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Original article

Correlation between inflammatory markers and organ dysfunction among Intensive Unit Care patients

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Summary. *Background:* Nutrition in the Intensive Care Unit (ICU) encounters a variety of challenges. This study aimed to examine the correlation of Tumor Necrosis Factor-alpha (TNF-α) and high sensitive C-reactive protein (hs-CRP) with the Sequential Organ Failure Assessment (SOFA) score in traumatic ICU patients. *Patients and Methods:* Twenty five critically ill patients were recruited for assessment of the inflammatory factors' correlation with the SOFA score. Statistical analyses were done using parametric tests. *Results:* Statistical analysis showed a strong correlation between TNF-α on day 3 of admission with SOFA scores on days 5 and 7 (r> 0.5). A similarly strong correlation also was seen between hs-CRP and SOFA on days 3 and 5 (r>0.5). *Conclusion:* The study results showed serum levels of TNF-α on day 3 of admission can predict organ dysfunction in traumatic ICU patients and TNF-α is a better prognostic factor than hs-CRP.

Key word: enteral nutrition, Tumor Necrosis Factor-alpha (TNF-α), Intensive Care Unit (ICU)

Introduction

Nutrition in the Intensive Care Unit (ICU) encounters a variety of challenges such as: general condition, severity of illness and specific needs (1, 2). Patients admitted in ICU have high nutritional requirements and can become malnourished quickly. In addition, critical illness is typically linked with a catabolic stress state in which patients commonly demonstrate a systemic inflammatory response (3). TNF-α is an inflammatory factor that may have a key role in the regulation of inflammation. TNF-α increases in multiple trauma patients (4, 5) and raised TNF-α level subsequent to trauma is damaging to the body (6). The inflammatory marker can produce intense inflammatory milieu with potential organ dysfunction. Inflammatory marker antagonists may be effective in symptom modulation of inflammatory disorders (7, 8). hs-CRP also is another inflammatory factor that has a role in inflammatory processes. Secretion of hs-CRP is dependent on other inflammatory markers like IL-6. This cytokine also increases in multi-traumatic patients (9-12). The sequential organ failure assessment (SOFA) score makes possible the prediction of organ dysfunction over six organ systems (13), in addition to recognizing the severity of their dysfunctions: respiratory, coagulation, liver, cardiovascular, renal, and neurological systems. Since its introduction, the SOFA score has also been used for predicting mortality, although it was not developed for this purpose. The SOFA score could be useful in providing therapeutic decision making and guiding resource allocation (13-15).

Objectives

The present study was conducted to determine the dynamic changes of serum TNF-α and hs-CRP

and the corresponding changes of serial evaluation in the SOFA score and their correlation in critically ill patients.

Patients and Methods

Subjects

This prospective study was conducted in ICU Imam Reza Hospital of Tabriz University of Medical Science, Tabriz, Iran. During 8 months, all patients admitted to the ICU were screened for study eligibility. Study patients were prospectively followed-up until they had completed a follow-up of 7 days, or died, whichever occurred first. Those patients who did not fulfill the follow-up period (for any reason) were excluded. Sample size was calculated based on TNF-α from Yousef et.al. study (16) by following formula with power %95:

$$n = \frac{a\sigma^2}{\sum T_i^2}\emptyset^2$$

$$a = 4\,, \emptyset^2_{1-\alpha,1-\beta} = 2.5$$

$$\sigma^2 = 239/8, T_1 = -118/75\,, T_2 = 117/18\,, T_3 = 79/22\,, T_4 = -77/65$$

