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Outcomes/Predictors

The predictive value of soluble endothelial selectin plasma levels in children with acute lung injury☆,☆☆,★,★★,☆☆☆,★★★,☆☆☆☆

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ABSTRACT

The study aimed to evaluate the value of soluble endothelial selectin (sE-selectin) plasma level measurement in predicting acute lung injury (ALI) outcome in children.

Methods: The study was a prospective, controlled study that involved 50 children with ALI and 50 healthy children as a control. Soluble endothelial selectin and C-reactive protein plasma levels were measured at days 1 and 7 of development of ALI for the patient group and done only once for the control group.

Results: Plasma sE-selectin was significantly higher in the patients than the control group ($P = .001$). Mortality reached 32% of children with ALI. The deceased subgroup had significantly higher plasma sE-selectin levels both at days 1 and 7 than the survived ($P = .02$ and $P < .001$ respectively). There was positive correlation between plasma sE-selectin at day 7 with durations of both pediatric intensive care unit and mechanical ventilation. Levels of sE-selectin at days 1 and 7 had significant positive correlation with C-reactive protein level and ALI severity. Soluble endothelial selectin plasma levels of 302 ng/mL at day 7 were the best cutoff value to predict ALI-related deaths.

Conclusion: Plasma sE-selectin level served as a good predictor biomarker for both mechanical ventilation duration and the mortality risk in children with ALI.

1. Introduction

Since the adult respiratory distress syndrome was first described in 1967 by Ashbaugh and Petty, substantial progress has been made in understanding the pathogenesis of this complex syndrome [1]. Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are life-threatening conditions with significant morbidity and mortality especially in children [2]. Acute lung injury/ARDS is a spectrum of severity of pulmonary damage that may occur in association with many precipitating conditions including trauma, pneumonia, aspiration, or immune compromise [3].

Acute lung injury passes through 3 overlapping phases: an inflammatory or exudative phase, a proliferative phase, and ending by a fibrotic phase. Severe inflammation is the unique feature for this clinical syndrome, which results from dysregulated inflammatory response mounted from the immune system causing persistent elevation of circulating inflammatory cytokines and chemokines, which is responsible for multiple-organ dysfunction syndrome as well as the progression of ALI/ARDS [4,5]. The released inflammatory cytokines and chemokines including interleukin 1 and tumor necrosis factor α stimulate expression of cell adhesion molecules from the inflamed pulmonary vascular endothelium including endothelial selectin (E-selectin) [6].

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☆☆ Transparency declaration: All the authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. We declare that no important aspects of the study have been omitted.

★ Ethical approval: The study was approved by the Ethics Committee of the Faculty of Medicine, Tanta University, and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each child's guardian before any study procedure, with assurance of patient privacy.

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The selectins, a family of adhesion molecules expressed on various cell surfaces, mediate immunologic and inflammatory cell-cell reactions through selectin ligands and involved in the early phase of neutrophil rolling and homing to the site of inflammation. There are 3 types: endothelial (E), leukocyte (L), and platelets (P) [7]. E-selectin known also as endothelial leukocyte adhesion molecule 1 is expressed only by activated endothelial cells and is different from other selectins. The concentration of E-selectin is very low in resting endothelial cells. It is selectively synthesized under conditions of cellular stress such as hypotension or organ hypoperfusion. E-selectin expression is induced by proinflammatory cytokines in thrombosis, infectious diseases, malignant tumors, and autoimmune diseases leading to the attachment of leukocytes to endothelial cells and the accumulation of leukocytes in inflamed tissues [8,9].

Previous researchers studied the beneficial diagnostic role of elevated plasma levels of E-selectin in adult patients with ALI and its association with presence of complications [8]. Despite that many epidemiological, intervention, and outcome studies of ALI were undertaken by pediatric researches all over the world, our knowledge about this disorder in children still inadequate, and morbidity and mortality continue to be unreasonably high. The aim of this study was to evaluate the prognostic significance of soluble endothelial selectin (sE-selectin) measurement in plasma for prediction of outcome of ALI in children that may allow early recognition and intervention of critical cases.

2. Patient and methods

2.1. Study design

The study was conducted as a prospective, controlled cohort study from January 2014 to January 2015 in Pediatric Intensive Care Unit (PICU), Pediatric Department, Tanta University Hospital, Tanta, Egypt. The study included children with ALI who needed intensive care and mechanical ventilatory support and a group of healthy children as a control group. The patient group subsequently was divided according to the prognosis into survived and deceased subgroups. The study was approved by the Ethics Committee of the Faculty of Medicine, Tanta University, and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each child's guardian, with assurance of patient privacy.

2.2. Patient selection

Children included in the study were diagnosed to have ALI/ARDS by a PICU physician according to criteria set by The American-European Consensus Conference on ARDS [10] and the New Berlin definition of ARDS [11].

