http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 12 (22): 1468-1473, 2009
ISSN 1028-8880

Role of Protein Z and Protein C in Neonates with Respiratory Distress Syndrome in Egypt (Experience of One Centre)

[1]Safaa S. Imam, [3]S. El-Sahrigy, [3]M. Sedki, [2]S. Baker and [3]S. Marey
[1]Department of Pediatric, Ain Shams University, Egypt
[2]Department of Clinical Pathology, Ain Shams University, Egypt
[3]Department of Pediatric, National Research Center, Egypt

Abstract: The aim of this study is to evaluate Protein Z (PTZ) and protein C (PTC) levels in newborns suffering from RDS, healthy preterm and full term newborns and to compare PTZ serum levels in RDS preterm infants with healthy preterm before and after recovery. Sixty newborn infants, recruited from the neonatal unit, were enrolled in the study and divided into 3 groups: Group (I): 20 preterm with RDS, Group (II): 20 healthy preterm control newborns (CPT) and Group (III): 20 healthy full term control newborns (CFT). Protein Z and C were measured using ELISA kits. The results of the study showed lower levels of protein Z were obtained in RDS group compared to preterm controls whose levels were significantly lower than in full-term controls. A significant increase in PTZ levels in RDS' group after recovery, when compared to preterm controls. In RDS, no significant correlations existed between PTZ levels (before and after recovery) and routine investigations except for a significant negative correlation with platelets count. No significant differences were found in PTC levels between the 3 studied groups. To conclude: premature newborns suffering from RDS showed decreased serum protein Z levels than normal preterm control newborns with further increase in its pattern after recovery. Further studies are recommended to evaluate the role of PTZ on outcome in premature newborns with RDS and to evaluate the relationship between protein PTZ and PTC and other coagulation factors incriminated in the development of RDS.

Key words: RDS, protein Z, protein C

INTRODUCTION

Hyaline membrane disease or respiratory distress syndrome is one of the most common lung disorders in premature newborn. It results from a defect in the pulmonary surfactant metabolism. Abnormalities in the coagulation and fibrinolytic systems may play a role in the pathogenesis of RDS and contributes to the progression of the disease (Brus *et al*., 1997; Jaarsma *et al*., 2001; Bastarache *et al*., 2006). This is evidenced by fibrin deposition in pulmonary microcirculation and small airways (Mautone *et al*., 1997; Idell, 2001). Histo-pathologic studies proved that fibrin constitutes a major part of the hyaline membranes, which could be regarded as a local origin for clots in RDS (Chan *et al*., 1998). Fibrin deposition has been demonstrated in the pulmonary microcirculation and small airways in RDS suggesting the activation of the clotting system with a special role of protein C (PTC) and protein S. Protein Z (PTZ) -a vitamin k dependent protein-, was added to these factors. PTZ is a vitamin K-dependent plasma protein whose function remained unclear until many researchers found that its deficiency occurs in newborns affected by severe RDS due to activation of the coagulation process (Schettini *et al*., 2004). The structure of PTZ is very similar to that of the coagulation-related factors VII, IX and X and PTC (Yin *et al*., 2000). It forms a calcium-dependent complex with activated coagulation factor X leading to its inhibition and the suppression of thrombus formation (Broze, 2001). Deficiency of human PTZ has been incorporated with a pro-thrombotic tendency (Yin *et al*., 2000). PTC which a vitamin K protein-dependant is an important natural anticoagulant protein (Esmon, 2003) that also plays an anti-inflammatory role in pathogenesis of RDS (Miller *et al*., 2000; Liu *et al*., 2008). Present objectives are: (1) to evaluate PTZ and PTC levels in newborns suffering from RDS, healthy preterm and full term newborns and (2) compare PTZ serum levels in RDS preterm with healthy preterm before and after recovery.