$$\sigma^2 \Big/ \sum T_i^2 = 0/596 \cong 0/6$$

It shows that each group has to be at least six subjects. A total of 25 patients were included in the study and were fed via a Naso-Gastric (NG) or Percutaneous Endoscopic Gastrostomy (PEG) tube with a standard manufactured solution with 1 kcal/ml energy, by using continuous feeding pump. During the 24 hours after admission patients were weighed and, based on Harris-benedict equation, their calorie requirements calculated. Total calories have compromised by 55% from carbohydrate, 30% from fat and 15% from protein. An average 70 kg patient received 15 ml of this solution in the initial 3 hours which increased by 5 ml increments to a maximum of 70 ml every hour. Every six hours, Gastric Residual Volume (GRV) was checked and if it was greater than 300 ml, feeding was delayed by 3 hours and metoclopramide was administered. Patients who had received anti-inflammatory drugs or corticosteroids before admission, patients with bleeding in the GI or with enteral feeding intolerance, hemodynamically unstable patients, immunosuppressed patients, patients with chronic organ failure, patients with previous organ transplantation, pregnant females, those who received massive blood transfusion, post-cardiopulmonary resuscitation status, APACHE II (Acute Physiology and Chronic Health Evaluation) score less than 20 on admission or within 24 h of admission were excluded from the study. Other exclusion criteria: unknown outcome or losses of patient follow up due to transfer to other hospitals and refusal of the patient or relatives to sign the consent form. Inclusion criteria were: patients aged between 18–65 years, those predicted to be kept in ICU from more than 72 hours, APACHE II score on admission or within 24 h of admission >20, amenability to enteral feeding, no obstruction in the gastrointestinal (GI) tract, no GI bleeding, normal kidney function and enteral nutrition tolerance. Venous blood samples were taken just prior to beginning and then 3, 5 and 7 days after admission. Blood samples were collected in glass tubes and serum was extracted by centrifuge at 1,600 g for 15 minutes. Then, samples were frozen at refrigerator -70. Serum hs-CRP concentration was determined based on immunoenzymometric assay (Monobind Inc., Accu-Bind ELISA kit, hs-CRP: 3125-300, USA). Serum level of TNF-α was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (AviBion Human TNF-α ELISA kit, Orgenium Laboratories Business Unit, Finland) guided by the manufacturer's instructions. The SOFA score is composed of six variables, each representing an organ system: respiratory, cardiovascular, hepatic, coagulation, renal and neurological; graded from 0 to 4 according to the degree of dysfunction/failure (17). Each organ system is assigned a point value from 0 (normal) to 4 (high degree of dysfunction/failure). The SOFA score ranges from 0 to 24.

Ethical issues

The research followed the tenets of the Declaration of Helsinki; informed consent was obtained from patients or their kin, and they were free to leave the study at any time and the research was approved by the ethical committee of Tabriz University of Medical Sciences by number: 92205 (IRCT201403042017N19).

Statistical analysis

The continuous variables are presented as mean± SD and categorical variable as number and percentage. The data were descriptively analyzed by calculating the frequencies (percentages), means, and standard deviation (SD). TNF-α, Hs-CRP and SOFA changes during 4 examination were compared by Within-group repeated measures analysis. Correlation of TNF-α and hs-CRP with SOFA scores was assessed by Pearson correlation test. All statistical analyses were conducted with an α level of 0.05 using the statistical software package SPSS (version 20.0, SPSS Inc., Chicago, Illinois).

Results and Discussion

The description of clinical and demographic characteristics (sex, age and serum levels of TNF-α, hs-CRP and SOFA score before intervention) are shown in Table 1. The results of within-group statistical analysis are shown in Table 2 and the correlation assessment results are shown in Table 3. Within-group statistical analysis showed TNF-α at first significantly increases and then decreases significantly. The second examination of TNF-α was significantly higher than the first and 3rd examinations (P< 0.05) and the last examination of TNF-α was significantly lower than the 2nd and 3rd examinations (P< 0.05) but significantly higher than the first one (P< 0.05). The above-mentioned statistical analysis for hs-CRP also showed hs-CRP at first significantly increases and then decreases significantly. In the study, serum levels of hs-CRP on day 3 of admission were significantly higher in comparison to all other examinations (P< 0.05) and the last examination was significantly lower than the second and third days but no significant differences were seen between the first and last examination.

No strong correlation was seen between the first examination of TNF-α and SOFA scores but correlations of the second, third and fourth examinations of TNF-α with SOFA scores on days 5 and 7 of admission were strong. Like TNF-α, no strong correlation also was seen between the first and last examinations of hs-CRP and SOFA scores but a strong correlation was seen between second and third ones.

The present study seems to be, to the best of our knowledge, the first study to correlate simultaneously the serum hs-CRP and serum TNF-α dynamics among critically ill patients in addition to the corresponding changes in SOFA score. The study results revealed that hs-CRP and TNF-α have correlations with SOFA score but because of the rapid reduction to the base line levels it seems that serum levels of hs-CRP are affected by factors other than trauma or are not more sensitive to trauma. So the study recommends the use of serum levels of TNF-α for evaluation of nutritional interventions, even in multiple trauma ICU protocols.

