be falsely negative in some cases, there become other factors for faster diagnosis. Acute phase reactants are a group of peptides which are responsible for immediate response to infection or injuries. C - reactive protein (CRP), fibronectin and procalcitonin are three known acute phase reactants which are widely studied(3). Other acute phase reactant protein which is thought to play a role in sepsis is haptoglobin. Haptoglobin is a plasma glycoprotein which is synthesized in liver(4). After birth, as gene transcription in liver cells increase, concentration of haptoglobin will increase continuously till age of 20 years(4). The gene expression is strongly induced by IL-6 and to lesser extent IL-1, TNF and other cytokines are also considered as inducers(4). In this report we evaluated serum haptoglobin level in neonates with early onset sepsis who have positive blood cultures and in healthy neonates in order to determine specificity and sensitivity of this test in different cut off points.

Methods

This case control study took place in Neonatal intensive care unit of Akbar Abadi and Ali Asghar Hospital, Tehran, Iran. The research protocol of this study was approved by Tehran University of Medical Sciences and written contest was obtained from parents according to Ethic Committee regulation. During a one year period from April 2012; 43 term neonates with diagnosis

* *Corresponding author*: Seiedmohsen Emami, Pediatrician Department of neonatology and pediatrics, school of medicine, Sabzevar, University of Medical Sciences ,Sabzevar, Iran . Email: emamis1@medsab.ac.ir

of early onset sepsis as sepsis group and 41 healthy term neonates as healthy group enrolled in this study. Early onset neonatal sepsis (<7 days) in this study was defined as neonates with two or more of clinical futures with positive blood culture or presence of two or more laboratory findings. The clinical signs of sepsis were defined as temperature instability, respiratory distress and apnea (5). Specific body system features are as follow(3): Skin: Umbilical redness or discharge, pustules, mottling and sclerema. Central nervous system: bulging fontanel, excessive irritability, high pitch cry, seizures and neck retraction. Cardiac: poor perfusion and hypotension. Gastrointestinal: paralytic ileus, abdominal distention and necrotizing entercolitis. Hepatic: hyperbilirubinemia. Renal: acute renal failure. The laboratory markers of sepsis were defined as: Positive C reactive protein (CRP), low platelet count, low white blood cell count (≤5000) or high white blood cell count (≥25000) and immature neutrophils/total neutrophils >0.2(6-8). Two blood culture samples were obtained from 2 different peripheral venous sites by 20 minutes. Other laboratory testes such as neutrophil CD11b and CD64, procalcitonin, interleukins and tumor necrosis factor didn't evaluated in our center and were not used(3). Neonates with previous history of trauma or injuries, intra or extra vascular hemolysis and nephrotic syndrome, as well as neonates of mothers who were using androgens were excluded(9). Demographic data including age, gender, birth weight and gestational age at delivery was documented. Serum haptoglobin level was checked for each neonate who was suspected for sepsis and for control group at time of admission. Study data was analyzed by SPSS 18 software. Descriptive analytical as well as t-test, Chi-square and correlation tests were used.

Results

From total of 84 term neonates who enrolled in this study, 45 neonates were male (53.6%) and 39neonates were female (46.4%). The mean and standard deviation (SD) of gestational age at birth were 38.6(1.1%) weeks and these values for birth weight were 3208(419) grams (table-1).

Table 1. Demographic data of both sepsis and healthy groups.

Variable	Total	Sepsis Group (n=43)	Healthy Group (n=41)	P-value
Male Female	(% 53.6) 45 (% 46.4) 39	(%58.1) 251 (%41.8) 18	(%48.7) 20 (%51.2) 21	0.39
Gestational age (week)	38.6 ± 1.1	38.5 ± 1.0	38.7 ± 1.1	0.34
Birth weight (gram)	3208 ± 419	3185 ± 394	3221 ± 437	0.71
Haptoglobin Plasma Level (mg/dl)	24.9 ± 28.9	42.4 ± 31.2	6.5 ± 6.1	0.0001

Table 2.. Accuracy, specificity, sensitivity positive and negative predictive value of serum haptoglobin cut off points.

