Original Article

Tumor Necrosis Factor-Alpha and Interleukin-1 Alpha as Predictors of Survival in Peritonitis: A Pilot Study

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Abstract

Context: Peritonitis induces an inflammatory response characterized by the elevation of various cytokine levels. Included in this cascade of cytokines are tumor necrosis factor-alpha (TNF-α) and interleukin-1 alpha (IL-1α). The outcome of patient care may be associated with the pattern of elaboration of these cytokines. **Aim:** The aim of this study was to describe the pattern of cytokine response (TNF-α and IL-1α) in the course of peritonitis and evaluate them as predictors of mortality in peritonitis. **Setting and Design:** This was a prospective study conducted in the Division of Gastrointestinal Surgery, University College Hospital, Ibadan. **Methods:** Consenting patients with clinical diagnosis of generalized peritonitis over a 6-month period (July to December 2015) were recruited. The serum samples of these patients were obtained at presentation, immediately after surgery, and 24 h and 48 h after surgery with a follow-up period of 30 days. **Results:** Twenty-six samples out of thirty could be analyzed. Serum TNF-α and IL-1α levels were both elevated at presentation in all patients. However, the patterns of change after intervention varied between the survivors and nonsurvivors. **Conclusion:** Peritonitis triggers a simultaneous increase in serum levels of TNFα and IL-1α. Lower serum level of TNF-α is associated with survival, while on the contrary, higher level of IL-1α is associated with survival.

Keywords: *Cytokines, outcome, peritonitis*

Introduction

Secondary peritonitis is one of the most common indications for emergency surgery. Despite advances in surgery and critical care, it remains a potentially fatal condition in surgical practice. It has diverse causes, but the final pathway remains the same.[1] In peritonitis, there is spoilage of the peritoneal cavity with intraluminal contents of the intestines. This subsequently triggers a systemic inflammatory response. The inflammatory response is characterized by the activation of several physiological responses with the release of chemical mediators, inclusive of which are numerous cytokines.

The immunological cascade is multimodal. There is an initial systemic inflammatory response syndrome characterized by excessive proinflammatory with minimal anti-inflammatory plasma mediators. This flows into intermediate-phase "mixed anti-inflammatory response syndrome" consisting of both pro- and anti-inflammatory mediators. The final phase is compensatory anti-inflammatory response syndrome which consists of excessive anti-inflammatory mediators, but no/low proinflammatory mediators.[2]

The standard treatment for peritonitis is resuscitation to restore adequate tissue perfusion, restoration of intestinal integrity, and removal of peritoneal contaminants, which halts peritoneal spillage contaminants and administration of antibiotics. The severity of the response is difficult to estimate based on the regular clinical and laboratory parameters. Variable plasma cytokine levels have been demonstrated as prognostic indicators in patients with peritonitis.[3] To estimate the severity of the metabolic and physiologic, it is necessary to know the pattern of

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Table 1: Pattern of mean tumor necrosis factor and interleukin-1α in survivors and nonsurvivors

	Presentation	Immediate postsurgery	24 h after surgery	48 h after surgery
Mean TNF (all subjects)				
Mean TNF (survivors)	119.31	147.03	171.69	54.80
Mean TNF (mortality)	145.39	89.43	75.2	85.05
Mean IL-1α (survivors)	5.87	9.15	3.27	6.9
Mean IL-1α (mortality)	4.3	4.7	5.7	4.6

