The effect of omega-3 fatty acids prescription on serum levels of IL-6 and IL-1β in patients with traumatic brain injury

Wpływ stosowania kwasu omega-3 na poziom IL-6 i IL-1β w surowicy po obrażeniach mózgu

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Medical Studies/Studia Medyczne 2018; 34 (4): 276–280
DOI: https://doi.org/10.5114/ms.2018.80942

Key words: traumatic brain injury, omega-3, interlukin-1β, interlukin-6.

Słowa kluczowe: obrażenia mózgu, kwas omega-3, interleukina 1β, interleukina 6.

Abstract

Introduction: Survivors of traumatic brain injury (TBI) continue to suffer from long-term disabilities.

Aim: To investigate the effect of omega-3 on serum levels of interleukin (IL)-1β and IL-6 in patients with traumatic brain injury.

Material and methods: In this double-blind clinical trial study 80 patients with TBI divided into two 40-memebrr groups (50 mg/kg oral omega-3 capsule group, and oral placebo capsule group). Patients took these capsules for 7 days, occurrence of leukocytosis and leukopaenia and Glasgow Coma Score (GCS) was measured. Serum levels of IL-1β and IL-6 were measured on day 7 in each of the two groups. The data were analysed using SPSS software version 20.

Results and conclusions: There was no significant difference between basic demographic information such as age (p = 0.86), gender (p = 0.64), APACHE II (p = 0.16), and start of GCS (p = 0.36) in the two groups. On the seventh day, the mean GCS was 8.90 ±2.03 in the control group and 9.92 ±2.69 in the case group (p = 0.05), and the mean white blood cells (WBC) on the third day (p = 0.22) and seventh day (p = 0.58), mean of temperature (p = 0.21), without mechanical ventilation day (p = 0.89), and length of stay in the intensive care unit (ICU) (p = 0.27) showed no significant differences between the two groups. The serum level of IL-1β was 1154.94 ±234.31 for the control group and 2133.36 ±568.08 for the case group (p = 0.31), but the IL-6 level was 296.02 ±137.02 in the control group and 208.54 ±90.61 in the case group that showed significant differences between them (p = 0.001).
Introduction

Survivors of traumatic brain injury (TBI) continue to suffer from long-term disabilities. Even a mild TBI can leave cognitive deficits, concentration deficits, fatigue, and headache [1]. Despite the advances in preventive tools as well as diagnostic and surgical techniques, the TBI management approaches have undergone no significant changes, and almost no effective pharmacological treatment has been proposed to maintain neural support in targeting secondary injury mechanisms [2]. The main focus in TBI management is monitoring and maintaining intracranial pressure (ICP) and cerebral perfusion pressure (CPP) [3]. Currently, frequent neurological examination and computed tomography (CT) scans are used for assessment of the changes in ICP. Therefore, the use of biomarkers that demonstrate the degree of certainty in ICP conditions can improve patient management. Biomarkers help the clinicians obtain additional and exclusive information from each patient [4].

Classification of TBI patients by biomarkers coupled with common techniques can be used for specialized treatment of this disease [5]. Prognosis of critical patients is associated with their inflammatory conditions. Inflammation results from several reactions and confrontations between different cell types and chemical mediators [6]. Even in other medical studies and inflammatory research areas, the role of the systemic nature of molecular structure and inflammatory changes is important, and several interleukins and other markers such as C-reactive protein play an important role in the human body [7–9]. From them, the IL-1 cytokine family is recognised as a key mediator of peripheral and central inflammatory responses, a molecule that appears to be associated with acute TBI and is present in localised and diffuse injuries [10]. The IL-1 family consists of agonists (IL-1α, IL-1β) and antagonists (IL-1ra), while agonist IL-18 constitutes other family members [11]. Studies have shown a direct correlational between IL-1β levels and prognosis. Serum levels of IL-1β within the first 6 h of TBI are correlated with GCS over the next 48 h [12]. Interleukin 6 plays a role in many physiological and pathophysiological processes, and it regulates inflammation, bone metabolism, haematopoiesis, and neuronal evolution [13]. There is evidence of the beneficial effects of IL-6 expression followed by neuronal damage [14]. The rapid increase in IL-6 expression following injury and its maximum measurable levels over the next few hours has meant that this cytokine has been introduced as a biomarker. The serum concentration of this biomarker is measurable after injury [15]. Interleukin 6 is highly sensitive to TBI and can easily be detected in serum; however, the previous data associated with its prognosis potential and its relation to ICP are incomplete and limited. On the other hand, the anti-inflammatory effect of omega-3 unsaturated fatty acids shows that it may be used as a treatment agent in disorders with an inflammatory component. Changing the fatty acid composition of cells involved in the inflammatory response also affects production of peptidic mediators of inflammation such as adhesion molecules and cytokines [16]. Anti-inflammatory effects of omega-3 fatty acids have therapeutic value. Obvious or hidden inflammation is observed in certain human conditions and diseases, including rheumatoid arthritis, diabetes type 1, asthma, obesity, systemic response to surgery and trauma, or in patients with severe and chronic illness. The most common consequences of this phenomenon include the high and unpredictable production of inflammatory mediators, including eicosanoids and cytokines [17]. Cytokines such as IL-1 are potent peptidic mediators of immune response. They apply profound cellular effects at molecular concentrations in diverse target tissues, including vascular endothelium, central nervous system (CNS), and immune cells. Their synthesis is pharmacologically suppressed by steroids and other immunosuppressive agents such as cyclosporine A. Previous studies have shown that the synthesis of inflammatory cytokines is inhibited by the increase in the content of omega-3 fatty acids in leukocytes [18]. Studies have shown the effects of omega-3 administration on the function of inflammatory cells and the production or concentration of inflammatory mediators [19].

