Original Article

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Pulmonary coagulopathy in pediatric acute lung injury/acute respiratory distress syndrome

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Abstract

***Background*: Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are major causes of morbidity and mortality in pediatric intensive care units (PICUs). Prior work has shown disorder of inflammation and coagulation in ALI/ARDS. Activated protein C (APC) is a potential critical endogenous regulator of coagulation and inflammation in ALI/ARDS.**

***Material and Methods*: We prospectively studied children admitted with ALI/ARDS. We obtained clinical data, initial blood coagulation profiles including plasma protein C (PC) activity and free protein S antigen (PS Ag).**

***Results*: 27 patients with ALI/ARDS were recruited in our study; their mean age was at 6.4±5.2 years. Fifteen were survivors (55%), 12 were non-survivors (45%). Initial plasma PC activity was 72.0±27.6% and plasma free PS Ag was 58.52±29.8%. Platelets, PT & PTT were significantly abnormal compared between survivors and non-survivors (p=0.01, 0.02, 0.01). There was a significantly negative correlation between plasma PC with initial systolic blood pressure (r=0.5, p=0.008) and PS Ag (r=0.41, p=0.02). There was also a trend of negative correlation between plasma PC with ventilator day (r^2=0.0009, p=0.1) and length of stay in PICU (r^2=0.1, p=0.09).**

***Conclusions*: This study suggests that most of our pediatric ALI/ARDS had abnormal coagulogram. Coagulation dysfunction including initial plasma PC activity might be associated with the overall outcome.**

Introduction

Substantial progress has been made in the understanding of the pathophysiology of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). (1) Procoagulant activity in the setting of ALI/ARDS has been recognized for several years. Autopsy findings in patients with ARDS showed fibrin and micro thrombi in the lungs even though there was no evidence of disseminated intravascular coagulation (DIC). (2) Amplified coagulation and inhibition of the fibrinolysis systems are involved in basic mechanism of sepsis, which is the most common underlying etiology of ARDS. (3,4) The presence of DIC was correlated with impaired gas exchange and lung compliance. The inflammatory process involved activation of immune cells and the production of proinflammatory cytokines and direct activation of coagulation and inhibition of fibrinolysis. (5,6) Recent review suggested that mechanical ventilation might also lead to or aggravate pulmonary coagulopathy. (7)

Mechanisms that regulate the coagulation pathway under normal conditions involve natural inhibitors of coagulation,

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including APC, antithrombin (AT), and tissue factor pathway inhibitor (TFPI). These factors decline in sepsis due to a decrease in production as well as enhanced breakdown. (8,9) Our previous work demonstrated the relationship of APC levels and the risk of mortality in children with septic shock. (10) Alveolar thrombin generation in ALI/ARDS seems to be mediated by the tissue factor VIIa pathway. Tissue factor levels are low in the normal lung and elevated in disease. Although the lungs have a limited capacity to produce protein C, APC is present in broncho-alveolar fluids. It also has been shown to be suppressed in patients with pneumonia, ventilator associated pneumonia (VAP) and pulmonary inflammation. (11,12) The results of an upregulated host defense response are diffuse alveolar damage involving the epithelium, endothelium, and interstitial space. A key concept of the host response that emerged over the past decade is the importance of knowing the association between inflammation and coagulation. Thus our aim of this study is to further investigate the levels of initial coagulation profiles including PC/PS and their clinical correlation in Pediatric ALI/ARDS.

Material and Methods

We prospectively recruited infants and children age between 1 month to16 years who had diagnosis of ALI/ARDS and admitted to our PICU from July 1, 2007 to December 31, 2008. Our PICU is a 9-bed, referral university hospital. ALI/ARDS were defined by American/European consensus conference definition. (13) Clinical data were recorded and blood samples were kept for further analysis. We then measured the levels of PC activity, protein S antigen (PS), other baseline coagulogram and compared them with normal children. Our ethical committee on human research at King Chulalongkorn Memorial Hospital approved the study. Inform consents were obtained from parents or legal guardians.

