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Original Article

Prognostic Value of Anti-Thrombin III Level in Neonatal Sepsis

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Abstract

Background: To determine levels of Anti-thrombin III and its prognostic value in predicting neonatal sepsis.

Methods: In this descriptive study full term neonates (n=70)were recruited. For the diagnosis of neonatal sepsis 2 or more of the physical signs and laboratory criteria were taken into account for(temperature instability< 35 or > 38.5°C;tachypnea > 60/min; tachycardia > 200/min;capillary refill > 3 sec; C-reactive protein level > 1 ng/ml). Neonates in which factors which affect the prognosis irrespective of disease severity of neonatal sepsis and neonates who presented with complications of sepsis such as, multiple congenital anomalies, birth weight < 2 kg, birth asphyxia, neonates who received prior treatment or presenting with complications were excluded. Patients with Anti-thrombin III levels less than 35 UIU/dl were considered as bad prognostic group and those with Anti-thrombin III level between 50 – 75 IU/ dl were considered as good prognostic group .The neonates were followed for 2 weeks. Outcomes were assessed in terms of total duration of hospital stay, complications developed, discharge or death of the neonate. p- value less than or equal to 0.05 was considered significant.

Results: The mean Anti-thrombin III level in the good prognosis group was 53.09±8.8 whereas in the bad prognosis group was 41.66±10.58 IU/dl(p <0.05). Anti-thrombin III level below 50 IU/dl had a sensitivity of 62.8%, specificity of 77.1%, positive predictive value of 73.3% and a negative predictive value of 67.5% for predicting poor prognosis and death.

Conclusion: Anti-thrombin III levels can be a potential indicator of prognosis in neonatal sepsis.

Key Words: Sepsis,Newborn, Anti-thrombin III

Introduction

Infection is a major cause of fatality during the first month of life, contributing to 13-15% of all neonatal deaths.[1]The mortality rate in neonatal sepsis may be as high as 50% for infants who are not treated. [2]The incidence of culture-proven sepsis is approximately 2 per 1000 live births. Of the 7-13 % of neonates who are evaluated for neonatal sepsis, only 3-8% have culture-proven sepsis. Anti-thrombin 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 – Anti-thrombin complex formation. Lower initial Anti-thrombin levels in neonatal sepsis are associated with a severe disease and increased mortality.[3,4] It may be useful in predicting clinical outcome in neonatal sepsis. In a study conducted at Tanta University Egypt showed the lowest values of Anti-thrombin-III and protein C neonates who had died in the course of sepsis. The differences between survivors and non-survivors were statistically significant.[5]

Patients and Methods

This descriptive study was carried out at Department of Pediatrics, Benazir Bhutto hospital, Rawalpindi, from June 2010 to December 2010. Patients(n=70)were recruited by consecutive (non probability) sampling. All term neonates of both genders admitted in NICU fulfilling criteria of Neonatal sepsis were included. Following physical signs and laboratory criteria was used to define sepsis; manifestation of 2 or more of the following physical signs that are temperature instability < 35 or > 38.5°C, tachypnea > 60/min, tachycardia > 200/min, capillary refill > 3 sec and with a C-reactive protein level > 1 ng/ml were included. Neonates in which factors which affect the prognosis irrespective of disease severity of neonatal sepsis and neonates who presented with complications of sepsis such as, multiple congenital anomalies, birth weight < 2 kg, birth asphyxia, neonates who received prior treatment or presenting with complications were excluded. Patients were divided into two group (35 each) on the basis of Anti-thrombin III levels. Patients with Anti-thrombin III levels less than 35 UIU/dl were considered as bad prognostic group and those with Anti-thrombin III level between 50 – 75 IU/ dl were considered as good prognostic group . All

neonates were started with the same empirical antibiotics and were changed according to culture and sensitivity report and the same supportive care and treatment continued. The neonates were followed for 2 weeks. Outcomes were assessed in terms of total duration of hospital stay, complications developed, discharge or death of the neonate. For continuous variable like age, temperature, respiratory rate etc mean ±S.D was presented. For categorical variables like, gender, discharge within 2 weeks, duration of hospital stay > 2 weeks and death, frequency and percentages were calculated. Chi square test was used to associate Ant-thrombin III level with neonatal sepsis outcome. p- value less than or equal to 0.05 was considered significant.

Results

Twenty nine (41.4%) were male babies and 41 (58.6%) were female babies. Mean age of the neonates was 6.76±6 days with a range of 1 – 22 days. Capillary refill and respiratory rate revealed significant difference between the two groups (Table 1).

Table 1– Baseline clinical characteristics; good prognosis versus bad prognosis groups

	Good prognosis*	Bad prognosis**	p-value
Age in days	6.5±6.91	7.00±6.2	.764
Weight in kg	2.84±.461	2.98±1.85	.660
Temperature (°F)	101.13±1.22	101.28±1.48	.650
Respiratory rate/ min	73.83±16.03	84.17±10.93	.002
Heart rate/ min	195.11±38.86	189.11±35.35931	.499
Capillary refill(secs)	3.27±.74	3.91±1.12122	.006

*Anti-Thrombin III =50-75 IU/dl;** Anti-Thrombin III <50 IU/dl)

The neonates in the good prognosis group, all neonates were discharged within 2 week as opposed to bad prognosis neonates who stayed in the hospital for longer than 2 weeks. No mortality occurred in the good prognosis group and all neonates who died were included in the poor prognostic group.The mean Anti-thrombin III level in the good prognosis group was 53.09 IU/dl, while in bad prognostic group it was 41.66 IU/dl) (p-value =0.00) (Table 2;Figure 1)).

