Value Of Laboratory Tests And C - Reactive Protein In The Detection Of Neonatal Sepsis

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Abstract

Background: Neonatal sepsis are a major cause of death world wide ,which diagnosed by obtaining positive blood culture. The aim of study was to determine if any laboratory tests can predict neonatal sepsis prior to positive blood culture.

Method: the medical records of 200 infants, aged <30 days, with suspected infection, who where admitted in Mostafakhomeini hospital in Tehran, where reviewed retrospectively. Based on clinical and biological findings, diagnoses were categorized in to 3 groups as follow:
A: proven sepsis with positive blood culture.
B: probable sepsis with negative blood culture but laboratory consist with sepsis
C: clinically sepsis with out any positive culture or laboratory abnormalities.
The validity of laboratory tests which had performed as sepsis work-up, were compared against positive blood culture as gold standard test.

Results: of 200 infants 19(9.5%) had positive blood culture.
The most common causative organisms were klebsiella (5) staphylococous aurous (5) and staph Coagolase negative (5).
Among laboratory tests, CRP had the best sensitivity (79%) and negative predictive value (97%) ,but poor positive predictive value (36%), the specificity of it was 85%.

Conclusion: no laboratory tests alone can be used as early detection of septicemia accurately.

INTRODUCTION

Sepsis is a bacteria blood stream infection identified by one or more positive blood cultures in the presence of clinical signs of infection ([1], [2]).Neonatal septicemia is a major cause of mortality and morbidity world wide.([3],[4],[5]) early detection of sepsis in neonate is one of the most difficult problems facing neonatal care providers and clinicians today.([2],[6])

The clinical and laboratory signs of neonatal sepsis are often non specific ([1], [4], [7], [8]) how ever empirical treatment should not be delayed, because failure or delay in treatment may resulting significant mortality and morbidity. ([1], [5], [7]) On the other hand, the ability to early diagnosis or rule out neonatal sepsis results in to limit inappropriate antibiotic exposure and lowering the cost of therapy. ([9], [10]) Many studied have investigated a variety of laboratory tests to enhance the early detection of neonatal sepsis .([2],[5],[8],[10],[17])

Some evidence exist which support the use of C-reactive protein measures sole or in conjunction with other tests to identify neonate at risk for septicemia. ([2], [5], [10], [13], [15], [17]) In contrast some authors believed no advantage for using it.([8],[12],[14]) This study was conducted to determine the value of some laboratory test in early detection for neonatal septicemia .Besides this, we wish to know the comment causal organisms for neonatal sepsis in our situations.

MATERIAL AND METHODS

Through a retrospective study, we reviewed the medical records of infants, aged <30 days, suspected of sepsis who were admitted in NICU of Mostafakhomeini hospital in Tehran between Mar,2000 and sep,2001.

Infants who were received antibiotics prior to septic work up were excluded.

200 eligible infants had investigated for infection included CBC, serum electrolyte, Arterial blood gases, ESR and CRP measurements, blood, urine and cerebro spinal fluid cultures .CRP had measured qualitatively. (a positive test result indicates a CRP level more than 6mg/l or more than 10mg/l).

Based on clinical and biological data, diagnosis of infants categorized in to 3groups as follow:

1. proven sepsis with positive blood culture,
2. probable sepsis (clinically and laboratory consistent with sepsis but negative blood culture).
3. clinically sepsis (only clinically consistent with sepsis with out any laboratory abnormalities and positive cultures).

All infants following the septic work up, were received antimicrobial therapy. Statistical analysis was performed using one way ANOVA and TURKEY tests for continuous variables or χ^2 tests for categorical variables (spss 9.0 for window's). P values<0.05 were considered significant.

Positive blood culture was considered the "gold standard" against which the performance of CRP, ESR, total white cell count or some most common laboratory findings were compared. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for major laboratory finding were calculated.

RESULTS

200 infants had undergone sepsis work-up during study period with the mean (±SD) age of 6.9 days (± 6.5) and range 1 to 28 days. The mean (±SD) of gestational age was 37.1week (±1.2) with the range of 34-41 weeks. These parameters was 3068 (±604.9) gram (range: 1500-4550) respectively for their birth weight .109 infant were male. There were 19 cases of proven sepsis, 38 probable and 143 clinical sepses as defined in method and material section.

The characteristics of these groups were compared in table1. With respect to age, gestational age and birth weight there were no differences between them. The mean of duration of hospitalization in proven sepsis group was significantly longer than other two groups.(12.6 days versus 7.3 in group B and 5 days in group C,p<0.0001). Table 2 lists the causal organisms klebsiella,staph aurous and staph coagolase negative were the commonest pathogen ,which observed in blood culture.