MATERIALS AND METHODS

This is a prospective study that has been conducted on 60 newborn infants from the obstetrics and

Corresponding Author: Safaa S. Imam, Department of Pediatric, Ain Shams University, Egypt

gynecology hospital and neonatal intensive care unit Ain-Shams University Hospital in the period between 2/2007 and 7/2007. Special assessment of the score of Ballard and ultra ultrasound findings were done to determine the gestational age. Neonatal respiratory distress syndrome was based on clinical and radiological criteria (Kero and Mäkinen, 1979). They were divided into three groups: Group I: comprised 20 newly born developing respiratory distress syndrome within the first 6 h of life and called RDS patients group, Group II: included 20 healthy preterm newborns as preterm control group and Group III: was formed of 20 healthy full term newborns as the full term control group. Blood sampling: 1 umbilical cord sample was collected initially after delivery and before vitamin K administration for all cases. For those newborns that developed RDS, another sample was collected after their recovery to assess protein Z and C levels. Both samples were collected as follows: 9 mL sec in tubes containing 0.11 M sodium citrate (1 mL) then centrifuged within 20 min at 2500 rpm for 10 min. platelet poor plasma was fractioned and frozen at (-70°C) until estimation of PTZ and PTC. The samples were thawed for 15 min at 37°C just before use. For each newborn enrolled in the study, the following was completed:

- General examination: (1) Full history taking including parity, gestational age, antenatal history and mode of delivery, (2) thorough clinical examination, (3) expanded score of Ballard, (4) apgar scoring at 1 and 5 min
- Routine laboratory investigations including (1) Blood gases, using blood gas analyzer BEARS supplied by CIBA corning Diagnostics Corp. (medfield, MA, USA), (2) complete blood picture (Coulter counter T660), (3) liver functions, (4) kidney functions test
- Radiological grading of severity of RDS was done (Kero and Mäkinen, 1979)

Protein Z estimation: PTZ Concentrations were measured by a quantitative immuno enzymatic kit supplied by HYPHEN Bio Med 95000 Newville-sur-oise-France. Assay principle: the immunoconjugate, which is a polyclonal antibody specific for PTZ coupled to Horse Radish Peroxides (HRP), is introduced into the microwells coated with a polyclonal antibody specific for PTZ then, the diluted tested sample is immediately introduced and the immunological reaction starts, PTZ binds onto the polyclonal antibody coated solid phase through one epitopes and fixes the polyclonal antibody coupled to HRP through free epitopes following a washing step, the peroxides substrate, 3, 3', 5, 5'-tetramethylbenzidine (TMB), in presence of hydrogen peroxide (H_2O_2), is introduced and a blue colour develops. When the reaction is stopped with sulfuric acid, a yellow colour is obtained and the amount of color developed is directly proportional to the concentration of human PZ in the tested sample.

Protein C estimation: Protein C% was measured by ELISA test for quantitative determination of protein C antigen in citrated plasma. Assay Principle: The protein C antigen assay is a sandwich ELISA. A capture antibody specific for human protein C is coated to 96-microwell polystyrene plates. Diluted patient plasma is incubated in the wells, allowing any available protein C to bind to the anti-human protein antibody on the microwell surface. The plates are washed to remove unbound proteins or other plasma molecules. Bound protein C is quantified using Horse Radish Peroxidase (HRP) conjugated anti-human protein C detection antibody. Following incubation, unbound is removed by washing. A chromogenic substrate of Tetra Methyl Benzidine (TMB) and hydrogen peroxide (H_2O_2) are added to develop a colored reaction. The intensity of the color is measured in Optical Density (OD) units with a spectrophotometer at 450 nm. Protein C antigen relative percent concentrations in patient plasma is determined against a curve prepared from the reference plasma provided with the kit.

Statistical methods: Standard computer program SPSS for Windows, release 10.0 (SPSS Inc, USA) was used for data entry and analysis. All numeric variables were expressed as Mean±SD. Comparison of different variables in various groups was done using student's t test and Mann Whitney test for normal and nonparametric variables respectively. Chi-square (χ^2) test was used to compare frequency of qualitative variables among the different groups. Pearson's and Spearman's correlation tests were used for correlating normal non-parametric variables respectively. For all tests a probability (p) less than 0.05 was considered significant. Graphic presentation of the results was also done. The p values <0.05 were considered significant and p values <0.01 and <0.001 were considered highly significant.

