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Original Research Article

Role of Plasma Fibrinogen in Diagnosis of Neonatal Sepsis and it's Prognosis

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Abstract:

Purpose: To study the relation between plasma level of fibrinogen and neonatal sepsis and its outcome.

Methods: A prospective case control study was done including 48 neonatal sepsis cases in study group and 42 cases in control group. For all cases Plasma fibrinogen, prothrombin time (PT), activated plasma thrombin time (APTT), C-reactive protein (CRP) and blood culture were performed. Mean Plasma fibrinogen levels for both groups and cut off value of plasma fibrinogen for diagnosis was calculated using receiver operating characteristic curve.

Results: Plasma fibrinogen levels were found to be higher in study group with than in control group ($p< 0.050$). Cutoff value of plasma fibrinogen for diagnosing neonatal sepsis was found to be 305.5mg/dl with a sensitivity and specificity of 80% and 72.8% respectively.

Conclusion: In our study, we found that plasma fibrinogen act as an acute phase reactant and can be used as an immediate marker for detection of early onset neonatal sepsis.

Keywords: Plasma Fibrinogen, Neonatal Sepsis, Acute Phase Reactant, Complication.

Introduction

"Neonatal sepsis is a clinical syndrome resulting from the pathophysiological effect of severe bacterial infection in the first month of life." [1] Neonatal sepsis is the most common cause of morbidity and second most common primary cause of neonatal mortality next to perinatal asphyxia. Neonatal mortality rate was 25.3 per 1000 live births as per National Neonatal Perinatal Database (NNPD) 2002-2003 Report.

Since neonatal sepsis is a preventable cause of mortality, early detection of onset of sepsis is helpful for treatment and also in preventing complications. Neonatal sepsis symptoms and signs includes refusal to feed, fever, excessive cry, hypoglycemia, hypothermia, tachycardia, tachypnea, convulsions. These are not specific to neonatal sepsis and also seen in various other conditions, which pose difficulty in diagnosis. [2],[3],[4]

Blood culture, CSF, urine or other body fluids culture are gold standard methods for diagnosis of sepsis but they need at least 48 to 72 hours for reporting.4, 5 This delays crucial periods during which antibiotics should be administered for treatment. Also there are few false negative blood culture cases present which need to be diagnosed. This necessitates other alternate methods for diagnosis or other indicators for sepsis which requires less time and hence reducing the time to start the treatment.

There are few other method which are used to support the diagnosis like, leukocyte indices, absolute neutrophil count, toxic granules, nRBC's, Acute phase reactants like micro ESR, C-reactive protein, procalcitonin.

Plasma fibrinogen is also one such an acute phase reactant. Mean value of plasma fibrinogen level in healthy preterm and full term neonates aged up to 30days range from 2.43 to 2.54g/L and 2.70 to 2.83g/L respectively [2],[6],[7] . It is seen to increase several fold in inflammatory conditions as a positive acute phase reactant. [2] It is produced in the liver as one of the coagulation pathway agent, which is needed for haemostasis. This feature is used for prediction of neonatal sepsis in this study.

This study was undertaken to study the relation between plasma levels of fibrinogen and neonatal sepsis and it's outcomes like prediction of complications in neonatal sepsis.

Materials and Methods:

Neonatal sepsis cases and hyperbilirubinemia cases as controls which fulfill inclusion and exclusion criteria were collected for case control study, from hospital NICU, in department of pediatrics and department of pathology in BLDEU Shri B .M. Patil Medical College, Hospital and Research Centre, Vijayapura from 1st December 2017 to 30th June 2019.

Data of the both study group like clinical history, antenatal history, clinical examination and demographic data were collected. Blood samples were collected in plain, EDTA and Citrate anticoagulated vacutainers from umbilical cord blood or arterial or venous blood for blood culture, CRP, analysis of hematologic parameters and coagulation profile consisting PT, aPTT and plasma fibrinogen respectively. For blood culture, sample from plain vacutainer was used. Sample blood was first inoculated in glucose broth and incubated for 48 hours and then streaked into Mc conkey agar for further growth. Also blood from plain sample was used for estimation of ESR.

Blood samples collected in Citrate anticoagulated vacutainers were used for estimation of PT, aPTT and plasma fibrinogen. Sample was centrifuged for 15minutes at 1500 rpm to obtain plasma and was run on 'Automated coagulometer ACL Elite Pro' to estimate PT and aPTT values.

Plasma fibrinogen was estimated by automated Erba Mannheim ECL 105 coagulometer by using 'Erba Thrombin reagent for fibrinogen determination' which is made up of approximately 100 NIH units/ ml bovine thrombin with stabilizers and erba owrens veronal buffer.