Figure 1

Table 1: comparison of demographic characteristics of proven probable and clinical sepsis

	Proven sepsis n=19	Probable sepsis N=38	Clinical sepsis N=143	* P.v
Age (day)	5/3(±6.4)	7/6(±7)	6.9(±6.4)	0.479
Gestational age (week)	36.9(±1.3)	36.7(±1.1)	37.1(±1.2)	0.145
Birth weight(gram)	30.60(±714	3092.7(±676.4)	3079.9(±57.5)	0.906
Duration of hospitalization(day)	12.6(±5.4)	7.3(±5)	5(±3.5)	<0.0001
Sex Male Female	 10(52.6%) 9(47.4%)	 20(52.6%) 18(47.4%)	 79(55.2%) 64(44.8%)	0.950

Figures are presented as mean (±SD) or (%)

Means compared via ANOVA and percentage compared via χ^2 test.

Figure 2

Table 2: causative organisms of sepsis (n=19)

organisms	No.	(%)
Klebseilla	5	(3)
Staphylococcus aurous	5	(3)
Staphylococcus coagalase	5	(3)
Entrobacter	1	(0.6)
e.coli	1	(0.6)
Entrococcous Cytobacter	1 1	(0.6) (0.6)

Temperature instability followed by poor feeding were the most clinical signs in each group. Tachypnea (53%), Tachycardia (42%) and icter (42%) were the other frequent clinical signs in proven sepsis group. (Table 3) Neurologic sign (convulsion, lethargy and bulging of fontanel) were more seen in group A ,although they were not frequent findings at whole.

Figure 3

Table 3: The clinical findings in proven, probable and clinical sepsis.

Clinical findings	Proven sepsis n=19	Probable sepsis N=38	Clinical sepsis N=143
Hyperthermia	13(68)	29(76)	100(70)
Hypothermia	0	3(8)	11(8)
Tachypanea	10(53)	14(37)	39(27)
Apnea	5(26)	4(10)	8(6)
Cyanosis	7(37)	10(26)	28(20)
Grunting	4(21)	9(24)	19(13)
Tachycardia	8(42)	10(26)	27(19)
Poor feeding	11(58)	21(55)	86(60)
Abdominal distension	6(32)	7(18)	12(8)
Vomiting	5(26)	13(34)	39(27)
Icter	8(42)	18(47)	65(45)
Convulsion	5(26)	7(18)	6(4)
Lethargic	6(32)	7(18)	42(29)
Bulging fontanel	2(11)	3(8)	1(0.7)
Motteling/petechia	9(47)	4(11)	1(0.7)

Figures are presented as No (%)

Totally 14 infants had skin presentations (mottling or

petechia), with the most frequently rate in group A (47%) versus 11% in group B and 0.7% in group C. Serum electrolite abnormalities were seen in 32 infants (19 of group A and 13 of group B). Hypocalcaemia (37%), hypo or hypernatremia (32%) and hypo or hyperkalemia (21%) were the most findings in group A.(table 4)

Figure 4

Table 4: laboratory findings in proven and probable sepsis

Laboratory findings	Proven sepsis N=19	Probable sepsis N=38
↑or ↓calcium	7(37)	4(10)
↑or ↓natrium	6(32)	1(3)
↑or ↓kalium	4(21)	0
↑Bun,creatnine	0	2(5)
Mixed of above changes hypoglycemia	2(10)	6(16)
WBC>15000/m³	6(32)	10(26)
neotrophil<1000/ m³	10(53)	30(79)
platelete<10000/ m³	0	5(13)
Band cell	4(21)	8(21)
ESR	0	1(3)
CRP	6(32)	25(69)
Metabolic acidosis	5(26)	27(71)
Metabolic Respiratory	3(16)	5(13)
Respiratory acidosis	1(5)	0
Respiratory alkalosis	3(16)	0
Respiratory acidosis+	0	1(3)
Metabolic alkalosis		
Respiratory Acidosis+	1(5)	2(5)
Respiratory Acidosis		

Figures are presented as No (%)

Arterial blood gas evaluation was abnormal in 21 subjects (13 of group A and 8 of group B). Metabolic acidosis was the commonest finding in each group.(26% in group A and 13% in group B).metabolic alkolosis (%16) and respiratory alkalosis (%15) were the next common finding in group A with out any case in group B.

79% of group A and 71% of group B had positive C-reactive protein result. The validity of most frequent findings for detecting infants with septicemia is shown in table 5.

Figure 5

Table 5: validity of more common clinical or laboratory signs in infant suspected of sepsis against blood culture as gold as standard test.

Clinical signs:	%sensitivity	%specificity	%PPV *	%NPV*
Tachypnea	53	71	16	93
Apnea	26	93	29	92
cyanosis	37	79	16	92
Tachycardia	42	80	18	93
Abdominal distension	32	90	24	93
Skin signs	47	97	64	95
Laboratory tests:				
Calcium abnormality	37	98	64	94
Hypoglycemia	32	94	38	93
Leukocytosis	53	83	25	94
ESR	32	36	19	92
CRP	79	85	36	97

*Positive predictive value
*Negative predictive value

CRP had sensitivity, specificity, PPV and NPV of 79%, 85%, 36% and 97% respectively. These figures were 53%, 83%, 25% and 94% for WBC>15000 /mm³ respectively. Skin presentation had sensitivity of 47%, specificity of 97% , PPV of 64% and NPV of 95%. There was one infant with positive CSF culture (hemolyticus streptococcus) and 20 infants with positive urine culture (15 cases with E.coli, 3 with klebsiella,one with staph.aureus and one with candida Albicans).