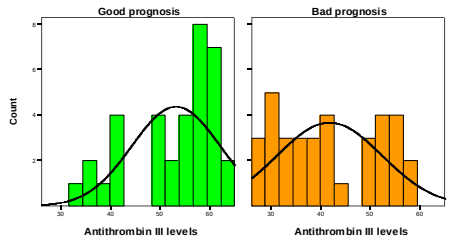

Figure 1– Antithrombin III levels among good and bad prognostic groups

Table 2– Mean Antithrombin III levels: good prognosis versus bad prognosis groups

Prognosis	N	Mean	Std. Deviation	Std. Error Mean	p- value
Good prognosis	35	53.09	8.896	1.504	0.00
Bad prognosis	35	41.66	10.580	1.788	

Anti-Thrombin III levels showed a positive predictive value of 73.3% and a negative predictive value of 67.5% (Table 3)

Table 3- Predictive Value of Antithrombin III

		Patients with poor prognosis (death)		
		Yes	Yes	
Reduced Antithrombin III (Below 50 IU/dl)	Yes	True Positive = 22	False Positive = 8	Positive Predictive Value= 73.3%
	No	False Negative =13	True Negative= 27	Negative Predictive Value= 67.5%
		Sensitivity = 62.8%	Specificity=77.1 %	

Discussion

Significant proportion of neonates with good prognosis had antithrombin III in the good prognostic range . AT III is rapidly consumed during sepsis. In a study by Fourrier et al the results of ATIII measurements show that a severe initial decrease in ATIII level is virtually a constant feature in sepsis. Sequential measurements were consistent with a persistent decrease and a progressive spontaneous correction in survivors only. Initial ATIII levels had a very high prognostic value for prediction of death in their patients. [6] An acute consumption with shortening of the half life is the main causative mechanism of this ATIII decrease.[7]A decreased AT III hepatic synthesis may also be observed in chronic or acute acquired liver failure.[8] An additional and perhaps preeminent mechanism in sepsis might be related to a specific activation of serine proteases and ATIII by elastase released from activated neutrophils.[9, 10] Whatever the cause, the magnitude of the initial decrease in ATIII level is considered to be a reliable index of poor prognosis.

Hesselvich et al found that on the day following hospital admission patients with septic shock had lower antithrombin III and protein C levels than those with infection but without shock. Studies reported signs of more intense activation of coagulation in patients with septic shock as compared with those with infection without shock. [11] These findings were confirmed by Phillipe et al who also reported signs of more marked activation of coagulation in non survivors of septic shock as compared with survivors on the day of hospital admission. [12] In our study, non survivors had a more marked activation of the coagulation system expressed by lower antithrombin III levels. Only survivors showed a pattern of progressive normalization of antithrombin III. Other studies, the first determination on day 1 did not detect significant differences in protein C and antithrombin III.[13]

A study conducted by Fourrier F et al showed that AT levels changed significantly with treatment in the group who recovered (P <0.01). Initial AT levels were significantly lower in the patient group that died compared to the one that recovered (P <0.01). 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. Specificity and sensitivity of both AT and fibrinogen showed 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% which are consistent with our findings. [14]

To clarify the effect of sepsis on the physiologic inhibition system of coagulation including protein S, protein C, and antithrombin III, and to study their further effect on thromboembolic accidents of septic newborns a study was conducted by Beshlawy et al. showed marked decrease in the level of the physiologic inhibition system of coagulation including antithrombin III, protein C, and protein S in 100% of cases, compared to the control group ($p < .001$). [15]

Antithrombin III (ATIII) has been found to be a marker for DIC and to be of prognostic significance in septic patients. Several studies have shown that administration of ATIII in patients with sepsis related DIC is effective in shortening the duration of DIC.[16] Measurement of plasma ATIII and, especially, PC levels may facilitate the recognition of sepsis and may have a prognostic value. [17]

Kountchev *et al*. showed that six hours after the bolus administration of antithrombin, plasma levels of D-dimer, as a marker for the generation of fibrin, was lower in virtually all patients. [18] These data come on top of recent additional analyses on the use of antithrombin concentrate in patients with severe sepsis and may form a new foundation for the further evaluation of this compound in prospective clinical studies.

A global improvement in coagulation markers was observed in survivors as compared with nonsurvivors.[19]Markers of ongoing thrombin generation improved more rapidly in survivors than in nonsurvivors over time. Lorente and coworkers[13] previously showed a similar difference in TAT trend in survivors compared with nonsurvivors at day 7. The prothrombotic host response to outcome observed in this study is consistent with data reported by Gando and co-workers indicating that tissue factor antigen levels positively correlated with the number of dysfunctional organs. [20] Higher levels of the anticoagulant factors protein C, protein S, and antithrombin in placebo survivors than in nonsurvivors at baseline, and the statistically significantly higher levels over time during the course of the disease, confirm previous observations from smaller studies.[21] Survivors exhibited greater normalization of fibrinolytic potential than did nonsurvivors, as indicated by lower levels of Plasminogen Activator Inhibitor (PAI)-1 and greater increases in plasminogen levels with time. Hesselvik and co-workers previously showed an association between higher PAI-1 levels and mortality from sepsis.[22]

Conclusion

Bad prognosis group of neonates with sepsis had significantly reduced Anti-thrombin III levels. Hence, antithrombin III can be a potential indicator of prognosis in neonatal sepsis.

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