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ORIGINAL ARTICLE

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ASSOCIATION OF CLINICAL AND LABORATORY PARAMETERS OF PATIENTS WITH NEONATAL SEPSIS

ABSTRACT

Neonatal sepsis is one of the leading causes of death among newborns, and diagnosis is a challenge to clinicians.

Objectives: The present study describes and compares the demographic, clinical, and hematological profile of neonates, and its association with culture positive and culture negative neonatal sepsis, admitted at National Children's Hospital.

Methods: This is a cross sectional study. About 135 neonates diagnosed with neonatal sepsis with a complete blood count and blood culture results were included in the study. Charts were retrieved from the medical records section. Primary outcome measures are the following: decreased platelet, increased WBC, increased ANC, IT ratio more than 0.2, and the presence of nucleated RBCs.

Results: Forty-seven (35%) subjects had a positive blood culture while 88 (65%) patients had a negative blood culture. The presence of fever is significantly associated with clinical sepsis (negative blood culture) (OR 0.45 p=0.04). On the other hand, the odds of having a positive blood culture is 2.29 times more when the patient has poor suck compared to those who did not present with poor suck (OR 2.29, p=0.04). There was no significant association with the patients' demographic and hematological profile in having neonatal sepsis.

Conclusion: There was no significant difference in having a positive blood culture or a negative blood culture among any demographic profile and hematological profile tested between culture proven and nonculture proven neonatal sepsis. Hence, in clinical sepsis, it is still acceptable to treat patients despite a normal complete blood count and or a negative blood culture.

KEYWORDS:

neonatal sepsis, clinical sepsis, neonatal infection

INTRODUCTION

Sepsis is one of the leading causes of morbidity and mortality among neonates. According to World Health Organization, neonatal sepsis is responsible for 33% of neonatal deaths.¹ The Department of Health data shows that bacterial sepsis of the newborn is ranked as the number one cause of infant mortality in the Philippines since 2004.² Its incidence in the Philippines is 4-9 cases per 1000 live births. In the Philippine General Hospital, it is estimated between 2 to 7 cases per 1000 live births with an average rate of 7%.³ According to the National Statistics Office, two-thirds of infant deaths occur during the first 28 days of life and in 2009 alone, there were 3,082 death cases of neonatal sepsis or 14.2 percent of the total.²

Diagnosing neonatal sepsis is challenging because the signs and symptoms of infection in neonates are non-specific and are subtle. Blood culture is considered as the gold standard in diagnosing sepsis however, it has a low positivity and is not always available in all health institutions. Only 2 in 1000 live births will have culture proven sepsis.⁴ Among the 7-13% neonates evaluated for sepsis, only 3-8% will have a positive blood culture.⁴ The majority of Filipinos also cannot afford the high cost of obtaining a blood culture. It also takes a week to obtain results, 2 days being the earliest. Therefore, there is a need to use other tests to predict neonatal sepsis. Obtaining a complete blood count is easy and is readily available in most health institutions with only a few erroneous results. Hence, this study will help us recognize neonatal sepsis more with the help of a complete blood count in relation to the patient's signs and symptoms. This study aims to compare the demographic characteristics, bacteriological, clinical presentation and hematologic laboratory parameters of culture

proven neonatal sepsis and clinical neonatal sepsis (culture-negative).

MATERIALS AND METHODS:

A cross sectional study was conducted which included all neonates diagnosed with neonatal sepsis admitted at a tertiary hospital from January 2011 to December 2012. Inclusion criteria included newborns less than 28 days of life, with early onset neonatal sepsis, male or female, those with signs and symptoms suggestive of sepsis, with or without maternal history of infection, with a complete blood count done on admission and blood culture done within 48 hours of admission, and a final diagnosis of neonatal sepsis or clinical sepsis. Exclusion criteria included patients who had previously received antibiotics, those who received a blood transfusion, and patients who were unconscious at the time of admission. Patients' records were retrieved and analyzed at the medical records. Patients were divided into two groups: Group 1 included patients with neonatal sepsis with a positive blood culture. Group 2 patients were the ones with clinical sepsis and had a negative blood culture. The hematological parameters that were studied included absolute neutrophil count (ANC), immature to the total neutrophil ratio (IT ratio), platelet count, nucleated red blood cells (nRBC), and white cell count (WBC). Primary outcome measures are the following: decreased platelet, increased WBC, increased ANC, IT ratio more than 0.2, and the presence of nucleated RBCs. The demographic profile (age, sex, weight, the manner of delivery, place of delivery), common clinical profile, and blood culture results of culture proven and nonculture proven sepsis were described and compared.

