Prognostic Value of Initial Antithrombin Levels in Neonatal Sepsis

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Objectives: *We determined whether initial antithrombin (AT) levels help in diagnosis and prognosis of neonatal sepsis.* ***Methods:*** *Sepsis was diagnosed according to clinical and laboratory findings and positive culture results in 34 of the 54 newborns who presented to the hospital with suspected sepsis. Between AT levels and hematological parameters (fibrinogen levels, prothrombin time (PT), activated partial thromboplastin time (aPTT) and liver function tests), these were correlated each other and with outcome of the babies.* ***Results:*** *Initial AT and fibrinogen levels were significantly lower in newborns with sepsis compared to control (P<0.05). Initial AT levels were lower in the ones who developed disseminated intravascular coagulation (DIC) compared to those without DIC (P <0.05). Initial AT levels were significantly lower in newborns who died as compared to survivors (P <0.05). Sensitivity of AT was highest at 15 mg/dL for prognosis in neonatal sepsis (sensitivity:92.3%, specificity:61.9%, positive predictive value : 61.9%, negative predictive value: 61.9%).* ***Conclusion:*** *Lower initial AT levels in neonatal sepsis are associated with a severe disease and increased mortality. It may be useful in predicting clinical outcome in neonatal sepsis.*

Key words: *AT, Fibrinogen, Neonatal sepsis, Septic shock.*

ANTITHROMBIN is a potent inhibitor of thrombin-mediated vascular injury in the micro-circulation during severe sepsis. This endogenous anticoagulant is rapidly depleted in the early phases of sepsis as a result of decreased synthesis, increased destruction, and enhanced clearance by thrombin-antithrombin complex formation(1,2). Although, there are published work about the decrease of AT levels during the early phase of adult sepsis, there is inadequate data about the significance of AT levels in neonatal sepsis. We conducted this study to evaluate the role of initial antithrombin levels in diagnosis and determination of prognosis in culture proven neonatal sepsis confirmed by culture results as well as its association with other hematological and biochemical parameters.

Subjects and Methods

Fifty-eight newborns between 38-40 weeks of gestation hospitalized at the Dr. Behçet Uz Childrens' Hospital with suspicion of sepsis were included in the study. Details of history and clinical examination were recorded and cultures of blood, umblicus, throat, and feces were obtained.

White blood cell and absolute neutrophil counts, immature:total neutrophil (I:T) ratio, micro-erytrocyte sedimentation rate (micro-ESR), C-reactive protein (CRP), aspartate amino transferase (AST), alanine aminotransferase (ALT), fibrinogen, prothrombin time (PT), active partial thromboplastin time (aPTT), and antithrombin (AT) levels were measured in all patients. Culture positive neonates (n = 34) were labelled as having sepsis, the rest were culture negative and designated as controls. The following organisms were recovered from cultures: *Klebsiella pneumoneae* (n = 17), *Escherichia coli* K1 (n = 4), *Staphylococcus aureus* (n = 8), *Pseudomonas aeruginosa* (n = 3), *Acinetobacter* (n = 1), and coagulase negative staphylococcus (n = 1). Second measurement of antithrombin levels was carried out following completion of the treatment in the patient group. Blood samples were not obtained from the control group for the second time. The study was approved by the Instutitional Ethics Committee.

Patients diagnosed with sepsis were followed

after the initiation of treatment and the course of illness was recorded. Complications including septic shock, hypotension and disseminated intravascular coagulation were specially looked for.

Patient and control group means were compared using student's *t* test and Mann Whitney U test. Correlation between two numeric variables was determined using the Pearson's correlation test. Factors which have an impact on AT levels were evaluated using multiple regression analysis. Logistic regression analysis was used to evaluate the impact of AT and fibrinogen on prognosis. Sensitivity and specificity were estimated for AT and fibrinogen. P<0.05 was considered as statistically significant.