Exclusion criteria

Patients with the following diseases/conditions were excluded from our study:

1. Preexisting chronic lung disease or lung resection.
2. End stage diseases (untreatable cancer etc).
3. ALI/ARDS for more than 72 hours.
4. Pre-existing coagulation disorder eg protein C/S deficiency.

Measurement of activate protein C (%)/free PS antigen

PC activity and free PS Ag were measured by using a commercial available, chromogenic assay (Berichrom-Dade Behring, Germany). PC/free PS activity results were reported as a relative percentage, as compared with pooled normal plasma.

Clinical data collection

The cause of ALI/ARDS was determined. Demographics, physiologic data, respiratory variables, medications, PRISM III were also recorded. The primary outcome variables included death in PICU.

Statistical analysis

The data are presented as mean±SD. To assess the relationship between each coagulation measure, non-parametric Spearman rank correlation was calculated. Chi-square, one way ANOVA and Mann-Whitney U tests were also applied where appropriate. Multivariable logistic regression analysis was performed to determine associated risk factors (SPSS, ver 13, Chicago, IL). The results were reported as odds ratios with 95% intervals. For all analysis, a two-sided p of less than 0.05 was considered significant.

Results

Of the approximately 720 pediatric patients admitted to our PICU during the study period, there were 27 (3.75%) children aged between 4 months and 16 years who were diagnosed with ALI/ARDS. Their mean age was at 6.4 ± 5.2 years. There were 17 male (63%) and 10 female (37%). There were 22 (81.5%) ARDS and 5 (18.5%) ALI. The most common underlying disease was hematologic malignancy (11, 40%) Their mortality was at 44.4% (12/27). The initial

PRISM III score was significantly higher in non-survivor group compared to survivor group. Initial oxygen index (OI) also had a trend to be higher in non-survivor children (**Table 1**).

Coagulation profiles

Their mean PC activity was 72.0±27.6% and free PS Ag was 58.5±29.8%. They were significantly lower than normal control ($p<0.05$). The levels of PC activity and free PS Ag were not significantly different between survivor and non-survivor groups as shown in **Table 2**. The levels of PC activity were significantly lower in infants (<1 year) compared to older children (>8 years) ($p<0.03$) as shown in **Table 3**. Furthermore, we found a significant correlation between PC activity levels and blood pressure (**Figure 1**) and had a trend of reverse correlation with length of PICU stay (**Figure 2**).

Discussion

ALI/ARDS are associated with high morbidity and mortality as shown in our study despite advances in supportive care. The pathogenesis of ALI/ARDS is similar to that of sepsis. (3,14) 18-40% of patients with sepsis develop ALI/ARDS. (14) In addition, sepsis-related ARDS has a higher overall severity, poorer recovery from lung injuries and higher mortality. It involved inflammation, endothelial cells damage, enhanced coagulation, diminished fibrinolysis and fibroproliferation. (15-17) Our study showed that 90% of our patients had abnormal PC activity and free PS Ag at an early stage of their disease even though it was not that low compared to previous report (55±28%) in adults. (12) Plasma PC activity and free PS Ag were lower than normal even in patients without sepsis. Nevertheless, their PC activity levels were higher compared to our previous data in children with septic shock (37.8±4.4%). (10) Patients with lower levels of PC activity had a significant correlation with degree of hypotension (**Figure 1**) and a trend to correlate with longer duration in PICU (**Figure 2**). These findings may suggest the relationship between clinical severity of septic shock and coagulation abnormalities. Disruption of PC pathway occurs in both septic and non-septic patients with ALI/ARDS. It may contribute to the pathogenesis. An uncontrolled host defense response that leads to more inflammation and fibroproliferation in the lungs may result in diffuse alveolar damage. (17) Tissue factors in association with factor VIIa and inhibition of urokinase by plasminogen activator inhibitor-1 (PAI-1) are major factors that are responsible for procoagulant and anti-fibrinolytic states. (12) These factors can be released during acute lung injuries. With regard to pulmonary vascular obstruction, it has long been recognized that embolization of both large and small pulmonary vessels is a prominent feature of severe ARDS. (2,18) It can further increase in pulmonary artery pressure and result in right ventricular dysfunction. The early stage of ALI/ARDS is characterized by acute endothelial cells injuries caused capillary engorgement and diffuse micro thrombi. Our findings also demonstrated the high levels of D-Dimer and significantly low platelet counts in non-survivors.