DEFINITION OF TERMS:

Neonatal sepsis- patients less than 28 days old with signs and symptoms suggestive of sepsis and a positive blood culture

Clinical sepsis- patients less than 28 days old with signs and symptoms suggestive of sepsis and a negative blood culture

Early onset neonatal sepsis- sepsis that presents within the first 72 hours of life¹⁴

Data Processing and Statistical Analysis:

Descriptive statistics were performed by determining the frequency and computing the percentage for qualitative variables and computing the mean and standard deviation for quantitative variables. The odds ratio with their corresponding 95% confidence intervals was computed to determine the strength of association between the independent and outcome variable (positive or negative blood CS). Logistic regression was used to determine the association of symptoms and outcome variable while controlling for possible confounders. P value of <0.05 was considered statistically significant.

Ethical Considerations:

This study applies the ethical principles for medical research involving human subjects stated in the provisions of the World Medical Association Declaration of Helsinki. The investigator of this study sought ethical approval from the hospital's Institutional Ethics Review Board (IRB) before the study began. To protect the privacy of research subjects and confidentiality of their physical, social, and mental integrity, every precaution was taken. Consent prior to the collection, analysis, storage, and re-use of data was sought from the medical records division of the hospital.¹⁴

RESULTS

A total of 135 subjects were included in the study. Forty-seven (35%) subjects had a positive blood culture while 88 (65%) patients had a negative blood culture.

The clinical characteristics of the patients included in the study are presented in table 1. Majority of the patients with culture proven sepsis were males (59.6%), weighing > 2500 grams (66%), appropriate for gestational age (74.5%), born via normal spontaneous vaginal delivery (95.7%) at a lying in clinic (55.3%), and with a history of maternal infection on the 3rd trimester (36.2%). On the other hand, majority of culture negative sepsis were male (64.8%), weighing >2500 grams (72.7%), appropriate for gestational age (83.4%), with a history of maternal infection during the 3rd trimester (50%), born via normal spontaneous delivery (94.3%) at a lying in clinic (55.7%). No statistical difference was observed in the characteristics of patients in the study.

Among the culture positive sepsis, poor suck (38.3%) was the most common symptom; while among culture negative sepsis, fever (48.9%) was the most common symptom. Univariate analysis did not show any significant association of any sign/symptom with blood culture.

Table 2 shows the association of signs and symptoms with blood culture results.

To control for possible confounders, a logistic regression model was made. Results showed that presence of fever is significantly associated with clinical sepsis (a negative blood culture) (OR of 0.045, p=0.04). On the other hand, the odds of having a positive blood culture is 2.29 times more when the patient has poor suck compared to those who did not present with poor suck (OR=2.29, p=0.04). Vomiting was not significantly associated with neonatal sepsis but with a trend towards 3 times odds of having neonatal sepsis than those without vomiting.

Table 1. Clinical characteristics of patients with neonatal sepsis admitted at a tertiary hospital last January 2011 to December 2012

Baseline Characteristics	Blood Culture (+) N=47	Blood Culture (-) N=88	p-value
Mean age (days): mean (SD)			
Term (37-41 wks)	4.3 (4.1)	4.1 (4.0)	0.82
Preterm (<37wks)	1.9 (0.8)	1.0 (1.4)	0.30
Sex n(%)			
Male	28 (59.6)	57 (64.8)	0.55
Female	19(40.3)	31 (35.2)	
Weight in grams n (%)			
<1500	5 (10.6)	3(3.4)	0.23
1500-2500	11 (23.4)	21 (23.9)	
>2500	31 (66.0)	64 (72.7)	
Weight for Gestational age n(%)			
AGA	35 (74.5)	76 (83.4)	0.08
SGA	12 (25.5)	12 (13.6)	
Trimester of occurrence of Maternal Infection n(%)			
1st	3(6.4)	6(6.8)	0.42
2nd	12 (25.5)	15 (17.1)	
3rd	17 (36.2)	44 (50.0)	
None	15 (31.9)	23 (26.1)	
Manner of delivery n(%)			
Normal	45 (95.7)	83 (94.3)	0.72
Cesarean section	2 (4.3)	5 (5.7)	
Place of delivery n(%)			
Home	14 (29.8)	22 (25.0)	0.74
Lying in/Health center	26 (55.3)	49 (55.7)	
Hospital	7 (14.9)	17 (19.3)	