Aim of the research

Due to lack of adequate research in this field, in the present study attempts were made to investigate the effect of omega-3 on serum levels of IL-1β and IL-6 in patients with traumatic brain injury.

Material and methods

The present study was a double-blind clinical trial on patients with TBI admitted to the intensive care unit of Ahvaz Golestan Hospital in 2017. After obtaining the approval of the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, and the written, informed consent of the patients’ parents, a total of eighty 18–50-year-old patients with TBI were selected as fulfilling the inclusion criteria. In addition, the exclusion criteria were patients with severe and chronic illness. The most common consequences of this phenomenon include the high and unpredictable production of inflammatory mediators, including eicosanoids and cytokines [17]. Cytokines such as IL-1 are potent peptidic mediators of immune response. They apply profound cellular effects at molecular concentrations in diverse target tissues, including vascular endothelium, central nervous system (CNS), and immune cells. Their synthesis is pharmacologically suppressed by steroids and other immunosuppressive agents such as cyclosporine A. Previous studies have shown that the synthesis of inflammatory cytokines is inhibited by the increase in the content of omega-3 fatty acids in leukocytes [18]. Studies have shown the effects of omega-3 administration on the function of inflammatory cells and the production or concentration of inflammatory mediators [19].
took these capsules for seven days, occurrence of leukocytosis (12000 WBC) and leukopaenia (< 4000 WBC) and GCS (Glasco Coma Score) were measured on days 3 and 7 as a measure of the patient’s consciousness [3–15], the duration of admission to the ICU was investigated on the days when a ventilator was not needed. Serum levels of IL-1β and IL-6 were measured on day 7 in each of the two groups, and these variables were investigated via a questionnaire that was completed by a blind operator.

**Statistical analysis**

Finally, mean, standard deviations (in quantitative variables), frequency, and percentages (for qualitative variables) were used for description of the data. T-test (if necessary, the Mann-Whitney test) and χ² test were used for univariate data analysis. The data analysis was performed using SPSS software version 20, and the significance level was assumed less than 0.05.

**Results**

Regarding the patients’ gender, 40% were female and 60% were male. 62.5% of the patients in the control group and 57.5% of the patients in the case group were male, and no statistically significant difference was found between the gender of patients in the two groups (p = 0.64). The mean age of the control group patients was 33.33 ±10.10 years, and the mean age of the case group was 33.68 ±8.49 years. There was no significant difference between the two groups in terms of age (p = 0.86). The APACHE II score within 24 h of ICU admission was 84.75 ±21.27 for the control group and 79.07 ±18.52 for the case group (there was no statistically significant difference between the two groups, p = 0.16). The level of consciousness obtained from the Glasgow Coma Scale (GCS) showed that at the beginning of the study the mean GCS was 6.97 ±1.47 in the control group and 6.97 ±1.47 in the case group (no statistically significant difference was found between the two groups (p = 0.36), moreover, on the seventh day, the mean GCS was 8.90 ±2.03 in the control group and 9.92 ±2.69 in the case group, and no statistically significant difference was found between the two groups, while the GCS score was much higher in the case group compared to the control group (p = 0.05). The study of WBC on the third day showed that the mean WBC was 2952.27 ±57.8504 in the control group and 2859.92 ±57.7823 in the case group (no significant difference was found between the two groups, p = 0.22). In addition, on the seventh day the mean WBC was 14668.63 ±10416.25 in the control group and 2859.92 ±9102.47 in the case group, and no statistically significant difference was found between the two groups (p = 0.58). Investigation of the inflammatory factors showed that the serum level of IL-1β was 1154.94 ±234.31 for the control group patients and 2133.36 ±568.08 for the case group patients, and there was no significant difference between the two groups in this regard (p = 0.31). The IL-6 levels was 296.02 ±137.02 in the control group and 208.54 ±90.61 in the case group (significantly lower in the case group compared to the control group, p = 0.001). In addition, the temperature of the patients in the control group was 37.78 ±0.94 while the temperature of the case group patients was 37.53 ±0.85 (no statistically significant difference was found between the two groups, p = 0.21). Also, the number of admissions without mechanical ventilation days was 4.39 ±8.70 in the control group and 8.55 ±5.23 in the case group, which showed no statistically significant difference between the two groups (p = 0.89). The length of stay in the ICU was equal to 5.33 ±12.37 for patients in the control group and 11.02 ±5.61 in the case group. There was no significant difference between the two groups in this regard (p = 0.27). Finally, the prevalence of mortality was 23.8% in the patients, with the control group and case group accounting for 25% and 22.5% of the mortalities, respectively. No significant difference was found between the two groups in this regard (p = 0.79) (Table 1).