DISCUSSION

In our study, the rate of proven sepsis was 9.5% .This rate ranged from 10.8% to 27% in other studies ([5], [12], [17], [18]) .The varying results may be due to different study population and different defining of proven sepsis. We did not find any positive blood culture with group B strep. And only had one positive blood culture with E.coli, in contrast with this statement that the group B strep, and E.coli are the two most common bacterial pathogens in term infants in the first 28 days of life.([1])

Klebsiella , staph aurous and coagulase negative staph were the common causal organisms in our study . Gram positive Coccies in Zamora etal ([18]) and klebsiella in Misallatie el al ([19]) papers, reported as commonest organisms in neonatal sepsis. Answer Sk. and colleague ([13]) have concluded from their etiological study that Gram positive organisms, such as enterococcus, staph aurous and staph epidermis were the main cause of neonatal sepsis and klebsiella sp Is the commonest organism causing early on set sepsis. It seems the prevalence rates for a specific bacterial pathogen vary from NICU to NICU and may change during time. Thus the

data about most commonly isolated bacteria in a NICU must be periodically reviewed and antibiotic policy revised according to susceptibilities of these organisms.

We found only one positive CSF culture and 3cases with evaluated WBC in CSF evaluation, which they treated as meningitis. The incidence of neonatal meningitis must be more investigated and the routinely performance of lumbar punctures must be revised. A jayl OA.and colleague ([20]) did not find any positive CSF culture among 263 infants <72 hours of age, and recommended that lumbar puncture be reserved for selected infants.

We found the hyperthermia and poor feeding as the most common clinical signs among 200 infants. Approximately 45% were Icterus but some clinical signs such as Tackypnea , apnea ,cyanosis ,Tacky cardia ,abdominal distension and skin presentations were more common in proven sepsis group. These sign had low sensitivity (26%for Apnea to 53% for Tachypenea) and low PPV (16% for Tachypnea to 64% for skin presentations.)

Data from 455 infant have revealed temperature imbalance, respiratory signs in neonatal sepsis. ([2])

Skin presentations had high specificity and NPV in our study but low sensitivity. De Felice C.etal ([21]) evaluated predictive value of skin color for illness severity in the high –risk new born and found that skin color reflects clinical severity in the new born accurately. Our findings demonstrated that CRP had a high NPV (97%) but low PPV (36%) with the sensitivity and specificity of 79% and 85% respectively. we measured it qualitatively at the onset of signs of infection. There is not an established standard practice for the use of CRP in infants, and a variety of approaches are described in the literature.([2]) A CRP level measured at the beginning of septic work-up has a sensitivity of 67% and NPV of 87% in Garland SM,et al study. ([17]).these figures were 76% and 96% in another study, respectively ([12]). Beger C, etal ([16]) which measured CRP qualitatively, with cut off point of >20 mg /l, reported 75% of sensitivity and 86% of specificity rate. The most studies measured CRP quantitatively with different cut off point and different times from onset the signs of infection. Nuntnarumit P ,etal ([5]) reported a sensitivity of 100% ,specificity of 94% ,PPV and NPV of 91.6% and 100% respectively ,of CRP for detecting proven sepsis and localized infection at cut off point >or =5mg/l.

The variations in the population studies with respect to age and ,gestational age ,the definition of sepsis and different evaluation manner as well as different cut–off point setting and various methods of measuring CRP with respect of the number and timing of sample collection, lead to getting different results. However, it can be emphasized that a single CRP level measured at the onset of infection lacks sufficient sensitivity to be useful in identifying neonate with septicemia. In addition CRP can not be recommended as a sole indicator of neonatal sepsis, but it may be used as part of a sepsis workup and in combination with other laboratory tests. Considering the lower sensitivity and PPV Leukocytosis in current study, render it less valuable than CRP for early detection of neonatal sepsis. The sensitivity and specificity of Leukocytosis have reported 41% and 73% by Ottolini MC, etal ([11]) and 14% ,93% by Anwer SK. and colleague ([13]) respectively. Since neonatal sepsis has a reported high mortality rate ([2]), it is critical that clinicians identify all infants with septicemia (high sensitivity) even if the trade off is over diagnosis and treatment of infants who are not septic.(low specificity).([26])

CONCLUSIONS

No single test alone was sufficiently reliable to use as predictor of neonatal septicemia.

COMMENTS

Further studies must be carried on determining the common pathogen in different NICUS and antibiotic policy revised accordingly. Also the necessity of routine lumbar puncture in all infant suspected to infection should be investigated and may be shift to reserving it for those infants with signs of severe sepsis.

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