Table 2. Clinical Presentation of patients with neonatal sepsis and clinical sepsis at NCH from January 2011- December 2012

Signs and Symptoms	Blood Culture (+) N=47	Blood Culture (-) N=88	Odds ratio (95%CI)	p-value
Fever	15(31.9)	43(48.9)	0.49 (0.22,1.09)	0.06
Tachypnea	6(12.8)	18(20.4)	0.57 (0.17-1.65)	0.26
Diarrhea	6(12.8)	17(12.6)	1.02 (0.29-3.28)	0.96
Poor suck	18.(38.3)	21(23.9)	1.98 (0.85,4.55)	0.08
Jaundice	12(25.5)	37(42.0)	0.47 (0.19-1.09)	0.006
Vomiting	7(14.9)	6(6.8)	2.24 (0.64-9.16)	0.13
Poor activity	9(19.1)	12(13.6)	1.5 (0.51-4.26)	0.40

Table 3. Logistic regression model of signs and symptoms of neonatal sepsis with blood culture result

Symptom	Odds Ratio	95% CI	p-value
Fever	0.45	0.21, 0.97	0.04
Poor suck	2.29	1.03,5.11	0.04
Vomiting	3.0	0.88,10.05	0.08

Table 4 shows the hematological profile of patients with neonatal sepsis. The following hematological profiles were included: WBC, platelet count, IT ratio, nucleated RBC, and absolute neutrophilic count. Majority of the patients with culture proven sepsis had normal WBC count (95.7%), normal platelet count (100%), no

Table 4. Hematological Profile of patients with Neonatal Sepsis vs Clinical Sepsis (National Children’s Hospital, January 2011- December 2012)

Parameter	Blood Culture (+) n=47 N(%)	Blood Culture (-) n=88 N(%)	Odds Ratio (95%CI)	p-value
WBC Count				
Normal	45(95.7)	87 98.9)		0.35
Inc WBC	1(2.1)		1.9 (0.02,153.5)	
Dec WBC	1(2.1)			
Platelet count				
Normal	47 (100)	88 (100)	-	-
<150,000	0	0		
IT Ratio				
Normal	47 (100)	88 (100)		
>0.2	0	0		
nRBC				
0	44(93.6)	87(98.9)		
>10	3(6.4)	1(1.1)		
Absolute Neutrophil Count				
Normal	9 (19.2)	29 (33)		
Increased	37 (78.7)	56 (65.9)	2.0(0.82, 5.4)	0.09
Decreased	1 (2.1)	1 (1.1)	3.2 (0.03, 261.4)	

Table 5. : Organisms isolated on culture of patients with neonatal sepsis (National Children’s Hospital, January 2011- December 2012)

Organisms Isolated N= 47	
Gram positive	23 (48.9%)
Coagulase negative Staphylococcus (MRSE=1, epidermidis, haemolyticus, saprophyticus)	17
Staphylococcus aureus (MRSA=1)	3
Staphylococcus intermedius	1
Diphtheroids (spp and Corynebacterium bovis)	2
Gram negative	14 (29.8%)
Klebsiella spp	3
Enterobacter spp.	5
E. coli	1
Pseudomonas putida	1
Acinetobacter spp.	2
Burkholderia spp	2
Candida spp	10 (21.3%)

nucleated RBC (93.6%), increased absolute neutrophilic count (78.7%), and normal IT ratio (100%). Among those with culture negative sepsis, the majority had normal WBC (98.9%), normal platelet count (100%), normal IT ratio (100%), no nucleated RBC (98.9%), and increased absolute neutrophilic count (65.9%). Analysis showed no significant association with any hematological parameter with blood culture result. (Table 4)

Table 5 shows the organisms isolated in the blood cultures of patients with neonatal sepsis. Among the 47 patients who tested positive on blood culture, the most common organism isolated was Candida (21.7%) followed by Coagulase negative staphylococcus (17%) and Enterobacter cloacae (8.6%) although altogether gram positive bacteria.