Results

Characteristics of study and control groups are shown in *Table I*. Eighteen patients (52.9%) developed septic shock and DIC during follow up. Levels of fibrinogen, antithrombin, platelet count, PT, aPTT, ALT and AST of 16 patients with uncomplicated sepsis are compared to those of the patients with septic shock and/or DIC in *Table II*.

Of the 34 septic infants that were included in the study 13 (38.2%) died while 21 (61.8%) recovered and were discharged *Table III*. The AT levels changed significantly with treatment in the group who recovered (P <0.01) (*Fig.1*). Initial AT levels were significantly lower in the patient group that died compared to the one that recovered (P <0.01). Similarly, fibrinogen levels and platelet counts were significantly lower, PT and APTT were significantly longer while ALT levels were higher in the patient group that died compared to the one that survived. The difference in AST levels of patients who survived compared to those who did not was not significant.

Prognostic value of independent variables such as AT, and platelet count were evaluated with logistic regression analysis. Fibrinogen level could not be included in the regression model because of its strong correlation with AT level. Platelet count did not have an impact on the clinical outcome of the patient (P = 0.9). It revealed that the only independent variable that had a significant impact was AT level (P = 0.002, OR 0.54, CI 95%: 0.37-0.96). An increase of one unit in AT levels decreased the risk of mortality by a factor of 0.5. Evaluation of fibrinogen levels with thrombocyte count with the logistic regression model demonstrated that one unit increase in fibrinogen level is associated with a 0.975 factor decrease in mortality risk (P = 0.011, OR 0.975, CI 95%: 0.95-0.99).

Specificity and sensitivity of both AT and fibrinogen were evaluated since a strong correlation exists between these two parameters. Highest sensitivity of AT with 92.3 % was reached at a level of 15 mg/dL. At this level, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 61.9%, 60.0% and 92.8% respectively. Lower level of 150 mg/dL for fibrinogen in newborns had a sensitivity of 92.3%, specificity of 80.9%, PPV of 25 % and NPV of 61.7%.

TABLE I–*Initial Hematologic and Biochemical Parameters at Diagnosis in Patients and Control Group*

Parameter	Patients (n = 34) Mean ± SD	Control (n = 24) Mean ± SD	P
Mean age (day)	5.8 ± 4.5	7.5 ± 4.6	>0.05
Length (cm)	49.7 ± 2.0	50.1 ± 2.1	>0.05
Weight (g)	3011.5 ± 520.5	3145.5 ± 430.4	>0.05
Head Circumference (cm)	34.5 ± 1.6	34.8 ± 1.4	>0.05
Antithrombin (mg/dL)	13.2 ± 4.5	21.81 ± 3.6	<0.01
Fibrinogen (mg/dL)	175.7 ± 94.42	230.67 ± 63.0	<0.01
Platelet count (mm^3)	67441.2 ± 74160.83	104413.64 ± 87654.34	<0.05
ALT (U/L)	152.3 ± 96.9	42.88 ± 16.87	<0.05
AST (U/L)	146.7 ± 101.2	44.62 ± 17.3	<0.01

TABLE II– *Initial Hematologic and Biochemical Parameters in Patients with Only Septicemia or Septic Shock and/or DIC*

Parameter	Only septicemia (n = 16) Mean ± SD	Septic shock and/or DIC (n = 18) Mean ± SD	P value
Antithrombin (mg/dL)	16.3 ± 3.0	10.4 ± 3.6	<0.001
Fibrinogen (mg/dL)	228.1 ± 86.5	129.2 ± 76.4	<0.01
Platelet count (mm^3)	104062 ± 93269	34888 ± 24823	<0.05
PT(s)	14.8 ± 1.8	26.7 ± 11.1	<0.001
aPTT(s)	32.0 ± 17.0	47.1 ± 12.9	<0.01
ALT (U/L)	45.1 ± 27.0	143.0 ± 99.0	<0.05
AST (Ü/L)	60.3 ± 60.4	137.6 ± 88.6	>0.05

TABLE III– *AT III Levels, Hematologic and Biochemical Parameters at the Time of Diagnosis in Patients who Survived and Who Did Not*

