J Bras Patol Med Lab, v. 52, n. 6, p. 367-373, December 2016

10.5935/1676-2444.20160060

Sepsis-associated organ dysfunction and increased supportive care are associated with high serum interleukin-6 levels

Disfunção orgânica associada à sepse e aumento de suporte assistencial relacionados com níveis séricos elevados de interleucina 6

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ABSTRACT

Introduction: Detection of sepsis and septic shock is essential, since any delay in initiating a proper treatment is associated with a worse prognosis. **Objective:** To evaluate levels of interleukin-6 (IL-6) early in the onset of the evolution of sepsis associated-organ dysfunction and its relation to the need for more advanced supportive therapies. **Methods:** This is a prospective study at a 43-bed mixed Medical-surgical Intensive Care Unit (ICU) in a university hospital. Patients admitted to the ICU, over 18 years of age, with severe sepsis or septic shock and who presented the first organ dysfunction in less than 48 hours of admission to the ICU were included. We monitored in a daily basis the advanced supportive therapies, need for vasopressors, mechanical ventilation, or renal replacement therapy (RRT), until hospital discharge or death. Blood samples to measure the serum IL-6 levels were collected at the time of inclusion in the study, at 12 and 24 hours later. Patients were divided into two groups according to serum IL-6 levels at admission (Low IL-6: < 1,000 pg/ml or High IL-6: > 1,000 pg/ml). **Results:** The need for norepinephrine was significantly higher in the group with High IL-6 (100%) than in the group with Low IL-6 (62.5%) ($p = 0.009$). RRT was also more frequent in patients with High IL-6 than in those with Low High IL-6 (87.5% vs. 55.5%, respectively, $p = 0.056$). **Conclusion:** These findings suggest that the evaluation of serum IL-6 level is useful in the early phase of the severe sepsis and septic shock in order to identify higher-risk patients.

Key words: sepsis; septic shock; biological markers; multiple organ failure; interleukin-6; hospital mortality.

INTRODUCTION

Sepsis has been defined as a clinically apparent systemic inflammatory response syndrome (SIRS) induced by a localized or generalized infection[1]. Detection of sepsis and septic shock is essential, because any delay in initiating a proper treatment is associated with a worse prognosis[2]. The patophysiological process during sepsis is determined by the activation of pro- and anti-inflammatory cascades that are controlled by cytokines, mediators, and cellular elements of the immune system[3].

Cytokines are proteins that are secreted by components of the innate and adaptive immune systems. They act as effectors or modulators of inflammatory response, which in turn play prominent roles in the development of sepsis[4]. Raised levels of many cytokines, including the tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, and IL-10 are indeed present in many sepsis patients and some have been associated with a worse outcome[5,6]. Indeed, IL-6 has been used as an entry criterion for clinical trial of an antisepsis therapy[7].

Early severity assessment and timely interventions can optimize sepsis patient's care. Ideally, biomarkers should provide

First submission on 02/05/16; last submission on 09/05/16; accepted for publication on 03/10/16; published on 20/12/16

valuable information regarding diagnosis and prognosis, and should permit monitoring patients responding to treatment[8]. Nevertheless, under certain limitations, only C-reactive protein (CRP) and pro-calcitonin have been used at the bedside to evaluate prognosis or to guide therapy. Our aim was to evaluate the levels of IL-6 early in the onset of the evolution of sepsis associated-organ dysfunction and its relation to the need for more advanced supportive therapies.

METHODS

This is a prospective study carried out between January 2006 and March 2007 at a 43-bed mixed Medical-surgical intensive care unit (ICU) in a university hospital. The local research ethics committee approved this study, and a written consent was obtained from the patients or the next of kin. Patients in the ICU with severe sepsis or septic shock, defined according to the criteria of the American College of Chest Physicians (ACCP)[1], and over 18 years of age, who presented the first organ dysfunction in less than 48 hours of admission to the ICU were included. Patients with terminal illnesses or with an expectation of life lower than three months were excluded.

Collections of cultures and resuscitation measures were left to the discretion of the attending physician. The Acute Physiologic and Chronic Health Evaluation (APACHE) II score was used to evaluate the severe condition of patient's admission in the study[9]. Organ function was evaluated daily during the first week by the Sepsis-related Organ Failure Assessment (SOFA) score[10]. Cardiovascular, respiratory, renal, central nervous system, coagulation, and liver failure were defined as a SOFA score of more than 2 for those systems.The need for vasopressors, mechanical ventilation or renal replacement therapy (RRT) was considered advanced supportive therapies. These therapies were monitored in a daily basis until hospital discharge or death.

