Original Article

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Inflammation and Outcome in Traumatic Brain Injury: Does Gender Effect on Survival and Prognosis?

Surgery Section

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ABSTRACT

Introduction: Traumatic Brain Injury (TBI) accounts for the majority of trauma deaths and there has been increased interest in the understanding the role of prognostic factors. C-Reactive Protein (CRP) level increases rapidly in response to trauma.

Aim: Aim of the present study was to indicate the role of CRP as a predictor of outcome in TBI patients based on their gender category.

Materials and Methods: A prospective cohort study in a surgical Intensive Care Unit (ICU) in one of the Zanjan University of Medical Science hospital was designed. Fifty nine head trauma patients were divided into two groups based on their gender. Serum CRP was measured 48 hours after trauma. All data including the length of ICU stay, the duration of mechanical ventilation, the Glasgow Coma Scale (GCS) at discharge, and mortality were collected. The relationship between the clinical features and serum CRP level was also studied.

Results: In the male group, CRP level was not significantly correlated with the length of ICU stay, the duration of mechanical ventilation and GCS at discharge. In the female group, CRP level was positively correlated with the length of ICU stay and the duration of mechanical ventilation; however, CRP level was not significantly correlated with GCS at discharge. These results remain constant in female sub group with severe head injury contrast to female with mild injury.

Conclusion: The GCS level can predict the outcome of females with severe head injury better than females with mild head injury and males.

Keywords: Brain cells, C-reactive protein, Intracranial inflammatory response

INTRODUCTION

Traumatic Brain Injury (TBI) accounted for the majority of trauma deaths and one of the major causes for long-term disability worldwide [1]. Over 1.5 million individuals are treated for TBI in the USA [2]. Despite recent improvement in the management of TBI, mortality and morbidity still remains high [3]. Most of TBI patients are young for which their relatives and physicians need early determination of prognosis [4]. Therefore, there has been increased interest in understanding the role of prognostic factors in TBI outcome [5].

TBI rapidly induces inflammation. This inflammation is made both by endogenous brain cells and circulating inflammatory cells [6]. Intracranial inflammatory response after TBI results in an adverse effects [7].

Various biomarkers have been evaluated to predict mortality in critically ill patients [8]. A pro- or anti-inflammatory status is a probable risk factor for an unfavourable outcome, and high CRP concentrations have shown to correlate with organ failure [9]. CRP is an acute phase protein produced by the liver as part of the systemic inflammatory response [10]. The assessment of CRP which increases rapidly in response to trauma is relatively cheap and available [11]. Based on this fact, the role of CRP as a predictor of outcome in TBI has been investigated in several studies; however, the effect of gender has been neglected in majority of them. In this respect, we designed a prospective cohort study in a surgical ICU of a university hospital. This ICU is a 20-bed surgical intensive care unit in a Zanjan University of Medical Science hospital. The aim of this study were to assess the reliability CRP as a predictor of outcome in TBI based upon gender.

MATERIALS AND METHODS

Criteria of Patient Selection

After approval by the local ethics committee (Code number: ZUMS.REC.1393.08), patients were enrolled in this prospective cohort study. From June 2013 to July 2014, 66 patients were enrolled in this study who were admitted to the ICU of our tertiary health care institution within 24 hours of head trauma. Patients were included if their age was older than 16 years, if they were not receiving Nonsteroidal anti inflammatory or Corticosteroid drugs, if there were not having burn injury, if there were not any kind of trauma (except for head trauma) and whether they had no history of autoimmune, cardiac, respiratory, neuromuscular, hepatic or renal diseases.

Exclusion criteria were sepsis during first 72 hours of admittance and if patients didn't survive for at least 72 hours after the admittance.

Seven patients were excluded due to failure to meet the inclusion criteria. Three patients were excluded due to age < 16 years, two patients because of burn trauma, and two patients due to their drug history. So, a total of 59 patients (n) were studied. They were divided into two groups of 33 males (55.9%) and 26 females (44%). Each group was fragmented further into two subgroups with respect to the GCS scores (GCS>8 or GCS≤8).

Within the initial 24 hours after the head trauma, age, gender, chronic diseases, GCS and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score were recorded. CRP was measured 48 hours after trauma. As clinical features, all data of the GCS at discharge, the outcome at discharge (dead or alive), the length of ICU stay, and the duration of mechanical ventilation were all collected. Finally, the relationship between the clinical features and the serum CRP level was compared between two groups.

Collection of Blood Sample

Blood samples were obtained by venipuncture. CRP was measured

via a high-sensitivity latex-enhanced immunonephelometric assay 48 hours after trauma. The minimum and upper reference limit reported in the package insert for CRP was 0.2 and 5 mg/l.