Haptoglobin (mg/dl)	Sepsis group		Healthy group		Negative predictive value	Positive predictive value	Accuracy	Sensitivity	Specificity
	True positive	False negative	True positive	False negative					
5<=	43	0	27	14	1	0.61	0.67	1	0.34
10<=	37	6	5	36	0.85	0.88	0.86	0.86	0.87
15<=	32	10	3	38	0.79	0.91	0.83	0.76	0.92
20<=	32	11	3	38	0.77	0.91	0.83	0.74	0.92
25<=	29	14	2	39	0.73	0.93	0.80	0.67	0.95
30<=	29	14	2	39	0.73	0.93	0.80	0.67	0.95
35<=	23	20	0	41	0.67	1	0.76	0.53	1

Neonates in sepsis and healthy group had quiet the same gestational age at birth (38.5(1.0) and 38.7(1.1) weeks respectively (P=0.34)). Also, both groups didn't have significant different in term of gender (P=0.39) and birth weight (p=0.71). Plasma level of haptoglobin in sepsis group was significantly higher than control group (42.4(31.2) mg/dl versus 6.5(6.1) mg/dl respectively (p=0.0001)). Plasma level of haptoglobin was not related to neonate's gender (P=0.55). Both

gestational age at birth and birth weight were not related to haptoglobin serum level (P=0.09, r=0.18 versus p=0.63, r=0.05 respectively). Nine neonates with clinical suspicion of sepsis had positive blood cultures (20.9%). Mean (SD) of serum haptoglobin level in neonates with positive blood cultures were 80.0(32.7%) mg/dl and 32.5(22.3%) mg/dl in infants with negative cultures. Positive blood cultures were significantly related to serum haptoglobin level (P=0.0001). Table-2 shows cut-off points for different levels of plasma haptoglobin in term neonates. Plasma haptoglobin in diagnosing early onset neonatal sepsis has the most sensitivity and specificity at cut-off point of 25mg/dl.

Discussion

Both developed and developing countries are faced neonatal sepsis as an important cause of mortality(2). After confirmation of neonatal sepsis, appropriate identification of infection source, appropriate antibiotic treatment and in time management can prevent adverse outcomes(2). Despite of recent development in diagnosing of neonatal sepsis, there are still many ongoing researches about preferable and accurate marker for sepsis(10). Complete blood count indices are helpful in determining early onset sepsis after four hours and if sepsis is suspected before that time, antibiotic treatment could be initiated immediately after taking blood cultures and CBC(11). Despite of C-Reactive Protein (CRP) role in determining infections in newborns, cytokines and inflammatory response proteins are becoming indicators of sepsis in this age group(2). IL-6 and procalcitonin are two of these indicators which are widely studied and shown to be promising in determining neonatal sepsis(2). CRP and procalcitonin are both used in determining illness severity; however, IL-6 may be altered by risk indexes and physiologic severity(2). Some of these markers such as CRP and IL-6 take influence from gestational age, maternal and perinatal factors. Because of this fact, CRP level can be influenced in first 3 days of life. Also, CRP is most accurate when combined with other biomarkers such as procalcitonin(11). Also, evaluation of both IL-6 and IL-8 will increase the accuracy of diagnosis of sepsis in neonates(12). Neutrophil CD64 is another factor with good diagnostic accuracy which can be accessed by rapid (Turn around time)TAT(11). In our study the available laboratory tests were CRP, platelet count, white blood cell count and neutrophil count. These tests were used in our laboratory criteria for diagnosis of neonatal sepsis and we evaluate haptoglobin level in septic neonates meet our clinical and laboratory criteria. Haptoglobin is an acute phase protein which is synthesized in liver and is used in determination of hemolytic events and infection (10). There are many acute phase reactant proteins studied for neonatal sepsis such as CRP, fibronectin, lactoferrin and lipopolysaccharide binding protein; however haptoglobin is not widely studied(13). Chavez-Bueno et al stated that haptoglobin level rise in second and forth days of life in term and preterm neonates. In neonates with bacteremia, haptoglobin level was higher than healthy neonates and they suggested that haptoglobin may have clinical utility for neonatal sepsis (14). KALAYCI et al study stated that haptoglobin and fibronectin levels are significantly higher in neonates with sepsis than normal neonates. However, they accepted values greater than 250 mg/dl as sepsis and stated that serum haptoglobin alone had low sensitivity and specificity in diagnosis of sepsis(10). In our study we found that cut off point of 25mg/dl has the highest sensitivity and specificity in determining neonatal sepsis. They also found that serum haptoglobin level decreased to normal values after treatment. They concluded that combination of haptoglobin with other homological markers are more predictive of neonatal sepsis rather than haptoglobin alone(10). Khair et al study evaluated hematologic scoring system, haptoglobin and CRP in diagnosis of neonatal sepsis. They used blood culture as gold standard of diagnosing neonatal septicemia and unlike our study; they evaluate preterm and low birth weight neonates. They concluded that haptoglobin is significantly related to sepsis and has low sensitivity(15). According to small number of studies performed for haptoglobin in early neonatal sepsis, conducting more studies with larger sample sizes seems reasonable in order to count haptoglobin and as an indicator of sepsis.

