Diagnostic and Prognostic Role of VEGF in Critically ill Pediatric Patients with Sepsis and Sepsis Induced Capillary Leak Syndrome

Thesis

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Candidate

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Abstract

Objectives: Vascular endothelial growth factor (VEGF) is a potent vascular permeability factor. The development of capillary leak is common in septic patients, and several sepsis-associated mediators may induce VEGF production. The potential role of VEGF during sepsis has not been studied to date. The aim of the study was first to assess whether circulating VEGF levels increase during sepsis, and second, to examine whether plasma VEGF levels are associated with disease severity and sepsis induced capillary leak syndrome.

Patients and methods : A prospective randomized trial was conducted on 40 children who were divided into two groups; the first group contained 20 healthy children , and the other group contained 20 septic children . one plasma sample was obtained from each child of the first group, and two plasma samples from each child of the second group , the first sample before occurrence of sepsis induced capillary leak syndrome and the second sample after occurrence of sepsis induced capillary leak syndrome, VEGF levels were measured in all plasma samples obtained from the 40 children. VEGF levels were correlated to clinical signs and symptoms.

Results: plasma VEGF levels were significantly elevated in patients with severe sepsis versus controls (182.45±81.54pg/mL vs. 24.2± 11.14; $P< 0.001$). and There was significant increase in VEGF level in septic patient after development of Sepsis Induced Capillary Leak Syndrome (295.20 ± 105.29 pg/mL vs. 182.45± 81.54; $P< 0.001$). The septic patients in our study population showed signs of generalized vascular leakage, such as decreased serum albumin values. also Maximum VEGF levels during the course of disease were higher in non-survivors than in survivors (345 ± 91.92pg/mL vs. 164.39± 59; $P<0.001$), These findings clearly indicate that VEGF levels are negatively associated with outcome.

Conclusions: These data show that plasma VEGF levels are elevated during severe sepsis, and elevated more after occurrence of sepsis induced capillary leak syndrome . Furthermore, our data indicate that plasma VEGF levels are associated with disease severity and mortality.

Introduction

Sepsis is defined as systemic inflammatory response syndrome (SIRS) resulting from a suspected or proven infectious etiology. Further deterioration leads to septic shock (severe sepsis plus the persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement for vasoactive agents, multiple organ dysfunction syndrome (MODS), and possibly death. Outcomes improve with early recognition and treatment **(Turner DA and Cheifetz IM. ,2011)**.

Magnitude of the problem

Increasing severity correlates with increasing mortality, which rises from 25-30% for severe sepsis up to 40-70% for septic shock **(Levy MM, et al,2001).**

In developed countries, mortality from septic shock ranges between 10% and 50% among children **(Martin GS, et al,2003).**

The systemic capillary leak syndrome (SCLS), also called Clarkson syndrome, is now known as a disorder of unknown cause characterized by transient but severe hypotension that results in vascular collapse and shock, hemoconcentration, and ultimately anasarca because of accumulation of fluids and macromolecules (≤ 900 kDa) in tissues. The most typical presenting signs are the triad of hypotension, elevated Hgb and hematocrit, and hypoalbuminemia. The symptoms reverse almost as quickly as they arise, with massive fluid remobilization from tissues into circulation, resulting in diuresis. Severe sepsis is one of the most important causes of systemic capillary leak syndrome **(DhirV,et al,2007).**

The most common treatment modality during episodes is judicious use of intravenous fluids and vasopressors to maintain perfusion to the brain and other vital organs.The 5-year survival rate is ~ 75%, and deaths are most commonly related to acute SCLS events **(Gousseff M, et al,2011),(Druey KM, Greipp PR.,2010).**

Vascular endothelial growth factor (VEGF) was first identified as a tumor-produced vascular permeability factor VEGF is a key molecule in the control of vascular permeability via interactions with the VEGF-receptor-2 on the endothelial cell. In addition, VEGF is essential for angiogenesis and plays a crucial role in wound healing **(Ferrara N, et al, 2003).**

A wide variety of cells produce VEGF, including peripheral blood monocytes, neutrophils, and platelets **(Kusumanto YH, et al, 2003), (Bottomley MJ, et al ,1999).** In response to several agents often associated with sepsis such as gram-negative bacterial lipopolysaccharide, gram-positive bacterial components, and tumor necrosis factor-α, VEGF production or secretion of the intracellular pool of VEGF is increased . In addition, hypoxia increases VEGF production via hypoxia-inducible factor-1a transcription factor **(Mittermayer F, et al,2003), (van der Flier M, et al ,2000).**

C-reactive protein (CRP) is an acute-phase protein, the blood levels of which increase rapidly in response to infection, trauma, ischemia, burns, and other inflammatory conditions. CRP is a marker of inflammation that has been used to monitor the course of infection and inflammatory diseases. Recently, CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. CRP is predominantly produced and secreted by hepatocytes, although other cells including alveolar macrophages may also synthesize CRP. The relatively short half-life of approximately 19 h makes it a useful monitor for follow-up of inflammatory response, infection, and antibiotic treatment **(Van der Meer V, et al,2005),(Simon L, et al, 2004).**

Aim of the Work

The aim of this study is to estimate the serum level of VEGF among pediatric patients with sepsis and sepsis induced capillary leak syndrome (SCLS) to evaluate its possible diagnostic and prognostic value among them.

Severe Sepsis and Septic Shock

Sepsis is one of the oldest and most elusive syndromes in medicine.

The International consensus definitions for pediatric sepsis are: **(Turner and Cheifetz, 2011)**

Infection: Suspected or proven infection or a clinical syndrome associated with high probability of infection.

Systemic inflammatory response syndrome (SIRS): 2 out of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count:

1 Core temperature >38.5°C or <36°C (rectal, bladder, oral, or central catheter)

2 Tachycardia:

- Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli *OR*
- Unexplained persistent elevation over 0.5-4 hr*OR*
- In children <1 year old, persistent bradycardia over 0.5 hour (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease).

3 Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia.

4 Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils.

Sepsis: Systemic inflammatory response syndrome (SIRS) plus a suspected or proven infection.

Severe sepsis: Sepsis plus 1 of the following:

1. Cardiovascular organ dysfunction, defined as

• Despite >40 mL/kg of isotonic intravenous fluid in 1 hour

• Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age *OR*

• Need for vasoactive drug to maintain blood pressure*oR*

2 of the following:

• Unexplained metabolic acidosis: base deficit > 5 mEq/L

• Increased arterial lactate: >2 times upper limit of normal

• Oliguria: urine output <0.5 mL/kg/hr

• Prolonged capillary refill: >5 sec

• Core to peripheral temperature gap >3°C

2- Acute respiratory distress syndrome (ARDS) as defined by the presence of a PaO2/FIO2 ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure *OR*

Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic).

Septic shock: Sepsis plus cardiovascular organ dysfunction as defined above.