STATISTICAL ANALYSIS

SPSS software (version 22, SPSS Inc, Chicago) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Continuous variables in two groups were compared using Independent sample t-test, when data were normally distributed. The Mann–Whitney U-test was used, when numerical data were not normally distributed. Between-group comparisons of proportions were performed using χ^2 test or the Fisher's exact test, as appropriate. Spearman's correlation test was used to evaluate correlations between the CRP level and data if data were not normally distributed, and in the case of normally distributed data, Pearson's correlation test was used. Significance was defined as a p-value <0.05.

RESULTS

Patient Characteristics

As shown in [Table/Fig-1], patient characteristics were similar in age, APACHE II Score, GCS at admission and the CRP level (p>0.05).

Comparison of Data between Male and Female Groups

There was no statistically significant difference according to the length of ICU stay, the duration of mechanical ventilation and GCS at discharge between two groups (p>0.05) [Table/Fig-2].

Correlation between Serum Level of CRP and Other Data in All Patients

The CRP concentration was increased above the normal levels of 5 mg/l in all patients [Table/Fig-1]. CRP level in all patients was positively correlated with the length of ICU stay (Spearman's correlation coefficient-0.359, p = 0.003) as well as the duration of mechanical ventilation (Spearman's correlation coefficient 0.853, p = 0.005). However, CRP level was not significantly correlated with GCS at discharge in all study patients (Spearman's correlation coefficient was -0.216, p = 0.085).

	Male group (n = 33)	Female group (n = 26)	p-value
Age years	48±20	52.3±20	0.486
GCS at ICU admission	7.2±2	8.5±3	0.068
APACHE II Score	11.9±7	11.4±6.5	0.819
CRP level mg/l	149±125	113±101	0.174

[Table/Fig-1]: Characteristics of the study population based on their gender.
Data are presented as Mean±SD
SD: standard deviation, GCS: Glasgow Coma Scale, APACHE II Score: Acute Physiology and Chronic Health Evaluation II, ICU: intensive care unit, CRP: C-reactive protein, n= no. of patients

	Male group (n = 33)	Female group (n = 26)	p-value
Length of ICU stay, days (mean±SD)	8±5	4.7±4	0.619
Length of mechanical ventilation, days (mean±SD)	5.4±4	3.2±3	0.199
GCS at discharge (mean±SD)	10.7±5	10±4	0.165
ICU mortality, no. (%)	5(15.1%)	3(11.5%)	0.071

[Table/Fig-2]: Outcome of the included patients based on their gender.
SD: standard deviation, GCS: Glasgow Coma Scale, ICU: intensive care unit, n= no. of patients

Correlation between Serum Level of CRP and Other Data in Male Group

In the male group, CRP level was not significantly correlated with the length of ICU stay (Spearman's correlation coefficient- 0.97, p = 0.59), the duration of mechanical ventilation (Spearman's correlation coefficient-0.147, p = 0.416) and GCS at discharge (Spearman's correlation coefficient-0.285, p = 0.108).

Correlation between Serum Level of CRP and Other Data in Female Group

In the female group, CRP level was positively correlated with the length of the ICU stay (Spearman's correlation coefficient-0.554, p = 0.001) and the duration of mechanical ventilation (Spearman's correlation coefficient-0.480, p = 0.005); however, the CRP level was not significantly correlated with GCS at discharge (Spearman's correlation coefficient-0.232, p = 0.201).

Influence of Severity of Trauma

In the female subgroup sustaining more severe head trauma (GCS≤8), the CRP level was positively correlated with the ICU admission (Spearman's correlation coefficient-0.707, p = 0.007) and the duration of mechanical ventilation (Spearman's correlation coefficient-0.749, p = 0.003), but not with the GCS at discharge (Spearman's correlation coefficient -0.117, p = 0.13).

In the males with severe head trauma (GCS≤8), the CRP level was not significantly correlated with the length of ICU stay (Spearman's correlation coefficient 0.601, p = 0.08), the duration of mechanical ventilation (Spearman's correlation coefficient 0.502, p = 0.21) and the GCS at discharge (Spearman's correlation coefficient -0.181, p = 0.17).

In the females with mild head trauma (GCS>8), the CRP level was not significantly correlated with the length of ICU stay (Spearman's correlation coefficient-0.622, p = 0.12), the duration of mechanical ventilation (Spearman's correlation coefficient-0.676, p = 0.105) and the GCS at discharge (Spearman's correlation coefficient -0.154, p = 0.09).

In the males with mild head trauma (GCS>8), the CRP level was not significantly correlated with the length of ICU stay (Spearman's correlation coefficient-0.709, p = 0.06), the duration of mechanical ventilation (Spearman's correlation coefficient-0.547, p = 0.173) and the GCS at discharge (Spearman's correlation coefficient -0.186, p = 0.089).

Mortality

There was not any difference in the survival between male and female groups (p= 0.071). Mean serum CRP levels were not significantly higher in non-surviving compared with surviving patients in male (p = 0.09) and female (p = 0.06) groups.