TNF: Tumor necrosis factor, IL: Interleukin

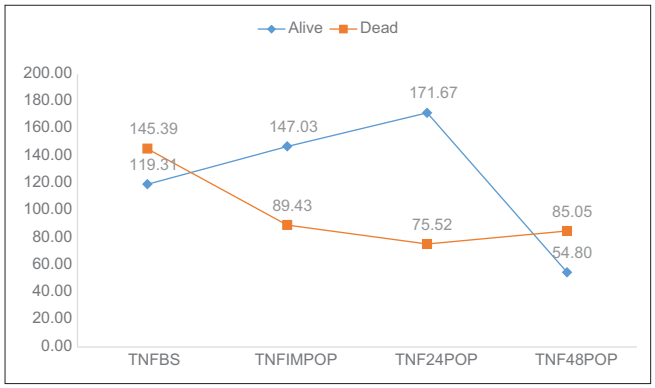

Figure 1: Pattern of serum tumor necrosis factor in survivors and nonsurvivors

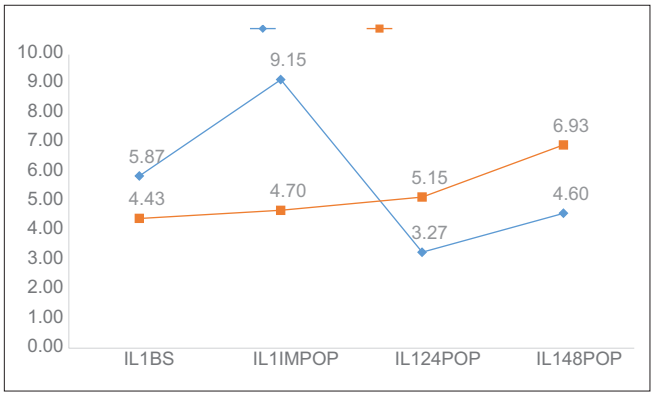

Figure 2: Pattern of serum interleukin-1 alpha in nonsurvivors and nonsurvivors

tumor necrosis factor-alpha (TNF-α) and interleukin-1 alpha (IL-1α) elaboration as both are elevated in patients with surgical acute abdomen.

Consequently, the outcome of peritonitis may be influenced by the magnitude and probably the pattern of immunologic response to the physiological stress by the body. Correlating cytokine levels with clinical outcomes has been hampered by the erratic nature of mediator release and the sample collection time in relation to the peak concentration of cytokines.

The objectives of this study are as follows:

1. To characterize the pattern of inflammatory mediator response (TNF-α and IL-1α) in patients' serum
2. To determine whether the early cytokine profile can prognosticate the outcome of patient care
3. To evaluate the potential differences in patterns of change of cytokine (TNF-α and IL 1-α) levels between survivors and nonsurvivors.

Materials and Methods

This was a prospective study conducted in the Division of Gastrointestinal Surgery, Department of Surgery, University College Hospital, Ibadan, on patients with clinical diagnosis of generalized peritonitis over a 6-month period (July to December 2015) with a follow-up 30 days for survivors. The subjects in this study included all consenting patients who fulfilled the inclusion criteria.

Inclusion criteria

All consenting patients aged 18 years and above with a diagnosis of peritonitis who had exploratory laparotomy for the surgical condition were included.

Exclusion criteria

Exclusion criteria included pediatric patients, patients with primary peritonitis, patients who required laparotomy for trauma, patients who had exploratory laparotomy for an initial diagnosis of peritonitis but subsequently found to have a contrary diagnosis, and patients who died within 24 h of surgery.

The study was approved by the state ethical review committee. All the patients were resuscitated with intravenous crystalloids and broad-spectrum antibiotics (ceftriaxone and metronidazole) given at appropriate doses during and after resuscitation. We obtained demographic and clinical data including age, gender, pulse, blood pressure, and respiratory rates. The parameters measured included the complete blood count, urea and electrolytes and serum lactate levels, serum glucose level, and TNF-α and IL-α level at presentation, immediately after surgery, and 24 h after surgery.

Method of measurement tumor necrosis factor-alpha and interleukin-1 alpha

Venous samples were collected at presentation and stored in ethylenediaminetetraacetic acid bottles once

the diagnosis was made. Similar samples were collected immediately after surgery and 24 h and 48 h after surgery and stored at 70°C until the assay was done. Enzyme-linked immunosorbent assays were used to measure the cytokines. The collected data were analysed using the SPSS, version 15.0 Chicago, SPSS Inc.

Results

Of the 30 consenting patients recruited in this pilot study, 26 patients had appropriate documentation and analyzable blood samples. These consisted of 16 males and 10 females. Ten of the patients died within the study period from sepsis-related complications. The mean age (standard deviation) was 41 ± 8.7 years. The duration of symptoms ranged between 8 h and 6 days. Preoperative resuscitation before surgical intervention was for between 1 and 3 days. The mean volume of peritoneal contents drained at surgery was 900 ml (400–3300 ml). Table 1 shows a descriptive pattern of the chronologic mean levels of TNF-α and IL-1α in various subsets of the population. Figure 1 is a line graph which describes the temporal pattern of variation in mean serum levels of TNF-α in survivors and nonsurvivors, while Figure 2 is a line graph which describes the temporal pattern of variation in mean serum levels of IL-1α in survivors and nonsurvivors.