RESULTS

The results of this study are displayed in Table 1-6. The RDS group were 17 with mean gestational age 32 weeks, mean birth weight 1350 g while the control preterm group were 20 infants with mean gestational age 32 weeks, mean birth weight 2100 g and the control fullterm group were 20 with mean gestational age 39.5 weeks, with mean birth weight 3300 g (Table 1). Laboratory parameter for the RDS group showed mean

Table 1: Demographic presentation of the population

Groups	No.	Gender F	Gender M	Gestational age (week)	Weight (g)	APGAR (1 min)	APGAR (5 min)
RDS	17	10	7	32.0 (30-37)	1350 (750-2900)	5 (4-6)	7 (5-7)
Control preterm	20	11	9	32.0 (30-36)	2100 (2000-3150)	8 (8-10)	9.5 (9-10)
Control full term	20	12	8	39.5 (37-41)	3300 (2900-3950)	9 (8-10)	10 (9-10)

Table 2: Laboratory parameters of the studied RDS patients

Laboratory parameters	RDS (Mean±SD)	Normal values	Significance
Hb	12.84±3.48	15.06 (±1.92) g/100 mL) %)	Normal
TLC	15.42±4.32	$15.34±5.2×10^9$ L^{-1}	Normal
Platelets	296.00±108.04	150-450,000 mm^{-3}	Normal
PH	7.24±3.38	7.26±0.07	Acidosis
PCO_2	51.47±2.48	37±2.2 (35-45)	Respiratory acidosis
Base excess	3.00±1.70	4±3 (mmol L^{-1})	Normal

Table 3: Comparison between protein Z and protein C levels (before and after recovery RDS) with control preterm group and full term

Variable	RDS before	RDS after	P	RDS before	Control preterm	P
Protein Z (ng mL^{-1})	0.585±0.415	1.659±0.594	0.000HS	0.585±0.415	0.855±0.459	0.052S
Protein C (%)	36.82±15.33	37.82±19.84	0.795NS	36.82±15.33	35.95±14.93	0.988NS
Variable	RDS after	Control preterm	P	Control preterm	Control full term	P
Protein Z (ng mL^{-1})	1.659±0.594	0.855±0.459	0.000 HS	0.855±0.459	1.253±0.577	0.020S
Protein C (%)	37.82±19.84	35.95±14.93	0.745 NS	35.95±14.93	42.25±16.61	0.211NS

S: Significant, NS: Not significant, HS: Highly significant

Table 4: Correlations between protein Z before and after recovery and gestational age, weight, APGAR 1, APGAR 5, hemoglobin %, total leucocytes counts, platelets counts, pH and PCO_2 in patients with RDS, control preterm and control full term

Variable	Statistical value	GA.	Wt.	APG1	APG 5	Hb	TLC	PLAT	pH	PCO_2
RDS protein Z ng mL^{-1} before	R	-0.055	0.004	-0.285	-0.307	0.503	0.029	-0.466	-0.394	0.349
	P	0.833	0.987	-267	0.231	0.390	0.914	0.050	0.117	0.170
RDS protein Z ng mL^{-1} after	R	-0.130	-0.266	0.069	0.136	0.301	0.180	-0.038	-0.314	0.252
	P	0.618	0.302	0.792	0.602	0.241	0.886	0.886	0.220	0.329
CPT	R	-0.011	0.155	-0.245	0.017					
PTZ	P	0.963	0.513	0.297	0.942					
CFT	R	0.091	0.320	-0.183	-0.131					
PTZ	P	0.704	0.169	0.440	0.581					

APG1: APGAR1, APG5: APGAR5, CFT: Control full term, CPT: Control preterm, GA: gestational age, Hb%: Hemoglobin %, HS: Highly significant, Negative results: negative correlation, NS: Non significant, P: p-value, platelets counts PLAT: Positive results:positive correlation., S: Significant, R: Correlation, TLC: Total leucocytic counts, Wt: Weight

Table 5: Correlation between protein C before and after recovery and gestational age, weight, APGAR 1, APGAR 5, hemoglobin %, total leucocytes counts, platelets counts, pH and PCO_2 in RDS group, CPT and CFT

Variable	Statistical values	GA.	Wt.	APG1	APG 5	Hb.	TLC	PLAT	pH	PCO_2
Protein C % before	R	-0.276	-0.436	0.271	0.162	-0.057	0.139	0.356	0.496	0.007
	P	0.284	0.080	0.293	0.536	0.827	0.594	0.161	0.043	0.979
Protein C % after	R	0.055	0.236	-0.167	-0.272	0.310	0.067	-0.358	-0.492	-0.586
	P	0.833	0.362	0.521	0.291	0.226	0.798	0.158	0.045	0.742
Protein C % in	R	0.041	0.206	-0.095	-0.367					
CPT	P	0.863	0.383	0.691	0.712					
Protein C % in	R	-0.070	-0.023	0.039	0.774					
CFT	P	0.769	0.924	0.871	0.463					