Mechanical ventilation may also interplay with coagulation dysregulation. Some suggested the existence of tissue factor mediated coagulation. Patients with ventilator induced lung injuries (VILI) resulted from high tidal volume showed a larger increase in alveolar tissue factor mediated coagulation compared to protective lung strategies. Alveolar fibrin deposition is an important feature of pulmonary infection as well as sepsis. They could further aggravate the reduction of gas-exchange and lung compliance. Furthermore, in ALI/ARDS, abnormalities in fibrin turnover are not restricted to the lungs. Systemic levels of PC are also quite low. Several investigators have shown that ARDS patients significantly released potent inflammatory cytokines both in BAL and systemically. (19,20) Potent inflammatory cytokines especially IL-6 and TNF-alpha had been shown to cause massive systemic activation of coagulation while significantly inhibits both fibrinolysis and anticoagulant. APC is essential in maintaining proper balance between coagulation and fibrinolysis, and also had anti-inflammatory properties. (4,12,21) Recent multicenter open-label study showed that an infusion of rh-APC in patients with ARDS could attenuate pulmonary coagulopathy and injury. (18) Its function also can suppress the production of PAI-1 activity that will effect pulmonary fibrin turn over. (22) However, it had no beneficial effect demonstrated in a recent large pediatric sepsis trial. (23) It could be partly explained by difference in baseline levels between neonate and adult. It may also suggest the difference in amount of APC requirement in individual sepsis patient. (24)

Everyone would certainly agree that management of ARDS patients required every facet of appropriate intervention, supportive and combination of emerging adjunctive care. As demonstrated in our findings, most of our ALI/ARDS children had abnormalities of initial coagulation profiles besides PC levels. Thus, it is essential for the future trials to further investigate the role of PC on this complex disease.

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Table 1. Baseline clinical data between survivors and non-survivors

Baseline clinical characteristic	Survivors (n=15)	Non-survivors (n=12)	p
Age (yr)	4.9±4.9	8.3±5.0	0.09
Sex (M/F)	11/4	6/6	0.23
PRISM III score	7.8±4.6	14.3±3.3	0.01
Oxygen index (%)	13.6±6.4	17.7±7.1	0.1
Underlying or prior condition (no)			
*Hematologic malignancy	4	7	
*Autoimmune disease/immune deficiency	0	3	
*GI tract	0	2	
*Cardiac	2	0	
*Neurologic disease	2	0	
*Others	4	0	
*No underlying disease	3	0	
Mechanical ventilator (days)	22.6±18.2	18.8±12.6	0.5
PaO2/FiO2 ratio	140.8±64	148±54	0.7

Table 2. Compare initial coagulation profiles measured in this study between survivors and non-survivors

