Original Article

Relation- ships of neonatal septicemia with the mean serum levels of IL-8 and IL-1∝ in three large hospitals in Baghdad

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Summary:

Background: Neonatal septicemia (NNS) is the most serious complication in Neonatal Intensive Care Units (NICU) that demand urgent diagnosis and accurate treatment.

Methods: Serum was obtained from 31 neonates aged 1 hour-28 days that were diagnosed clinically and bacteriologically to have neonatal septicemia.

Results: Mean serum levels of both IL-8 and IL-1∝ recorded a significant increase in neonatal septicemia cases.

Conclusion: Usage of IL-8, IL-1∝ as diagnostic marker for NNS reduces unnecessary antibiotic therapy and therefore unnecessary costs, pain, and possible side effects of antibiotic therapy and it may help to reduce development and spread of drug resistant bacteria.

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Introduction:

Neonatal Septicemia (NNS) is defined as generalized microbial symptomatic infection during the first 28 days of life (1). Etiological agents of neonatal septicemia are bacteria, fungi (mainly candida), viruses and rarely protozoa (2). In numerous studies, certain predisposing factors related to pregnancy, delivery, as well as neonatal diseases has been identified as important causes of sepsis in the newly born infants such as prematurity, prolonged rupture of amniotic membrane and low birth weight. Although antibiotics are potentially lifesaving, they have inherent risks when used in neonates, including drug toxicity, emergence of resistant organisms and super infection (3, 4, and 5). Interleukines (ILs) are small, single peptides or glycopeptides, produced by leukocytes of the host in response to infectious stimuli (such as lipopolysaccharide). They are important pro-inflammatory mediators in the early phases of the sepsis syndrome (6). The term cytokine has been designated to include soluble mediators secreted by lymphocytes (Lymphokines) and those secreted by monocytes and macrophages known as (monokines), while cytokines synthesized and secreted by leukocytes are named interleukins (ILs). All are secreted in extremely low concentration (picomolar to nanomolar range), and most manifest their biological effect through specific receptors, with high binding affinities, expressed at the surface of their target cell. Cytokines can either synergize or antagonize other cytokines, these cytokine interaction lead a cascade of functions. However, the central roles of cytokines include Cell to cell communication, inflammatoryresponse amplification, and immune response regulation (7). In the inflammatory response the cytokines playing a most important role include IL-1∝, IL-6 and tumor necrosis factor alpha (TNF-∝). These cytokines released by activated macrophages include adhesion molecules on the walls of vascular endothelial cells to which neutrophils, monocytes and lymphocytes adhere before moving out of the vessel through a process called extravasation, to the affected tissue. These cytokines also induce coagulation and increased vascular permeability, together with IL-8 and interferonϒ. They exert additional effects such as increased chemotaxis for leukocytes and increased phagocytosis (8).

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Patients and Methods:

The study was conducted in the NICU of Baghdad Teaching Hospital, Al-Mansur Hospital of Pediatrics, and Central Pediatrics Hospital. Thirty- seven neonates were selected to be included in the study, six of them were healthy neonates as control, thirty-one of them were suspected to have NNS by clinical and bacteriological diagnosis. Approximately one ml of blood sample was collected from each of neonates, centrifuged within 30 minutes of collection and the sera were transferred to plastic tubes. Sera then were stored at –18 or –70^{o}C temperature. The IL-8, IL-1∝ levels were measured by IL-8, IL-1∝ kits (ELISA) (9).

Results:

Table (1) shows that 37 neonates were studied for their serum levels of interleukine-8; the results of interest are illustrated as followings**:**

Ten patient neonates with positive blood culture have mean= 157.50, SD=70.51. However, twenty-one patient neonates with negative blood culture have mean=55.40, SD=48.83. Six healthy control neonates have mean= 6.50, SD= 1.87. (P-value <0.001). Fig. (1) Shows serum IL-8 level (pg/ml) in the three studied groups. Table (2) shows that out of 37 neonates were studied for their serum levels of interleukin-1∝; ten patients neonates with positive blood culture have mean=86.90, SD= 7.59. While twenty-one patient neonates with negative blood culture have mean=52.98. SD= 18.35. Six healthy control neonates have mean= 9.33, SD= 2.80 (P-value <0.001). Fig. (2) Shows serum IL-1∝ level in the three studied groups.