APG1: APGAR1, APG5: APGAR5, CFT: Control full term, CPT: Control preterm, GA: Gestational age, Hb%: Hemoglobin, Wt: weight, PLAT: Platelets counts, TLC: Total leucocytic counts

platelet count 296,000 cm^{-3}, Hb% 12.84 g dL^{-1} and total leucocytic count 15.42 cells cm^{-3} to exclude early sepsis with pH 7.24 Co_2 51.47 denoting respiratory acidosis (Table 2). In Table 3, RDS group of patients showed a significant decrease in PTZ levels which increased significantly after recovery ($p<0.001$). Alternatively, protein C% didn't differ in the same group of patients before and after recovery ($p>0.05$) PTZ level showed a significant increase in RDS group after recovery which was noticed when compared to preterm controls ($p<0.001$). A significant difference in PTZ levels existed between preterm and full term controls ($p<0.05$). With no significant difference in PTC% was noticed either between RDS and preterm control group ($p>0.05$), or between preterm control and full terms control groups ($p>0.05$). No correlations were found between PTZ in RDS group (before and after recovery) and gestational age, weight, APGAR 1, APGAR 5, hemoglobin, TLC, Platelets, pH, or PCO_2, except for the presence of a significant negative correlation between PTZ before recovery and platelets

Table 6: Correlation between protein Z and protein C before and after recovery in RDS patients group

Variable	Statistical value	PZ before	PZ after	PC before	PC after
Protein Z before	R	-	0.466	-0.455	0.548
	P		0.050	0.066	0.023
Protein Z after	R	0.466	-	0.138	0.261
	P	0.050		0.596	0.311
Protein C before	R	-0.455	0.138	-	-0.534
	P	0.066	0.596		0. 027
Protein C after	R	0.548	0.261	-0.534	-
	P	0.023	0.311	0.027	

count in RDS patients (Table 4). No significant correlations existed between PTC% and the laboratory parameters in all the studied groups included in the work (Table 5). There was a positive correlation between PTZ before and PTZ after and a negative correlation in PTC before and after recovery Table 6.

DISCUSSION

Neonatal RDSs are characterized by leakage of plasma proteins of varying sizes into the airspace, which leads to interstitial and intra-alveolar thrombin generation with subsequent fibrin deposition (Stevens *et al*., 2000; Idell, 2001); systemic activation of clotting, complement and polymorphonuclear lymphocytes (Ware *et al*., 2007). PTZ which is a vitamin k dependent protein proved to play a role in the prevention of coagulation (Kemkes-Matthes and Matthes, 2001). In the present study, RDS group showed a high significant increase in PTZ level after recovery (by one or two days) compared to its levels before recovery. This was in contrast to Schettini *et al*. (2004) who noted no increase in PTZ levels after vitamin K administration in RDS patients. Patients of RDS group showed significant lower levels of PTZ when compared to preterm control group, which increased significantly after recovery in comparison to preterm controls. This was in agreement with Yurdakok and Yigit (1999), Yurdakok *et al*. (2002) and Schettini *et al*. (2004). Schettini *et al*. (2004) related the difference in PTZ levels between RDS patients and preterm controls to the coagulation theory, where there is activation of the coagulation mechanism in RDS patients. PTZ acts as an essential cofactor for PTZ-dependent protease inhibitor (ZIP), which in turn is a potent down-regulator for coagulation factor X. Lower levels of PTZ in RDS patients will result in activation of coagulation with intra-alveolar fibrin deposition which would significantly impair the surfactant's function (Heeb *et al*., 2002). The current study showed no effect of either gestational age, weight, APGAR score, hemoglobin %, TLCs, pH or PCO2 on PTZ levels in all groups included in the study. This was in agreement with Corral *et al*. (2007), who noted no effect of either the gestational age or weight on PTZ levels. However, a significant negative correlation was found between PTZ before recovery and platelets counts in RDS group of patients. Yurdakok *et al*. (2002) stated that the hypercoagulable state in RDS patients is responsible for the increase in the platelets levels. They related the abnormalities in fibrinolytic system in these patients to lung damage and local platelet activation which lead to coagulation abnormalities other than DIC.