Discussion

Cytokines, TNF-α, and IL-1α inclusive are released by macrophages in response to endotoxin, Gram-positive organisms, or pathogen-associated molecular patterns.[4] These cytokines initiate the complex inflammatory cascade. TNF-α has been extensively studied and described as a central mediator of metabolic changes associated with sepsis. Elevated levels of TNF-α have been described, especially in the peritoneal cavity in peritonitis.[5] The concentration of TNF-α initially increases astronomically in the peritoneal cavity before spilling into plasma, which is described as the "pyramidal effect." Several studies done to establish correlation between plasma levels of TNF-α and IL Iα have demonstrated inconsistent results. This may be due to the rapid transient elevation in plasma only after an initial peak concentration in the peritoneal cavity with varying periods of sample collection. IL-1α, on the other hand, demonstrates an early peak in response to sepsis, and elevated levels have been correlated with mortality.[6] The reference ranges of TNF-α and IL-1α are <22 pg/mL and 3.9 pg/mL, respectively.

In this study, serum levels of TNF-α and IL-1α were elevated in 29% and 28%, respectively. A comparison of the serum levels of TNF in the survivors and the nonsurvivors shows a significant difference in pattern. While the elevated serum levels of TNF-α of survivors at presentation increased progressively until 24 h after surgery with a decline at 48 h, the pattern in the nonsurvivors reflected a steady decline in the serum levels at presentation over the next 48 h [Figure 1]. However, the level does not fall below the reference value. This consistent decline in serum TNF levels in nonsurvivors suggests that a critical peak intraperitoneal concentration had been reached before surgical intervention with a consequent spill into the serum before surgery. Consequently, the cascade effect of TNF had been activated before intervention with imminent sequalae of organ dysfunction.

IL-1α demonstrates a slightly different course in time. In survivors, there is an initial rise in the immediate postoperative period with a subsequent fall in serum levels in the next 24 h. On the other hand, there is a continuous rise in serum level of IL-1α in nonsurvivors [Figure 2]. However, the magnitude of this increase in IL-1α serum levels neither attains the mean peak level as demonstrated in survivors before the decline in serum levels as observed in [Figure 2] nor falls to similar levels observed in survivors. IL-1α has some anti-inflammatory effects. Low level of IL-1α is beneficial to patients as this reduces the severity of the inflammatory response to sepsis. However, the persistently increasing serum level in nonsurvivors may be associated with persistent suppression of the protective inflammatory response tends toward immunosuppression. Statistical analysis of serum level of IL shows that the level of IL-1α at presentation is a significant predictor of mortality. Our results support the "tip of the iceberg" theory[7] which suggests that the peritoneal cavity is the initial site of increased cytokine concentration, which then spills into the blood only after saturation of tissues within the peritoneal cavity. This exhibits the theory of compartmentalization of the inflammatory cascade.[8] At surgery (laparotomy), the peritoneal cavity is violated with a release of cytokines into the blood. TNF levels in the survivors reached peak levels after surgical intervention, while on the contrary, the peak value in nonsurvivors was at presentation. This tends to suggest that a lot of the toxemia of sepsis was contained in the survivors' peritoneal cavity with surgery and tissue handling probably causing transiently increasing serum levels. On the other hand, one may suggest that the peak level of serum concentration had been attained before intervention in nonsurvivors. This peak may have been attained for an unknown duration of time before translocation to the bloodstream. The duration of the symptoms and the pathogen involved may be related factors, but this was not be demonstrated statistically in this study. The response of IL-1α in both sets on patients

demonstrates an increase in serum concentration in both groups; however, the survivors were able to muster a more intense response compared to the nonsurvivors. This also suggests that the peak concentration in the peritoneal cavity may have been attained with a consequent spill into the serum before the presentation. An application of these findings may suggest a critical value of TNF values at presentation and a minimal elevation of IL-1α in the immediate postoperative phase as one of the predictors of survival in peritonitis although this requires a larger study population.

Conclusion

While this study shows some strong potential for these cytokines as one of the possible predictors of outcome in peritonitis, a larger study is required to make permanent inferences.

Limitations

Our sample size is small. This was a pilot study which was funded solely by the authors.

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Conflicts of interest

There are no conflicts of interest.

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