Conclusion

According to our study, we suggest serum haptoglobin cut off point of 25mg/dl as a sensitive and specific diagnostic value for early neonatal sepsis in combination with other appropriate diagnostic tests. We suggest researchers to evaluate haptoglobin with other diagnostic tests to find the appropriate combination of tests for more accurate diagnosis.

Acknowledgment

None declared.

References

1. Lawn JE, Osrin D, Adler A, Cousens S. Four million neonatal deaths: counting and attribution of cause of death. Paediatric and perinatal epidemiology. 2008;22(5):410-6.
2. Chiesa C, Panero A, Osborn JF, Simonetti AF, Pacifico L. Diagnosis of neonatal sepsis: a clinical and laboratory challenge. Clin Chem. 2004;50(2):279-87.
3. Kale A, jaybhaye D, Bonde V. Neonatal Sepsis: An Update. Iranian Journal of Neonatology IJN. 2013;4(4):39-51.
4. Kasvosve I, Speeckaert MM, Speeckaert R, Masukume G, Delanghe JR. Haptoglobin polymorphism and infection. Advances in clinical chemistry. 2010;50:23-46.
5. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatric clinics of North America. 2013;60(2):367-89.
6. Hornik CP, Benjamin DK, Becker KC, Benjamin DK, Li J, Clark RH, et al. Use of the Complete Blood Cell Count in Early-Onset Neonatal Sepsis. The Pediatric Infectious Disease Journal. 2012;31(8):799-802.
7. Yao Y, Tu Y, Lu Q. [Values of C-reactive protein, percentage of neutrophils and mean platelet volume in early diagnosis of neonatal sepsis]. Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics. 2015;17(5):425-9.
8. Zareifar S, Pishva N, Farahmandfar M, Benaei S, Cohan N. Prevalence of G6PD Deficiency in Neonatal Sepsis in Iran. Iranian Journal of Pediatrics. 2014;24(1):115-6.
9. Alexander Kratz EL-L, Kent B.Lewandrowski. The Plasma Proteins. In: McClatchey KD, editor. Clinical laboratory medicine. 2nd ed: Lippincott Williams & Wilkins; 2002. p. 272.
10. KALAYCI AG, YILMAZER F, ADAM B, SANCAK R, KÜÇÜKÖDÜK Ş. The importance of fibronectin, haptoglobin, ceruloplasmin and transferrin in the early diagnosis of neonatal sepsis. Turkish Journal of Medical Sciences. 2000;30(2):151-6.
11. Bhandari V. Effective Biomarkers for Diagnosis of Neonatal Sepsis. Journal of the Pediatric Infectious Diseases Society. 2014;3(3):234-45.
12. Zhao FX, Liu GH, Zhang J. [Value of IL-6 and IL-8 in the diagnosis of neonatal sepsis]. Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics. 2015;17(12):1311-5.
13. Singh Laishram R, Devi Khuraijam R. Hematological and Biological Markers of Neonatal Sepsis. Iranian Journal of Pathology. 2013;8(3):137-46.
14. Chavez-Bueno S, Beasley JA, Goldbeck JM, Bright BC, Morton DJ, Whitby PW, et al. 'Haptoglobin concentrations in preterm and term newborns'. Journal of perinatology : official journal of the California Perinatal Association. 2011;31(7):500-3.
15. Khair KB, Rahman MA, Sultana T, Roy CK, Rahman MQ, Ahmed AN. Early diagnosis of neonatal septicemia by hematologic scoring system, C-reactive protein and serum haptoglobin. Mymensingh medical journal : MMJ. 2012;21(1):85-92.