In the present study, PTC percent was estimated in patients with RDS as a vitamin K dependent and a natural anticoagulant protein. RDS group showed no significant difference in PTC level before and after recovery. This was in contrast to Schettini *et al*. (2004), who found an increase in PTC activity in newborns with RDS from day 1 to day 3. No significant difference existed between PTC in the RDS patients' group and preterm control, as well as between preterm and full terms control groups. These results were in accordance with Yurdakok *et al*. (2002) who reported no significant difference in PTC% in patients with RDS and the control newborns. They related this finding to the fact that the activation of clotting is not prominent in the early stages of RDS. This was in disagreement with Kobayashi *et al*. (1998) and Idell (2001), who found a decrease in Activated Protein C (APC) levels in the broncho alveolar lavage fluid in patients with moderate to severe RDS when compared to normal controls. They attributed this finding to activation of coagulation in their patient's group. In addition, Bartolome *et al*. (2008) stated that in response to hypoxia, an inflammatory cascade is initiated and microvascular injury ensues. Specifically, within 10 min leukocyte adherence to the endothelium begins and leukocyte emigration and vascular leak soon follow. The discrepancy in the results between the present work and the others may be due to the use of different samples for PTC assessment.

Similar to PTZ, no significant correlations were found between, PTC before or after recovery in RDS group and gestational age, weight, APGAR 1 and APGAR 5. These results were in agreement with Emmerich *et al*. (2005), who proved no effect of body weight, or age on PTC, as its deficiency is acquired in a number of clinical coagulation conditions such as RDS.

In the present study, in the RDS group, there was a significant negative correlation between PTC before and after recovery. On the other hand, a significant positive correlation existed between PTZ before and after recovery. PTZ acts by forming a complex with factor Xa at the phospholipids surfaces (Han *et al*., 2000), while PTC exerts its anticoagulant effect by degrading factor VIIIa and factor Va (Abraham, 2000) and also affects the fibrinolytic activity by forming a complex or degrade plasminogen activator inhibitor, thus diminished PTC

activation leads to increased pro-coagulant activity and decreased fibrinolysis in RDS patients. Although, both factors deficiency influence coagulation pathways differently, they end with activation of coagulation pathways (Dahlbäck, 2005).

In view of this study, PTZ levels in RDS patients, showed a significant increase in its level after recovery reaching near normal levels. Negative correlation was present between PTZ and platelets count in RDS patients. Serial measures of plasma PTZ levels in premature may be of benefit in RDS to follow up their condition. Further studies are recommended to evaluate the role of PTZ on outcome in premature newborns with RDS and to evaluate the relationship between protein PTZ and PTC and other coagulation factors incriminated in the development of RDS.

ACKNOWLEDGMENT

Authors are great full to the Chief of Ain Shams University Hospital-NICU department and the parents of the babies.

REFERENCES

Abraham, E., 2000. Coagulation abnormalities in acute lung injury and sepsis. Am. J. Respir. Cell Biol., 22: 412-421.

Bartolome, S., J.G. Wood, A.J. Casillan, S.Q. Simpson and A.R. O'Brien Ladner, 2008. Activated protein C attenuates microvascular injury during systemic hypoxia. Shock. Mar., 29: 384-397.

Bastarache, J.A., L.B. Ware and G.R. Bernard, 2006. The role of the coagulation cascade in the continuum of sepsis and acute lung injury and acute respiratory distress syndrome. Semin. Respir. Crit. Care Med., 27: 365-376.

Broze, G.J., 2001. Protein Z-dependent regulation of coagulation. Thrombosis Haemostasis, 86: 8-13.

Brus, F., W.O. Van, A. Okken and S.B. Oetomo, 1997. Disease severity is correlated with plasma clotting and fibrinolytic and kinin-kallikrein activity in neonatal respiratory distress syndrome. Pediatr. Res., 41: 120-127.

Chan, A.K., L. Berry, L. Mitchell, B. Baranowski, H. O'Brodovich and M. Andrew, 1998. Effect of a novel covalent antithrombin-heoarub complex on thrombin gene-ration on fetal distal lung epithelium. Am. J. Physiol., 274: L914-L921.