Table (1): The difference in mean serum interteukin-8 level (pg/ml) between three studied groups (37 neonates)

Study groups N= 37				P-value
Values	Patient neonates with positive blood culture	Patient neonates with negative blood culture	Healthy control neonates	
Number	10	21	6	P< 0.001
Mean (pg/ml)	157.50	55.40	6.50	
SD* (pg/ml)	70.51	48.83	1.87	

SD*: Standard Deviation

Table (2): The difference in mean serum interleukin- 1∝ level (pg/ml) between three studied groups (37 neonates)

Study groups N= 37				P-value
Values	Patient neonates with positive blood culture	Patient neonates with negative blood culture	Healthy control neonates	
Number	10	21	6	P< 0.001
Mean (pg/ml)	86.90	52.98	9.33	
SD* (pg/ml)	7.59	18.35	2.80	

SD*: Standard Deviation

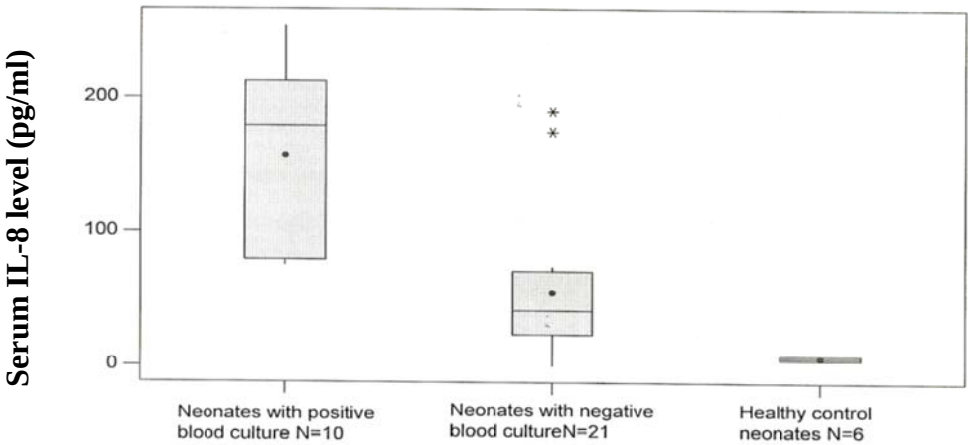
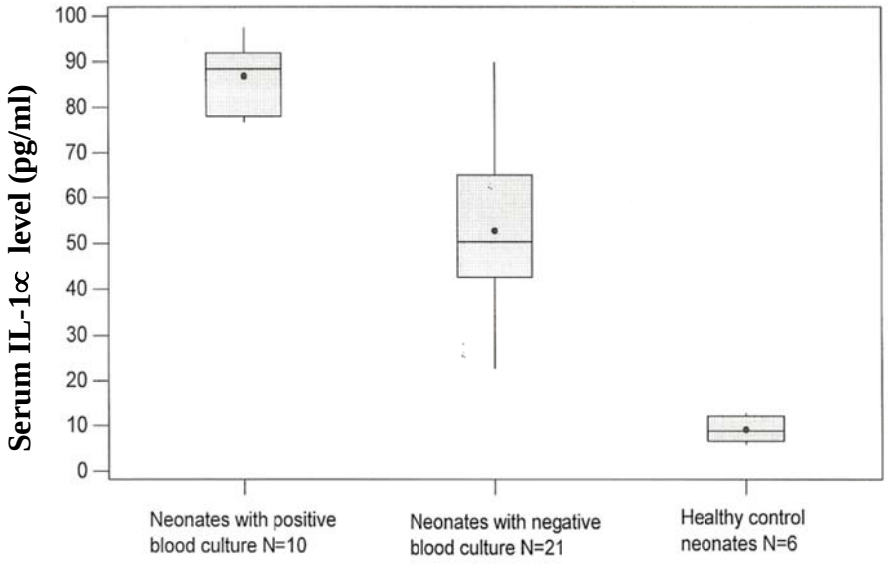