Parameter	Patients who did not survive (n = 13)	Patients who survived (n = 21)	P
PT (s)	27.0 ± 10.9	17.4 ± 7.6	0.002
aPTT(s)	50.5 ± 10.8	33.4 ± 16.4	<0.001
Platelet count (mm^3)	31384 ± 22721	89761 ± 86004	0.02
Fibrinogen level (mg/dL)	105.6 ± 49.1	219.0 ± 90.0	<0.001
ALT (U/L)	172.7 ± 28.4	50.0 ± 30.6	0.049
AST (U/L)	162.1 ± 17.9	63.5 ± 55.6	0.246
Antithrombin (mg/dL)	15.6 ± 3.2	9.2 ± 3.1	<0.001

Discussion

In this study, we measured and analyzed three hemostatic markers (antithrombin, fibrinogen, and platelets) in newborns suspected of having sepsis. Initial AT and fibrinogen levels and platelets of patients confirmed to have sepsis by clinical and laboratory findings were determined to be significantly lower than that of patients who had negative laboratory findings. ALT and AST levels were found significantly higher in septic newborns when compared to the control group.

Many previous studies have reported that initial AT levels of patients with sepsis who developed septic shock and DIC are an indicator of prognosis and cases with very low AT levels have a higher mortality rate(3,4). We confirmed these findings. Moreover, significantly lower initial AT and fibrinogen levels in patients who did not survive compared to those in the ones who survived parallelled the results of the previous reports(3,4). Similar results were obtained in research about adult sepsis. In these studies, it was emphasized that plasma AT level can be a useful marker of organ failure and clinical outcome(3-5). In our study, newborns with lower AT and fibrinogen levels initially, had a higher rate of developing DIC and death. There are no previous research reported in literature about this issue in neonatal sepsis.

We conclude lower initial AT levels are common in newborn with sepsis and are associated with several severely negative clinical outcomes, including increased mortality and development of DIC and/or septic shock. Therefore, in newborns with suspected sepsis, AT levels should be measured initially. Fibrinogen levels may be predictive of AT

What this Study Adds

- Lower initial antithrombin levels may be useful in predicting clinical outcome in neonatal sepsis.

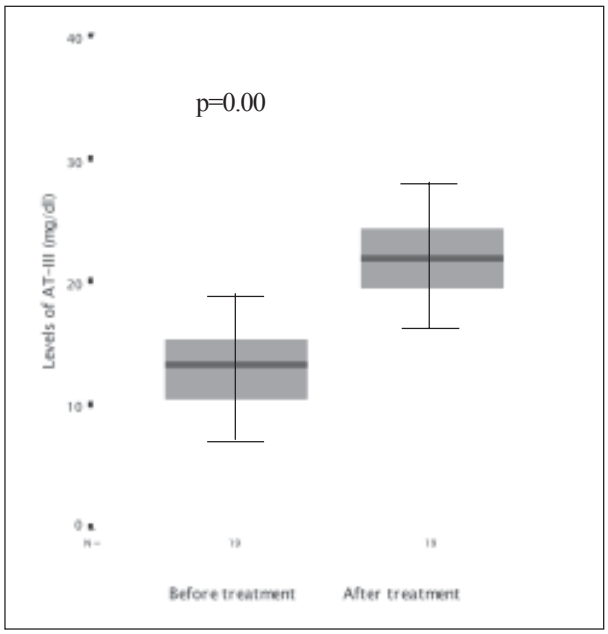

Fig. 1. Pre and post-treatment antithrombin levels in patients who survived. The increase in antithrombin III levels after the treatment was statistically significant. The central horizontal bars, columns and peripherial horizontal bars indicate, the medium values, 25th to 75th percentiles, and 10th to 90th percentiles respectively.

levels when it is not possible to measure the latter. When sepsis is suspected in neonates with very low levels of AT, AT replacement therapy may improve the prognosis because low levels are associated with increased risk of mortality.

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