Corral, J., R. Gonzalez, D. Espinosa and V. Vicente, 2007. Protein Z/Z-dependent protease inhibitor (PZ/ZPI) anticoagulant system and thrombosis. Br. J. Haematol., 137: 99-108.

Dahlbäck, B., 2005. The importance of the protein C system in the pathogenesis of venous thrombosis. Hematology, 10: 138-139.

Emmerich, J., C.Y. Vossen and P.W. Callas, 2005. Chronic venous abnormalities in symptomatic and asymptomatic protein C deficiency. J. Thromb. Haemost., 3: 1428-1431.

Esmon, C.T., 2003. The protein C pathway. Chest, 124: 265-325.

Han, X., R. Fiehler and G.J. Broze, 2000. Characterization of the protein Z dependent protease inhibitor. Blood, 96: 3049-3055.

Heeb, M.J., A. Pagamini-Hill, J.H. Griffin and M. Fisher, 2002. Low protein Z levels and risk of ischemic stroke: Differences by diabetic status and gender. Blood Cells Mol. Dis., 29: 139-144.

Idell, S., 2001. Anticoagulats for Acute respiratory distresss syndrome. Am. J. Respir. Crit. Care Med., 164: 517-520.

Jaarsma, A.S., M.A. Braaksma, W.B. Geven, W. van Oeveren and S.B. Oetomo, 2001. Early Activation of Inflammation and clotting in the Preterm Lamb with Neonatal RDS: Comparison of Conventional Ventilation and High Frequency Oscillatory Ventilation. Pediatric Res., 50: 650-657.

Kemkes-Matthes, B. and K.J. Matthes, 2001. Protein Z, Seminars in Thrombosis and Hemostasis. Semin Thromb. Hemost., 27: 551-556.

Kero, P.O. and E.O. Mäkinen, 1979. Comparison between clinical and radiological classification of infants with the respiratory distress syndrome (RDS). Eur. J. Pediatr., 130: 271-278.

Kobayashi, H., E.C. Gabazza, O. Taguchi, H. Wada and H. Takeya *et al*., 1998. Protein C anticoagulant system in patients with interstitial lung disease. Am. J. Respir. Crit. Care Med., 157: 1850-1854.

Liu, K.D., J. Levitt, H. Zhuo, R.H. Kallet and S. Brady *et al*., 2008. Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am. J. Respir. Crit. Care Med., 15: 554-555.

Mautone, A., P. Giordano, O. Montagna, M. Quercai, M. Altomare and D. De Mattia, 1997. Coagulation and fibrionlytic system in the ill preterm newborn. Acta Paediatr., 86: 1100-1104.

Miller, D.L., K.E. Welty-Wolf, M.S. Carraway, Y.C.T. Huang and S. Idell *et al*., 2000. Blockade of extrinsic coagulation decreases lung injury in baboons with gram negative sepsis. Am. J. Respir Crit. Care Med., 161: 517-517.

Schettini, F., N. Laforgia, M. Altomare, A. Matuone and G.C. Del-Vecchio, 2004. Plasma protein Z levels in healthy and high-risk newborn infants. Acta Paediatr., 93: 654-657.

Stevens, T., J.G.N. Garacia, D.M. Shasby, J. Bhattachary and A.B. Malik, 2000. Mechanisms regulating endothelial cell barrier function. Am. J. Lung Cell Mol. Physiol., 279: L419-L422.

Ware, L.B., M.A. Matthay, P.E. Parsons, B.T. Thompson, J.L. Januzzi and M.D. Eisner, 2007. Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. Crit. Care Med., 35: 1821-1828.

Yin, Z.F., Z.F. Huang, J. Gui, R. Fiehler, N. Lasky, D. Ginsburg and G.J. Broze, 2000. Prothrombotic phenotype of protein Z deficiency. Proc. Natl. Acad. Sci. USA., 97: 6734-6738.

Yurdakok, M. and S. Yigit, 1999. Hemostatic system in early respiratory distress syndrome: Reduced fibrinolytic state. Turkish J. pediatr., 41: 489-493.

Yurdakok, M., A. Korkmaz, S. Kirazli, C. Aygun and S. Yigit, 2002. Global fibrinolytic capacity in Early Respiratory distress syndrome: A pilot study. Am. J. Hematol., 69: 255-257.