The concentrations of CRP in serum were estimated by nephelometry (Behring, Berlin-Germany). Blood samples for IL-6 measuring were collected at the time of study inclusion (D1-0 h), 12 hours (D1-12 h) and 24 hours later (D1-24 h). The samples were centrifuged and stored in a freezer at -80ºC for the subsequent preparation of laboratory tests. The IL-6 was quantitatively determined by the enzyme immunoassay technique (Quantikine® HS – High-Sensitivity ELISAs), and assays were performed according to the manufacturer's instructions. Dilutions were carried out to a level of 1000 pg/ml, if necessary. Patients were then divided into two groups according to serum IL-6 levels (Low IL-6: ≤ 1,000 pg/ml or High IL-6: > 1,000 pg/ml).

STATISTICS

The Minitab Statistical Software 17 was used for statistical analysis. The categorical variables were treated as proportions and analyzed using the chi-square test. The Kolmogorov-Smirnov test was used for normality test. The continuous variables that presented normal distribution were represented as means and standard deviations and evaluated using the *t*-test, while the variables that did not present normal distribution were evaluated using the Kruskal-Wallis test and presented as medians and interquartile ranges (IQRs). A p-value < 0.05 was considered statistically significant.

RESULTS

Thirty-three consecutive patients, nine with severe sepsis (27.3%) and 24 with septic shock (72.7%), were included in the study. Mean age was 59.2 ± 18.9 years and median SOFA score and APACHE II at day 1 were 8 and 14, respectively. Overall hospital death rate was 45.5%.

The characteristics of all cohorts, survivors, and non-survivors, are shown in **Table 1**. Non-survivors were significantly older (67.1 ± 14.1 vs. 52.6 ± 20.1 years; $p = 0.025$), and had more comorbidities (93.3% vs. 75.5%; $p = 0.023$).

Table 2 shows the pattern of SIRS signs, organ failure and therapeutic support in the groups with Low and High IL-6 at 0 h. Hyperthermia or hypothermia was more frequent in the Low IL-6 group (91.7%) than in the High IL-6 group (55.5%) ($p = 0.023$). However, tachypnea was more frequent in High IL-6 group (100%) in comparison to Low IL-6 group (75%) ($p = 0.038$).

The prevalence of cardiovascular failure was significantly higher in the group High IL-6 (100%) than in the group Low IL-6 (71%) ($p = 0.023$). The need for norepinephrine was also significantly higher in the group with High IL-6 (100%) than in the group with Low IL-6 (62.5%) ($p = 0.009$). Corticosteroids were given more frequently to High IL-6 group ($p = 0.024$) (Table 2). RRT was less frequent in patients with Low IL-6 than in patients with High IL-6 (55.5% vs. 87.5%,

respectively, $p = 0.056$). Mortality rate was higher for patients with High levels of IL-6 (66.7%) at 0 h in comparison to patients with Low levels (37.5%) although not statistically significant ($p = 0.133$) (Table 2).

