Egyptian Pediatric Association Gazette 66 (2018) 28–34

HOSTED BY

Contents lists available at ScienceDirect

Egyptian Pediatric Association Gazette

journal homepage: www.elsevier.com/locate/epag

Promising roles of erythropoietin and lymphotoxin alpha in critical illness: A pilot study in critically ill children

Seham A. EL Sherbini [a,*], Aliaa A. Ali [a], Sally Kamal [a], Huda Marzouk [a], Laila Rashed [b]

[a] Department of Pediatrics, Cairo University, Cairo, Egypt
[b] Department of Medical Biochemistry, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 30 January 2018
Accepted 9 February 2018
Available online 15 February 2018

Keywords:
Critical illness
Erythropoietin
Lymphotoxin alpha

ABSTRACT

Background: Several studies proved the anti-inflammatory role of erythropoietin. Little is known about the anti-inflammatory role of lymphotoxin alpha (LT-α). This study was designed to investigate the patterns of erythropoietin (EPO) and LT-α levels in children with acute critical illness.
Patients and methods: Thirty-two critically ill children were prospectively subjected to serial estimation of EPO and LT-α levels, during the first 10 days of admission to one of the pediatric intensive care unit of Cairo University. Thirteen healthy children served as control.
Results: Serial EPO and LT-α measurements showed significant increases over time early in their critical illness ($P < 0.001$, respectively). Both cytokines showed significant increases in survivors ($P < 0.001$, respectively). Kaplan Meier survival analysis revealed a significant increase in mortality with LT-α levels below 108.7 pg/ml, ($P < 0.01$) on admission. However, EPO did not show any significant difference between survivors and non-survivors. For both LT-α and EPO, levels at day 1 showed a significant decrease in septic patients. EPO levels were significantly elevated on day 1 of admission in non-anemic [mean hemoglobin level (11.8 ± 0.9) g/dL, mean EPO level (110.85 ± 44.5) mIU/ml] compared with anemic patients [mean hemoglobin level (9.3 ± 1.3) g/dL, mean EPO level (69.84 ± 30.763) mIU/ml], 95% CI [13.896–68.112], P < (0.01).
Conclusions: Both EPO and LT-α showed significant increment in critically ill children especially in survivors. Our data strongly suggest that, LT-α may have an anti-inflammatory role in children with acute critical illness.

Introduction

Patients in intensive care units (ICUs) mostly have some organ dysfunction.[1] Multiple organ dysfunction syndrome (MODS) is a systemic inflammatory response, with more than one organ dysfunction, which prolongs intensive care unit (ICU) stay and increase mortality rate, depending on the number of organs involved.[2] MODS is induced by a variety of acute insults, including sepsis; which is the most leading cause to MODS, but also non-infectious causes; as trauma and hypovolemic shock can lead to MODS.[3]

A part from the role of Erythropoietin (EPO) hormone on erythroid progenitor cells, It is also a multi-functional cytokine with anti-apoptotic and immune modulatory properties.[4] It plays an anti-ischemia role in the body[5], in addition to promoting neovascularization, mobilizing endothelial progenitor cells, and enhancing angiogenesis.[6,7] These actions give EPO a cardioprotective role in the context of cardiac ischemic injury as well as a neuroprotective role in the event of ischemic injury to the central and peripheral nervous systems.[8]

In addition to EPO, interleukin (IL)-1 receptor antagonist; IL-4, IL-10, IL-11, and IL-13; and specific cytokine receptors for IL-1, tumor necrosis factor (TNF)-α, and IL-18, also function as inhibitors of pro-inflammatory cytokines.[9] Further, mediators such as TNF-α, interferon (IFN)-ϰ, transforming growth factor (TGF)-β, and prostaglandin 2 serve as examples of molecules whose actions can switch from pro-inflammatory to anti-inflammatory depending on the timing and context.[10]

Lymphotoxin (LT)-α, one of the TNF superfamily ligands, previously known as TNF-β, is less able to promote tumor necrosis factor receptor (TNFR)1-induced cell death and nuclear factor (NF)-κB activation,[11] expression of cell surface markers,[12] and cytokine production compared with TNF-α.[13]

Peer review under responsibility of Egyptian Pediatric Association Gazette.
* Corresponding author.
E-mail address: awadseham@yahoo.com (S.A. EL Sherbini).

https://doi.org/10.1016/j.epag.2018.02.001
1110-6638/

Previous studies showed that, LT-α gene polymorphisms can enhance transcription and susceptibility to myocardial infarction[14] and can be a risk for ischemic stroke in non-hypertensive patients.[15]

From these points of view, we aimed to investigate the patterns of EPO, and LT-α in acute critical illness by estimating their trends through serial measurements in critically ill children, and to correlate the levels with outcomes. Our study shed light on different roles of cytokines, and opens a new gate for co-management of critical illness in the future.