DISCUSSION

CRP has been recently considered not only as a biochemical marker of inflammation, but also as a predictor of prognosis and outcome in TBI [11]. In this context, the correlation of CRP levels was evaluated with outcome and mortality after ICU admission in a head trauma group of ICU patients based upon gender in the present study.

In this study, the level of CRP had increased from normal level to 48 hours after trauma in all patients. An acute brain trauma is accompanied by a strong and immediate inflammatory response so-called acute phase response. During this phase, hepatic synthesis of several plasma proteins (the acute phase proteins) such as CRP increases significantly. This inflammation is due to a reaction to the tissue damage which has been extensively documented previously in experimental and clinical TBI [12]. Many studies have demonstrated that the peak of CRP is 48 hours after trauma [13]; so, this time was chosen to measure the level of CRP. It was able to explain the rise of CRP level after trauma in all patients at this time. Previous studies have found that the median CRP level for the top quartile of the population was higher in women than men [14]. However, in our study CRP level was not

significantly different between two groups 48 hours after trauma, which indicated that inflammatory response to trauma was similar between male and female and was not dependent on baseline CRP.

Schoeneberg et al., demonstrated that the ICU stay in female patients was shorter than males, which is consistent to our findings. Furthermore, they reported no significant difference in the mortality rate between males and females after the TBI [15]. This finding is consistent with our analysis in which survival was not different between two groups. However, Kraus et al., have demonstrated 1.75 times greater risk for poor outcome in females [16]. Differences in age and severity of injury in the study population were able to explain this inconsistency.

In this study, the CRP level was positively correlated with the length of the ICU stay as well as the duration of mechanical ventilation in all patients, but after separating the female and male, this correlation was not observed in the male group. Laboratory findings have shown that males and females would respond differently after traumatic injury [17]. Choudhry et al., reported that male and female patients responded differently after trauma [18]. Experimental animal studies demonstrated that sex hormones could explain these gender-based differences [19]. Here, the different correlation between data in two groups can be explained by sex hormones, too. Schroeder et al., have shown that trauma can effect on the levels of sex hormones. They have reported that testosterone decreased in male, but remained normal in females; while in both male and female patients, estrogen increased dramatically [20]. Hsieh and Colleagues conducted a review of metabolic modulators following trauma sepsis. The authors reported that sex steroids not only modulate the immune/cardiovascular responses, but also influence various metabolic processes following trauma [21]. Zolin et al., have shown that early increasing testosterone level is associated with an exaggerated inflammatory response and a significantly greater risk of multiple organ failure and nosocomial infections following trauma. High estrogen level is associated with an increased risk of multiple organ failure. They suggest that poor outcome is possible with an early elevating testosterone to estrogen hormonal level following traumatic injury [22]. Based on this fact, sex hormones could have effect on the role of CRP as a predictor of outcome in TBI. In the present study CRP level was significantly correlated with the length of ICU stay and the duration of mechanical ventilation only in female with severe trauma (GCS<8). This relationship was not observed in women with mild trauma (GCS>8). Thus, it can be speculated that female sex hormones might have variable influence on the different levels of injury-induced inflammation.

A study by O. Sogut et al., in 100 patients with blunt head trauma had revealed a significant positive association between the mortality and CRP [23]. According to another investigation in a heterogeneous ICU population, elevated concentrations of serum CRP on ICU admission were correlated with an increased risk of death. Patients with high CRP levels at ICU admission had higher mortality rates than patients with normal ICU admission CRP levels [24]. This is roughly inconsistent with this study in which there was no correlation between CRP level and mortality. Possible reasons for the difference were as follows: first, difference between population study and second, different time of CRP level measurement. On the other hand, they demonstrated that patients with high CRP levels at ICU admission had longer ICU stay. This finding is similar with our data although we could not find any study to show the effect of gender in TBI patients. A research on cardiovascular patients showed that elevated CRP was more associated with mortality hazards in men, but not in women [14]. This finding opposed with the present study in which there was no correlation between the mortality and CRP level in none of the genders. These controversial findings can be explained by difference in the study population.

Our results indirectly suggest that sex hormones may have crucial effects on the trauma-induced inflammation, which is able to predict the patient's outcome. The CRP level is better predictor in females than males suffering TBI. This difference can be explained by an interaction between the immune system with endocrine system. In order to confirm these findings, a larger patient population is necessary.

LIMITATION

The main limitation of this study was its conduct in a single institute and only on patients in a same race. Furthermore, sample size was small. It is believed that other researchers may conduct use it in a larger trial.

CONCLUSION

This study demonstrated that the CRP level was able to predict the outcome of females with severe head injury better than males and females with mild head injury in TBI patients. It is unclear why elevated CRP is more associated with prediction of the outcome in females and not males. Hormonal effects may play a role in attenuating the effects of CRP, but this theory requires further investigation.

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