TABLE 1 – Characteristics of the patients

	All ($n = 33$)	Survivor ($n = 18$)	Non-survivors ($n = 15$)	p-value
Age (years)	59.2 ± 18.9	52.6 ± 20.1	67.1 ± 14.1	0.025
Male (%)	26 (78.7)	13 (72.2)	13 (86.6)	0.876
Medical admission (%)				
APACHE II	14 [9-19]	12 [9-17.5]	17 [9-24]	0.224
SOFA 1	8 [5-11]	7 [5-11]	10 [7-11]	0.213
SOFA 2	9 [6-11]	8.5 [5-11]	10 [7-11]	0.284
SOFA 3	9 [5.5-10.5]	8.5 [4-10]	10 [7-11]	0.139
High IL-6	9 (27.28%)	3 (33.3%)	6 (66. 7%)	
CRP 0 h (mg/dl)	14.1 ± 9.2	13.2 ± 8	15.5 ± 10.9	0.814
CRP 24 h (mg/dl)	12.5 ± 11.3	12.7 ± 3.3	12.3 ± 15	0.948
Nosocomial-acquired infection (%)	20 (60.6)	8 (50)	12 (80)	0.138
Type of infection (%)				
Abdominal	13 (39.3)	7 (38.8)	6 (40)	0.948
Pulmonary	12 (36.4)	7 (38.8)	5 (33.3)	0.741
Urinary	3 (9.1)	1 (5.5)	2 (13.3)	0.438
Skin	5 (15.1)	3 (16.6)	2 (13.3)	0.79
Septic shock (%)	24 (75.7)	9 (55)	15 (100)	
Isolates (%)				
Positive isolates	28 (84.4)	15 (83.3)	13 (86.6)	0.79
Positive hemoculture	14 (42.2)	5 (27.7)	9 (60)	0.06
Gram-positive	13 (39.3)	9 (50)	4 (26.6)	0.168
Gram-negative	25 (75.7)	14 (77.7)	11 (73.3)	0.767
Comorbidities (%)				
Number of patients	25 (75.7)	11 (61.1)	14 (93.3)	0.023
COPD	9 (27.7)	2 (11.1)	7 (46.7)	0.02
HT	8 (24.2)	4 (22.2)	4 (26.7)	0.767
Diabetes	7 (21.2)	4 (22.2)	3 (20)	0.876
Cancer	5 (15.1)	2 (11.1)	3 (20)	0.918
Heart failure	3 (9.1)	3 (16.6)	0 (0)	0.049
Immunossupression	3 (9.1)	2 (11.1)	1 (6.7)	0.655
Chronic renal failure	3 (9.1)	1 (5.5)	2 (13.3)	0.438
Type of supportive care				
Mechanical ventilation (%)	26 (78.8)	18 (100)	15 (100)	0.05
Mechanical ventilation (days)	10 [5.7-17]	10.5 [6-28]	10 [4-17]	0.29
Norepinephrine (%)	24 (75.7)	9 (55)	15 (100)	< 0.001
Norepinephrine (days)	4.5 [2.2-7.7]	4 [2-4.5]	6 [3-11]	0.031
Dopamine (%)	5 (15.1)	2 (11.1)	3 (20)	0.479
Dopamine (days)	1 [1-3]	2	1 [0.25-2.5]	0.64
RRT (%)	26 (78.8)	16 (88.9)	10 (66.6)	0.117
Outcomes				
ICU LOS (days)	10 [5.5-18.5]	10.5 [6.7-18]	8 [3-20]	0.69
Hospital LOS (days)	23 [16.5-41.5]	21.5 [16.2-37.2]	23 [16-44]	0.786

Numbers are presented as number of patients (%); mean ± standard deviation or median [25%-75%].

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sepsis Organ Failure Assessment; IL: interleukin; CRP: C-reactive protein; COPD: Chronic Obstructive Pulmonary Disease; HT: hypertension; RRT: renal replacement therapy; ICU: intensive care unit; LOS: length-of-stay.

TABLE 2 – SIRS signs, organ failure, and therapeutic support measures in patients with Low and High IL-6