Statistical Analysis

The data obtained were recorded in a Microsoft Excel sheet, and statistical analysis was performed using statistical package for the social sciences (Version 17). Results are presented as drawings, Mean± SD, counts and percentages. Optimal cut off values of Fibrinogen and CRP for were defined by Youdens index. Sensitivity and specificity of these variables were performed using ROC curves. Categorical variables were compared using chi square test, quantitative variables were compared using Independent t test & Mann Whitney U test. For all tests, significant value was achieved at $p< 0.05$. All statistical tests performed were two tailed.

Inclusion criteria: Neonatal cases with early signs of sepsis and neonates born to mothers with premature rupture of membranes and fever.

Exclusion criteria: Neonates with congenital anomalies.

Results

In this study we found out that among 48 suspected cases of neonatal sepsis, blood culture was positive for 12 cases and positive for viral infection in 6 cases and 2 case having co-infection of both bacteria and virus. Out of 12 culture positive cases, 3 (25%) cases were of E. coli, 2(16.66%) cases each were of Klebsiella pneumonia, Staphylococcus and Coagulase negative Staphylococcus. 1(8.34%) cases each of Staphylococcus Aureus, Staphylococcus pneumoniae and Streptococci. Among these 1 case of CON Staphylococcus with CMV positive was obtained from CSF culture. 1 case was coinfection with Staphylococcus pneumoniae, CMV, Rubella & Toxoplasma. 2 cases were CMV positive, 2 cases were positive for Herpes IgG and 1 case was positive for CMV and Rubella.

There was no significant difference between gestation period and age of neonates. However plasma fibrinogen level (p value-0.010), CRP (p value -0.005) and total leucocyte counts(p value -0.008) were significantly higher in study group than control group. Values of parameters are given in table 1.

With the help of ROC curve, cut off value for plasma fibrinogen was obtained. In the ROC Curve for Blood culture, the AUROC of Fibrinogen, is 76% (95% of Confidence Interval=62 % to 90%) and the optimal cut-off value is 305.5. Using this cut-off value, the Sensitivity and specificity are 80% and 72.8 % respectively. The ROC curve is shown in figure 1.

Discussion

The current study was undertaken to evaluate the efficacy of plasma fibrinogen in the diagnosis of neonatal sepsis and its outcome as in complications. Along with it other haematological indices and CRP are also evaluated for their efficacy.

In current study we evaluated role of plasma fibrinogen levels on neonatal sepsis and its outcome and we found out that plasma fibrinogen levels were significantly elevated in study group containing suspected cases of neonatal sepsis compared to control group. In this study mean plasma fibrinogen was 307.25 ±SD 90.015 for study group and 273.21 ±SD 80.884, which was higher statistically significant with p value of 0.010.

It was also observed that 4 cases which develop complications showed lower level of plasma fibrinogen but PT and APTT were prolonged where as in cases which did not develop complications, plasma levels of fibrinogen was elevated but PT and APTT were within normal range.

In current study after comparing proven neonatal sepsis cases with our control population, on analysis of ROC curves we got cut off value of 305.5mg/dl with sensitivity and specificity of 80% and 72.8%, which was comparable to study conducted by Mitra P et al. [2] who got cut off value of 301.9mg/dl with sensitivity and specificity of 70.8% and 82.7%.

According to study conducted by Guibourdenche J et al [4] concluded that Plasma fibrinogen acts as an acute phase reactant. They got cut off value of 300mg/dl for Plasma fibrinogen in diagnosing neonatal sepsis which was comparable to present study.

In present study the most common organism isolated was E coli followed by Klebsiella pneumonia, staphylococcus and coagulase negative staphylococcus. Similar findings were seen in Cortese F et al [8], Manroe et al [9] Chandna A et al [10] and Renolder B et al [11]. Most common viral infection was CMV.

In this study mean total leucocyte count was higher than control group (p value of 0.008). As per study done by Ahirrao BM et al [12]. Total WBC count has lower sensitivity but higher specificity in detecting neonatal sepsis. It is because of wide normal range of WBC count between 5000-34000cells/cumm. [13-32]

Conclusion

Plasma fibrinogen is normally present in blood as a factor of coagulation system but will be increased in concentration in any infection or inflammation and acts as positive acute phase reactant. It is a rapid, simple and cost effective test, can be used along with other hematological parameters & biochemical markers like CRP in diagnosis of neonatal sepsis. The present study concluded that plasma fibrinogen is not only immediate reliable marker in diagnosing neonatal sepsis but also aids in predicting the complications thus improving the diagnostic efficacy. So this complimentary test also helps the clinicians to start the treatment as early as possible & thereby reducing neonatal mortality, bringing a significant impact in the neonatal health care.

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