Material and methods

Study setting and population

In this prospective observational cohort study, we screened 38 critically ill children, who were admitted to one of the pediatric intensive care units (PICUs) of Cairo University Pediatric Hospitals (14-bed capacity), during the period from January 2016 to June 2016. Thirty-two patients were enrolled (18 boys, 14 girls). Their ages ranged from 1 month to 12 years (median 1.4 years). Thirteen healthy children (5 boys, 8 girls), their age ranged from 1 month to 3 years served as control. Their mean Hb level was 11.92 ± 0.74, ranging from 11 to 14 g/dl.

EPO and LT-α were estimated serially during the first 7 to 10 days of admission. Patients who were admitted for <7 days were excluded from the study. Patients with chronic renal failure, chronic hepatic insufficiency, severe chronic pulmonary disease, iron deficiency, or aplastic anemia and patients on immunosuppressive agents were also excluded from the study.

Study definitions and scores

Sepsis and organ dysfunction were defined according to the International Pediatric Sepsis Consensus Conference.[16] The severity of illness on admission was defined by the pediatric logistic organ dysfunction (PELOD) score,[17] and the pediatric risk of mortality (PRISM III) score at that time.[18] Anemia was defined according to the World Health Organization definition.[19]

Workup

Demographic data and diagnosis on admission were recorded, the presence of organ dysfunction or sepsis was recorded, and the PRISM III and PELOD scores were calculated. Complete blood count, blood gases, blood glucose, blood chemistry, and the serum levels of TNF-α, LT-α, and EPO were evaluated.

In addition, blood transfusions, length of stay, and outcome were recorded.

Laboratory methodology

Three blood samples were taken from enrolled patients; on days 1, 3, and a third sample during the period between the 7th to the 10th day of PICU admission and were collected in a sterile ethylenediaminetetra-acetic acid (EDTA) vacutainer tube.

Measurement of TNF-α

TNF-α was measured by using an enzyme-linked immunosorbent assay kit (ELISA; Quantikine, R&D Systems, USA) according to the manufacturer's instructions.[20]

EPO assays

EPO levels were determined using an ELISA kit (Quantikine, R&D Systems USA), and optical densities were determined with an Stat Fax plate reader (Dynatec Laboratories, El Paso, TX, USA). Procedures were performed in accordance with the manufacturers' instructions.

Measurement of LT-α

LT-α was measured by ELISA kit supplied by RayBiotech, Inc. (Norcross, GA, USA) according to the manufacturer's instruction.

Ethics

Informed consent was obtained from the parents of all patients. The study design conformed to the revised Declaration of Helsinki[21] and was approved by the Scientific Ethics Committee of the Department of Pediatrics, Faculty of Medicine of Cairo University.

Statistical analysis

Data were analyzed using Statistical Package for Special Science software computer program version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as median, minimum, and maximum. Categorical variables were expressed as numbers (n) and percentages (%) and were compared using the chi-square test or Fischer's exact tests, as indicated. Continuous variables were compared using Mann-Whitney and Kruskal-Wallis tests, as indicated. Kaplan-Meier survival analysis was used to explore the mortality pattern of EPO and LT-α below and above the 25th percentile values. A P-value less than or equal to 0.05 was considered statistically significant.

Results

The baseline clinical and laboratory data of the study population are shown in Tables 1 and 2, respectively.

EPO, LT-α, and TNF-α levels were elevated in critically ill children compared with controls; [mean ± SD (86.49 ± 41.6) mIU/ml versus mean ± SD (15.19 ± 4.88) mIU/ml in controls, $P < 0.0001$], [mean ± SD (136.08 ± 36.06) pg/ml versus mean ± SD (56.83 ± 20.12) pg/ml in controls, $P < 0.0001$], [mean ± SD (57.74 ± 24.5) pg/ml versus mean ± SD (29.42 ± 4) pg/ml in control, $P < 0.0001$], respectively.

A statistically significant positive correlation existed between the EPO and LT-α levels on admission ($r = 0.652$, $P < 0.001$). While, a non-significant negative correlation exited between the EPO and TNF-α levels ($r = -0.244$, $P > 0.05$). Furthermore, a non-significant negative correlation existed between the LT-α and TNF-α levels ($r = -0.330$, $P > 0.05$).

A non-statistically significant negative correlation existed between number of organ failure on admission and both levels of EPO and LT-α ($r = -0.061$, $r = -0.188$) respectively. While, a significant positive correlation existed between number of organ failure on admission and TNF-α levels ($r = 0.379$, $p < 0.05$).

We found a non-significant difference between EPO levels in patients with acute kidney injury (AKI), 10 patients [mean EPO level (82.81 ± 41.01) mIU/ml] and patients without acute kidney injury, 22 patients [mean EPO level (88.15 ± 42.72) mIU/ml], $P = 0.779$.

Trends in Hb, EPO, and LT-α levels

Hb levels in the study population did not differ significantly over time ($P > 0.05$) because transfused patients were included. However, both EPO and LT-α levels increased significantly over time ($P < 0.001$) (Fig. 1, Table 3).