	All (n = 33)	Low IL-6 (n = 24)	High IL-6 (n = 9)	p-value
SIRS signs (%)				
Temperature	27 (81.8)	22 (91.7)	5 (55.5)	0.023
Tachycardia	28 (84.4)	21 (87.5)	7 (77.8)	0.501
Tachypnea	27 (81.8)	18 (75)	9 (100)	0.038
Leucocytes	27 (81.8)	20 (83.3)	7 (77.8)	0.717
Organ failure at any time (%)				
Cardiovascular	26 (78.8)	17 (70.8)	9 (100)	0.024
Respiratory	23 (69.6)	16 (66.7)	7 (77.8)	0.528
Renal	12 (36.4)	7 (29.1)	5 (55.5)	0.166
Coagulation	12 (36.4)	10 (41.6)	2 (22.2)	0.289
CNS	10 (30.3)	7 (29.1)	3 (33.3)	0.818
Liver	3 (9.1)	2 (8.3)	1 (11.1)	0.059
SOFA day 1	8.6 ± 3.9	7.8 ± 3.7	10.7 ± 3.4	0.099
SOFA day 2	8.8 ± 3.8	8.1 ± 3.7	10.9 ± 3.9	0.112
SOFA day 3	8.6 ± 3.8	7.8 ± 3.6	10.7 ± 4.2	0.077
SOFA day 4	8.6 ± 3.6	8 ± 3.7	10.2 ± 2.9	0.143
SOFA day 5	7.6 ± 3.6	7.1 ± 3.6	9.3 ± 3.2	0.093
SOFA day 6	6.5 ± 3.7	5.9 ± 3.9	8.3 ± 2.6	0.051
SOFA day 7	6.7 ± 3.5	6.3 ± 3.7	7.7 ± 3.2	0.23
Type of supportive care				
Norepinephrine (%)	24 (72.7)	15 (62.5)	9 (100)	0.009
Norepinephrine (days)	4.5 [2.2-7.7]	5 [2-7]	4 [2.5-10.5]	0.362
Dopamine	5 (15.1)	4 (16.6)	1 (12.5)	0.807
Dopamine (days)	1 [1-3]	2 [1-3]	1 (11.1)	0.414
RRT (%)	26 (78.8)	5 (55.5)	21 (87.5)	0.056
Mechanical ventilation (%)	26 (78.8)	18 (75)	8 (88.9)	0.361
Mechanical ventilation (days)	10 [5.7-17]	9.5 [6-17]	11 [4-17.7]	0.362
Corticosteroids (%)	26 (78.8)	17 (70.8)	9 (100)	0.024
Corticosteroids (days)	8 [5.7-9]	8 [7-9]	8 [2.5-8.5]	0.249
Outcomes				
ICU LOS, days	10.5 [6.7-18]	9 [6-14]	21 [10-21]	0.172
Hospital LOS (days)	21.5 [16.2-37.2]	20 [14-34]	27 [24-56]	0.138
Hospital death	15 (45.4)	9 (37.5)	6 (66.7)	0.133

Numbers are presented as number of patients (%) or median [25%-75%].
*Note: day 4 and 5 (*n *= 32); day 6 (*n *= 29); day 7 (*n *= 28).*

IL-6: interleukin-6; SIRS: systemic inflammatory response syndrome; CNS: central nervous system; SOFA: Sepsis Organ Failure Assessment; RRT: renal replacement therapy; ICU: intensive care unit; LOS: length-of-stay (only in survivors).

DISCUSSION

Cytokines are potential inflammatory markers that may be useful to help recognizing and guiding certain treatments of patients with septic shock. However, currently, only a few had a suitable profile for use at the bedside. In our study, we found the presence of higher levels of IL-6 early in the evolution of severe sepsis or septic shock significantly associated with need for vasopressor therapy and death.

Plasma concentrations of IL-6 are increased in sepsis and are related to the progression to shock and death[11]. Reinhart *et al*. (2001) found an IL-6 immunostrip test able to identify two distinct sepsis populations with significantly different mortality rates in the study with the anti-tumor

necrosis factor-alpha monoclonal antibody[7]. We chose to use the cut-off used in their study (> 1000 pg/dl) to categorize our sample of patients in groups with Low and High serum IL-6 levels.

Cardiovascular failure, that means the use of dopamine in doses higher than 5 (g/kg/min) or norepinephrine in any dose, and the need for norepinephrine were significantly more frequent in patients with High serum IL-6 levels at 0 h than in patients with Low IL-6 levels. All patients in the group High IL-6 needed vasopressor therapy with norepinephrine, including one patient initially not responding to dopamine. The purpose of vasoactive drug therapy in the ICU setting is to restore tissue perfusion in shock states. In vasodilatory shock such as sepsis, there is a complex interaction between pathologic vasodilatation, which is the failure of the vascular smooth muscle to contract, relative and absolute hypovolemia, myocardial depression and altered blood flow distribution, which occur as a consequence of the inflammatory response to injury[12]. Our clinical findings do support those of Hartenmink *et al*. (2010) in which peripheral vasodilatation was strongly and independently associated with IL-6 signaling and release in human sepsis[13]. In addition, the role of IL-6 in triggering vascular leakage in vascular endothelial cell may contribute to hypovolemia[14]. Furthermore, myocardial dysfunction is an important component of septic shock[15]. It was elegantly demonstrated by Parrillo *et al*. (1985) a depressive effect on the contractile property of isolates rat myocytes[16]. IL-6, among other cytokines, was later related to these effects[12, 15-18].