DISCUSSION

Neonatal sepsis has a high morbidity and mortality in the Philippines and the need for early diagnosis of this disease is important. Blood culture remains to be the gold standard tool in the diagnosis of sepsis. But this test has a low positivity. Therefore, risk factors using a patient’s demographic profile and clinical signs and symptoms are helpful in the early diagnosis of neonatal sepsis without the need to wait for a blood culture. Among 135 neonates included in the study, 47 (35%) had a positive blood culture. Majority of the patients with culture proven sepsis were males (59.6%), weighing > 2500 grams (66%), appropriate for gestational age (74.5%), born via normal spontaneous vaginal delivery (95.7%) at a lying in clinic (55.3%), and with a history of maternal infection on the 3rd trimester (36.2%). This is similar to the study done by Aguilar⁵, where the majority of those who tested positive in blood culture were males (56%) and appropriate for gestational age (74%). However, in contrast to their study where the

majority (56%) of culture proven sepsis was born via cesarean section, in the present study, the majority were born via the vaginal route of delivery (95.7%). Ignacio⁶ also reported males (53%) and vaginal route of delivery (63.24%) among the common demographic profile of neonatal sepsis.

Among the culture positive sepsis, poor suck (38.3%) was the most common symptom; while among culture negative sepsis, fever (48.9%) was the most common symptom. This is similar to the report done by Ignacio⁶ where poor suck (20%), respiratory distress (13%), fever (10%) were included among the most common signs and symptoms of neonatal sepsis.

Among the 47 patients who tested positive on blood culture, the most common organism isolated was *Candida* (21.7%) followed by Coagulase negative staphylococcus (17%) and *Enterobacter cloacae* (8.6%) but overall gram positive organisms dominated. This is in contrast with the study done by Maramba-Lazarte⁷ and Aguilar⁵, where *Pseudomonas* (non-aerogenes) was the most common organism isolated. This also differs from the study done by Imperial⁸ where *Enterobacter cloacae* was the most common organism isolated. In the same study, *Candida* sp. was found in only 11.6% of subjects.

The majority of the patients with culture proven sepsis had normal WBC count (95.7%), normal platelet count (100%), increased absolute neutrophilic count (78.7%), and normal IT ratio (100%). This is similar to the study done by Imperial⁸ where the majority of patients with culture proven neonatal sepsis had a normal WBC count (22%) and only 15% had an increase WBC count. However, in contrast to the study done by Mayuga⁴, a low platelet count has a high likelihood of having neonatal sepsis compared to other parameters such as WBC count, nucleated RBCs, and immature cells. This is also in contrast with a study by Ghosh⁹ where they found out

that an abnormal I:T ratio identified sepsis in more than 90% of patients, and that in the absence of this result, the likelihood of having neonatal sepsis is low.

CONCLUSION

As seen in this study, history and physical examination are still the most important tools in diagnosing neonatal sepsis. In comparing culture proven with nonculture proven sepsis, there was no significant difference in having a positive blood culture or a negative blood culture among any demographic profile and hematological profile tested. The absence of fever is associated with having culture negative sepsis. Hence, it is still acceptable to treat patients with neonatal sepsis if clinically suspected, even with normal complete blood count results or a negative blood culture.

RECOMMENDATIONS

This study only included patients with a final diagnosis of early onset neonatal sepsis. The use of healthy neonates as a control group is recommended for comparison so as to yield more accurate results. Preterm and term neonates should also be separated to determine the difference of their hematological characteristics. It is also recommended for future studies to collect the complete blood count at the same age of the neonate because blood levels change in neonates each day. Also, one person is also recommended to read the laboratory results of the complete blood count to decrease observer variability.

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