Table 1. Demographic characteristics of study subjects

Variable		Study subjects (n= 25)
Sex	Male [n (%)]	13 (52%)
	Female [n (%)]	12 (48%)
Age [Mean (SD)]		36.90±8.64
Basic TNF-α [Mean (SD)]		36.90±8.64
Basic hs-CRP [Mean (SD)]		3.14±0.24
Basic SOFA [Mean (SD)]		5.01±0.36

Table 2. Within-group statistical analysis

Variable	First examination	Second examination	Third examination	Fourth examination	P-value*
TNF-α	67.48±7.52	196.50±28.27	171.63±27.45	144.94±29.82	< **0.001**
Hs-CRP	3.14±0.24	3.51±0.24	3.49±0.22	3.13±0.27	< **0.001**
SOFA	5.01±0.36	5.39±0.44	6.12±0.63	5.77±0.74	< **0.001**

**P-value based on repeated measure test [TNF-α: P-value between all times is less than 0.001; hs-CRP: P-value between first and last examination is non-significant (more than 0.05); SOFA: P-value between all times is less than 0.05]*

Table3- Correlation of TNF-α and hs-CRP with SOFA scores

variables		$SOFA_1$	$SOFA_2$	$SOFA_5$	$SOFA_7$
$TNF\text{-}\alpha_1$	R	-0.172	-0.394	-0.272	-0.135
	P-value	0.412	0.051	0.188	0.522
$TNF\text{-}\alpha_3$	R	-0.275	-0.001	**0.540**	**0.589**
	P-value	0.184	0.997	***0.005***	***0.002***
$TNF\text{-}\alpha_5$	R	-0.322	-0.027	**0.559**	**0.592**
	P-value	0.116	0.796	**0.004**	**0.002**
$TNF\text{-}\alpha_7$	R	-0.342	0.062	**0.673**	**0.677**
	P-value	0.092	0.720	**< 0.001**	**< 0.001**
$Hs\text{-}CRP_1$	R	0.021	0.170	0.068	0.075
	P-value	0.921	0.417	0.745	0.721
$Hs\text{-}CRP_3$	R	0.315	0.194	**0.688**	**0.533**
	P-value	0.125	0.351	***< 0.001***	***0.006***
$Hs\text{-}CRP_5$	R	-.0414	0.080	**0.546**	**0.541**
	P-value	0.040	0.705	**0.005**	**0.002**
$Hs\text{-}CRP_7$	R	0.346	0.036	0.273	0.174
	P-value	0.091	0.865	0.186	0.406

"R" reported based on Pearson correlation test

SOFA score is an independent prognostic factor in critical illness and indirectly reflect the clinical severity status of the patients and the degree of organ systems dysfunction (18) . Ferreira et al. reported that SOFA scores during the first few days after ICU admission are a good prognostic indicator in critically ill patients(19) (20). The results from present study showed trauma induced inflammatory response do not take place immediately after trauma; the inflammatory factors significantly increase after 3 days of admission and then decrease. Yousef et al also reported delayed elevation of inflammatory markers after ICU admission and also reported that the TNF-α increment was done only on second day of ICU patients (18). In another study the author reported similar findings in ICU patients(19). Our study also showed that TNF-α is a better marker for assessment of inflammatory status in critically ill patients than hs-CRP because of the rapid reduction of hs-CRP after trauma. While the SOFA score remains high, hs-CRP reduces to almost normal range. Thus, it seems that hs-CRP is not a suitable marker for the assessment of nutritional interventions in trauma ICU patients. To the best of our knowledge, no study has been conducted to show hs-CRP status in trauma patients and this study is the first hs-CRP examination in the above-mentioned community group.

Conclusions

Serum levels of TNF-α on day 3 of admission can predict organ dysfunction in traumatic ICU patients and TNF-α is a better prognostic factor than hs-CRP.

Limitations of the study

The low number of patients is a limitation of our study.

Authors' contribution

SMHMJ: Study design, preparation of manuscript, final revision, and data interpretation. AS: Study design and data interpretation. AO: Study design, preparation of manuscript, data interpretation, final revision, and supervisor of the project. SH: Data collection, supervisor in ICU. FS: Data collection, supervisor in ICU.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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