SOFA scores were consistently higher in the High IL-6 group, although not significantly due to the limited number of patients included in the study. Development of multiple organ dysfunction syndrome (MODS) has a well-known impact in survival, and is very likely associated with increased resource utilization as demonstrated by the increased need for ventilatory support and intensive care unit length of stay. Likewise, Cuschieri *et al*. (2010) found increased IL-6 levels associated with higher risk of developing organ failure, more days on ventilator and more time spent at the hospital of patients admitted with hemorrhagic shock[19]. Machado *et al*. (2011)[20] found higher baseline IL-6, IL-8 and IL-10 levels associated with unfavorable organ dysfunction outcomes in patients with septic shock, and Vincent *et al*. (2011)[21] reported worsening and more importantly persistent organ failure, the more common pattern before death, associated with increased IL-6 levels. Indeed, high plasma IL-6 concentrations in patients receiving sustained low-efficiency dialysis (SLED) were found to be associated with death in a small cohort of sepsis patients[22].

Tachypnea was associated with High IL-6 levels and abnormal temperature with Low IL-6 levels. Tachypnea may be an early clinical sign of pulmonary, cardiovascular or metabolic dysfunction. Fever is a non-specific acute phase response occurring in approximately 90% of patients with severe sepsis[23]. In our study, 81.8% had abnormal temperature, mostly hyperthermia. The role of fever in the pathophysiology of sepsis is still not completely understood, and it has been associated with improved survival and shortened disease duration in some infections[23].

Our study adds some important clinical findings to the growing body of knowledge related to the use of biomarkers during severe sepsis and septic shock. However, several limitations of the study deserve consideration. First, the small number of patients in addition to the limited number of IL-6 tests only allows us to evaluate possible associations. Second, we only measured IL-6 levels, and other cytokines were not studied. Third, in eight patients the IL-6 values higher than 1000 pg/dl were unknown and were arbitrarily considered as 1000 pg/dl. Finally, another potential confounder was the use of corticosteroids that can induce anti-inflammatory cytokines and inhibit pro-inflammatory cytokines at the transcriptional level[24]. However, the number of patients receiving corticosteroids was similar in low and high level IL-6 groups. In addition, corticosteroids are frequently used in patients with septic shock due to the high incidence of patients presenting relative adrenal insufficiency[25]. The strength of this study is the prospective design and the enrollment of consecutive patients in the onset of sepsis-associated organ dysfunction.

CONCLUSION

In conclusion, we found high IL-6 levels (> 1000 pg/dl) in the first 48 h of severe sepsis associated with the need for for increased supportive care, more organ failure.

RESUMO

Introdução: *É primordial identificar a sepse e o choque séptico, uma vez que qualquer atraso no início do tratamento adequado associa-se ao pior prognóstico.* ***Objetivo:*** *Avaliar níveis de interleucina 6 (IL-6) no início da evolução da disfunção orgânica na sepse e sua relação com a necessidade de terapias de suporte avançado.* ***Métodos:*** *Estudo prospectivo em uma unidade de terapia intensiva (UTI) médico-cirúrgica com 43 leitos em um hospital universitário. Pacientes com sepse grave ou choque séptico internados na UTI com idade ≥ 18 anos que apresentaram a primeira disfunção orgânica em menos de 48 horas de admissão na UTI. Foram monitoradas diariamente, até a alta hospitalar ou o óbito, terapias de suporte avançado, necessidade de vasopressores, ventilação mecânica e terapia de substituição renal (TSR). Amostras de sangue para medir os níveis séricos de IL-6 foram coletadas no momento da admissão no estudo, 12 e 24 horas depois. Os pacientes foram divididos em dois grupos de acordo com níveis séricos de IL-6 na admissão (Baixa IL-6: < 1.000 pg/ml ou Alta IL-6: > 1.000 pg/ml).* ***Resultados:*** *A necessidade de norepinefrina foi significativamente maior no grupo com altos níveis de IL-6 (100%) do que no grupo com baixa IL-6 (62,5%) (*p = *0,009). TSR também foi mais frequente em pacientes com alta IL-6 do que naqueles com baixa IL-6 (87,5% vs. 55,5%, respectivamente, p = 0,056).* ***Conclusão:*** *Os resultados sugerem que a avaliação dos níveis séricos de IL-6 seja útil na fase inicial do choque séptico e da sepse grave a fim de identificar pacientes de maior risco.*

Unitermos: *sepse; choque séptico; marcadores biológicos; falência múltipla de órgãos; interleucina 6; mortalidade hospitalar.*

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