**Discussion and conclusions**

The results of this study showed that taking 50 mg/kg oral omega-3 capsules per night could significantly reduce the serum level of IL-6 in patients with traumatic brain injury and thus provide insight into a new and rarely-studied biomarker to provide the basis for increasing facilitation of patient monitoring, and to provide more robust results for the administration of oral omega-3 capsules to patients. Oral omega-3 capsules have already been used and studied for purposes similar to those discussed in the present study, and have been tested on humans and animals in different parts of the world. Regarding animal studies, Chen et al. examined the effect of omega-3 supplements on microglial inflammation following TBI in mice. They found that omega-3 fatty acid supplements can inhibit TBI-induced microglial activation and the incidence of inflammatory factors (TNF-α, IL-1β, IL-6, and IFN-γ), cerebral oedema reduces cell apoptosis and improves neurological functions after TBI [20]. In the present human study, although IL-1α did not change significantly, the level of IL-6 significantly decreased, which was consistent with the animal study and the basic hypotheses presented by Chen et al [17]. Zhang et al. investigated the long-term neuroprotective effect of omega-3 supplements against cerebral ischaemia (with consideration of anti-inflammatory function of this supplement) [18]. They monitored female mice with or without an omega-3-enriched diet from the second day of pregnancy until 14 days after childbirth. Seven-day-old newborn mice suffering from hypoxic ischaemia were monitored for 5 weeks. The researchers concluded that omega-3 complement can signifi-
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A review of other studies on similar patients and other diseases showed that omega-3 can reduce inflammatory factors; for example, Wang et al. investigated the effects of omega-3 supplementation on postsurgical inflammatory response. Forty-seven patients with gastric cancer, who underwent radical gastrectomy, were randomly assigned into an experimental group (with omega-3 diet) and control group (without omega-3 diet). The levels of inflammatory factors (CRP, TNF-α, IL-1, IL-6, and IL-10) were compared. They found that the pre-inflammatory cytokines clearly decreased in the experimental group and argued that the omega-3 supplement can inhibit the pre-inflammatory factors and enhance the release of inflammation inhibitors thus reducing the incidence of SIRS [21]. Although the research population and the patients differ in two articles, omega-3 has been able to significantly reduce inflammatory factors in both studies. In general, the present study suggests that oral administration of omega-3 to patients with traumatic brain injury can lead to a decrease in serum levels of IL-6. However, authors are required to cover more variables as well as other inflammatory and cytokine factors in future studies and to evaluate the effect of different doses of omega-3 at different time intervals.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 40)</th>
<th>Case (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.33 ±10.10</td>
<td>33.68 ±8.49</td>
<td>0.86</td>
</tr>
<tr>
<td>GCS: 1st day</td>
<td>6.97 ±1.47</td>
<td>7.25 ±1.23</td>
<td>0.36</td>
</tr>
<tr>
<td>GCS: 7th day</td>
<td>8.90 ±2.03</td>
<td>9.92 ±2.69</td>
<td>0.05</td>
</tr>
<tr>
<td>WBC: 3rd day</td>
<td>8504.57 ±2952.27</td>
<td>9323.85 ±3084.99</td>
<td>0.22</td>
</tr>
<tr>
<td>WBC: 7th day</td>
<td>10416.25 ±14668.63</td>
<td>9102.47 ±2859.92</td>
<td>0.58</td>
</tr>
<tr>
<td>Temperature</td>
<td>37.78 ±0.94</td>
<td>37.53 ±0.85</td>
<td>0.21</td>
</tr>
<tr>
<td>ICU duration</td>
<td>12.37 ±5.34</td>
<td>11.02 ±5.61</td>
<td>0.27</td>
</tr>
<tr>
<td>Days without vent.</td>
<td>8.70 ±4.39</td>
<td>8.55 ±5.23</td>
<td>0.89</td>
</tr>
<tr>
<td>IL-1β</td>
<td>1154.94 ±2340.31</td>
<td>2133.36 ±568.08</td>
<td>0.31</td>
</tr>
<tr>
<td>IL-6</td>
<td>296.02 ±137.02</td>
<td>208.54 ±90.61</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Acknowledgments

The present research article was extracted from the “Thesis” conducted as a research project funded by Research Deputy of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Conflict of interest

The authors declare no conflict of interest.

References


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