Fig. (1): Serum IL-8 level (pg/ml) in the three studied groups.



Study groups
N=37
Fig. (2): Serum IL-1∝ level in the three studied groups

Discussion:

Inflammation represents the response of tissues to either injury or the presence of microorganisms. It serves a vital role because it enhances the movement of phagocytic cells and defensive molecules (e.g. immunoglobulin, complement) from the blood stream to the site of infection or injury. The first step in this process is the recognition of tissue injury or microbial invasion (bacterial sepsis). Injured cells release preformed mediators (e.g. histamine) and synthesize proinflammatory substances, including eicosanoids and cytokines IL-1 and TNF, these mediators are responsible for the initiation of the nonspecific inflammatory response. Microbial invasion may result in tissue injury, thereby initiating this process, or specific bacterial cell components (endotoxines ; lipopolysaccharides and exotoxins from gram negative bacteria as well as peptidoglycans, lipoteichoic acids, enterotoxines, and superantigenic exotoxins from gram positive bacteria) may be recognized by immune cells (macrophages), which result in the production of inflammatory mediators including proinflammatory cytokine (e.g. IL-1, IL-6, IL-8 and TNF-∝) and the initiation of an inflammatory response (10,11) . Authors (8) showed that IL-1, IL-6, IL-8, tumor necrosis factor alpha (TNF-∝), and interferonϒ, were playing an important role in the inflammatory response. However, in recent years, other authors (9, 12), noted that IL-6, IL-8, and tumor necrosis factor were an important indicators of bacterial sepsis in both neonates and adults. The authors also noted that the cytokine determinations were very important in the early and speedy diagnosis of neonatal sepsis. The present study (table 1, 2) analyzed serum levels of IL-8 and IL-1∝ as indicators of the immune response in neonates' septicemic patients. Results of this study revealed high levels of IL-8 in sera of septicemic neonates (patient neonates with positive blood culture): (157.50 ± 70.51 pg/ml) as compared with patient neonates with negative blood culture: (55.40 ± 48.83 pg/ml) and healthy control neonates (6.50 ± 1.87 pg/ml) with P<0.001 which means significant difference. These results were in accordance with the previous results reported by Martin and Olander and Franz et. al., (1999) (2008) (9, 12), who found that neonatal septicemic patient display elevated levels of circulating IL-8 when compared with healthy neonates. Estimation of level of IL-1∝ in sera of three study groups; patient neonates with positive blood culture (septicemic neonates), patient neonates with negative blood culture, and healthy control neonates, were carried out. The results were (86.90 ± 7.59), (52.98 ± 18.35), and (9.33 ± 2.80) respectively as shown in Table (2) and Fig. (2). Statistical analysis revealed that there was significant elevation of IL-1∝ in septicemic neonates with positive blood culture as compared with patient neonates with negative blood culture and healthy control neonates, with P< 0.001 that

showed also a significant difference. In addition to that, levels of serum IL-8 and IL-1∝ are also elevated in patient neonates with negative blood culture but to a lower mean and SD. This may be due to the fact that interleukins are also elevated in other types of neonates' infections. This result was in agreement with Schultz et. al., (2002) (13). Generally, Cytokines constitute a complex network molecules involved in the regulation of inflammatory response. The change in the levels of these cytokines may have an important role in confirming the neonatal septicemia and other inflammations in cases of the NICU and have clinical progression (14), (15), (16).

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