The inclusion criteria included children between 6 months and 6 years who had Pa_{O_2}/fraction of inspired oxygen (F_{IO_2}) less than 300; positive end-expiratory pressure greater than 5 cm H_2O, new bilateral pulmonary infiltrates on chest x-ray, and with no evidence of left-sided heart failure and with normal pulmonary artery pressure. Exclusion criteria included neonates, presence of chronic interstitial lung disease, immunologic disorders, pulmonary vascular disease, cardiovascular disease, severe irreversible neurological injury, malignancy, thrombotic disorders, intractable shock, and those who died before collection of the 2 samples, that is, before 7 days of ALI.

All children were subjected to thorough medical history and clinical examination to assess Pediatric Risk of Mortality (PRISM) score and to exclude systemic disease, heart failure, and pulmonary hypertension. Chest x-ray was done to confirm/exclude presence of new bilateral pulmonary infiltrates. Echocardiography was done to exclude presence of cardiovascular disease and to evaluate the pulmonary pressure. Computed tomographic scan of the chest was done in selected cases when applicable.

Complete blood count, biochemistry, and coagulation profiles were routinely assessed. The liver and renal functions were done on admission to exclude organ failure. Complete blood pictures and markers of inflammation including acute phase reactants (C-reactive protein [CRP], erythrocyte sedimentation rate, and serum albumin) were also performed. Plasma levels of sE-selectin and CRP were measured at days 1 and 7 of development of ALI for the patient group and done only 1 time for the control group. For measuring sE-selectin in the plasma, 2-mL venous blood was collected, and plasma level of sE-selectin was assessed by enzyme-linked immunosorbent assay according to the manufacturer instructions (eBioscience, Vienna, Austria).

All cases included in the study received the appropriate treatment according to their primary diseases, for example, antibiotics for sepsis and pneumonia. All patients were intubated, sedated, and paralyzed. Cardiopulmonary monitor and pulse oximeter were applied. They were also subjected to pressure control conventional ventilation with lung protective strategy. The severity of ALI was also indicated by the ratio of arterial oxygen partial pressure to F_{IO_2} (Pa_{O_2}/F_{IO_2} ratio). All adverse effects were recorded accordingly. They were also monitored for the following outcome: survival/death, duration of mechanical ventilation, length of stay in PICU, and discharge outcome. All cases were followed starting from the day of admission with ALI until death, day of discharge, or up to 60 days passed, whichever comes first. The number of days on ventilator and in PICU was also recorded.

The power level of the primary end point of the study was more than 90% (using Power & Precision V3; http://www.Power-Analysis.com/). The statistical analysis was performed using TexaSoft (WINKS SDA Software, Sixth Edition, 2007; Cedar Hill, TX). Data were presented as mean (±SD) values. Comparison between the studied groups was performed with the Student t test, with $P < .05$ considered statistically significant. χ^2 Test was used to test the association between 2 variables of categorical data. Mann-Whitney U test was used to compare unpaired samples. Correlation between the level of sE-selectin and different variables was done. The correlation coefficient denoted symbolically as r defines the strength and direction of the linear relationship between 2 variables. Receiver operating characteristic (ROC) curve was used to test the validity of the study [12].

3. Results

The study included 100 children who completed the study and were divided into 2 groups: 50 children as a patient group and 50 healthy children as a control group. The patients group included children who were admitted to PICU with the diagnosis of ALI/ARDS. Their ages ranged from 6 months to 6 years with mean age of 35.7 ± 25 months and male/female ratio of 1.6:1. The control group included 50 children of matching age and sex with mean age of 39 ± 20 months and male/female ratio of 1:1. There were no significant differences between the studied group as regard to age and sex ($P = .47$ and $P = .2$, respectively). However, there was significant increase in sE-selectin plasma levels for both days 1 and 7 in the patients group when compared with the control group (Table 1). The table showed also the percentage of the causes of ALI/ARDS in the patient group where sepsis was the most common cause (42%), followed by pneumonia (30%), then aspiration (11.8%), near drowning (8.8%), and trauma (5.8%).

3.1. The outcome of the cases

From 50 patients; 16 children (32%) died, whereas 34 children (68%) survived. Five children died before the 14th day of study period, whereas 11 died after the 14th day. Sepsis was the most common etiology of ALI/ARDS (42%) observed in the 2 subgroups followed by bronchopneumonia (30%). Corticosteroids were used in all the patients. The deceased subgroup had significantly higher length of stay ($P = .002$) and duration of needed ventilatory support ($P < .001$) than the survived subgroup as shown in Table 2. The table also showed absence of significant difference as regard to age ($P = .5$), sex ($P = .9$), primary etiology ($P > .05$), and Pa_{O_2}/F_{IO_2} ($P = .07$) between the survived and the deceased groups, whereas PRISM score assessed at day 1, percentage of cases that