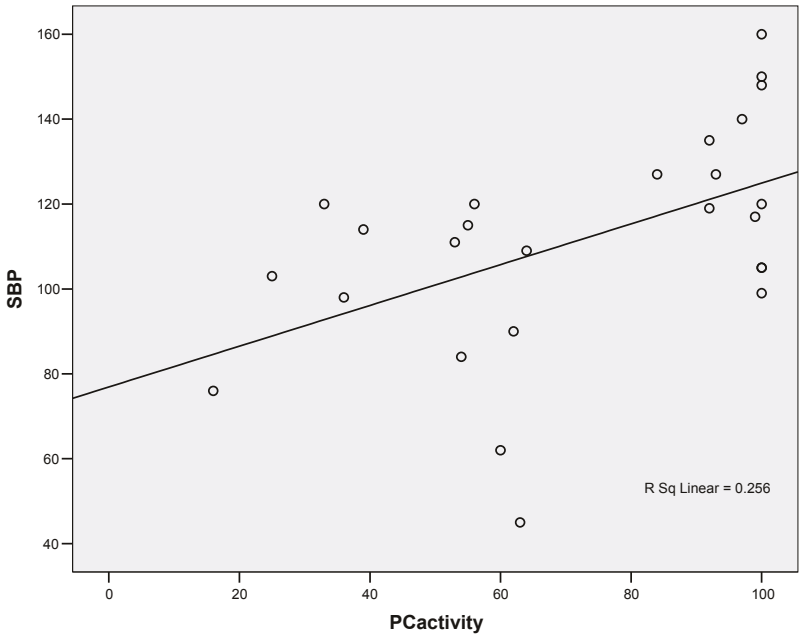
Coagulation profiles	Survivors	Non-survivors	p
PC activity (%)	75.0±25.5 (n=14)	68.6±30.7 (n=12)	0.56
Free plasma PS Ag (%)	57.5±35.3 (n=15)	59.7±22.9 (n=12)	0.85
D-dimer (ng/mL)	2,156.6±1,809.9 (n=11)	3,521.3±6,728.2 (n=8)	0.53
Platelets (cells/mm3)	149,533±123,941	48,575±6,771	0.01
PT (min)	13.1±1.7	20.7±12.3	0.02
PTT (min)	29.8±9.8	44.3±18.7	0.01

Table 3. Initial PC activity levels according to age groups

Age (yr)	Levels of PC activity (%)
<1	52.0±32.7
1-8	66.3±28.1
8-16	85.1±20.7*

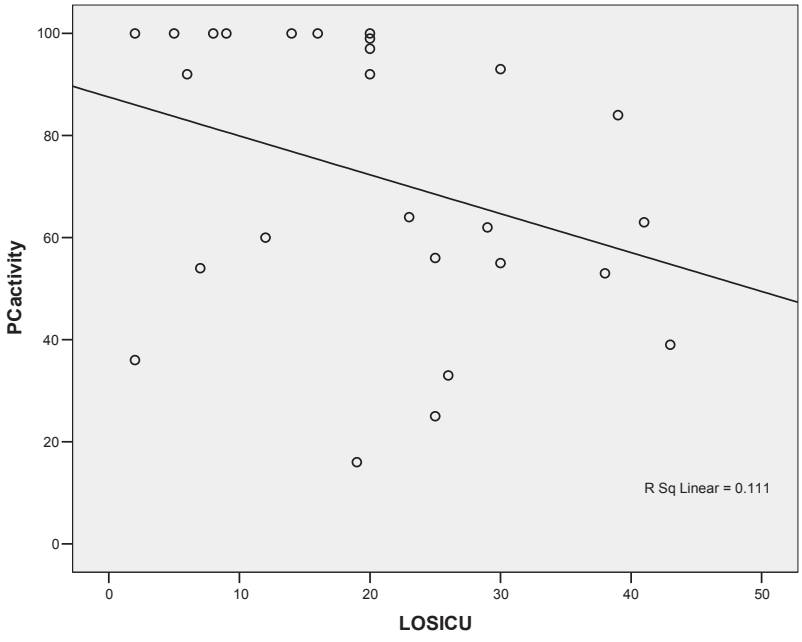
Legend: *=statistical significant compared between infants (<1yr) and older; children=age>8 years

Figure 1. Correlation between initial systolic blood pressure (mmHg) and PC activity levels (p=0.008, r=0.5)



Legend: SBP=systolic blood pressure

Figure 2. Correlation between initial PC activity (%) and length of PICU stay (p=0.09, r=0.3)



Legend: LOS ICU=length of PICU stay

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