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Research paper

Effects of omega-3 polyunsaturated fatty acids on psychophysiological symptoms of post-traumatic stress disorder in accident survivors: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: Psychophysiological symptoms (e.g., pounding heart) are known to be a prominent feature of post-traumatic stress disorder (PTSD). Although omega-3 polyunsaturated fatty acids (PUFAs) have a beneficial potential pharmacological effect of preventing these psychophysiological symptoms, no clinical data is yet available. Therefore, we conducted a randomized, double-blind, placebo-controlled trial of Japanese accident survivors.

Methods: A total of 83 participants received either omega-3 PUFAs (1470 mg docosahexaenoic acid and 147 mg eicosapentaenoic acid per day) or placebo within 10 days of the accidental injury. After 12-week supplementation, participants performed script-driven imagery of their traumatic event during monitoring of their heart rate and skin conductance.

Results: Analysis revealed that heart rate during both rest and script-driven imagery was significantly lower in the omega-3 group than the placebo group, whereas baseline heart rate was comparable between the two groups.

Limitations: The present trial was conducted at a single-center in Japan and psychophysiological symptoms of PTSD in most participants were not serious.

Conclusion: These findings suggest that post-trauma supplementation of omega-3 PUFAs might be effective for the secondary prevention of psychophysiological symptoms of PTSD.

1. Introduction

Psychophysiological symptoms were considered a prominent feature of post-traumatic stress disorder (PTSD) (Kardiner, 1941; Mott, 1919) even before its diagnostic criteria was first established in 1980 (American Psychiatric Association, 1980). A recent quantitative meta-analytic review confirmed that people with PTSD clearly displayed increased heart rate (HR) and skin conductance (SC) not only as a response to trauma-related cues but also at baseline, even in the absence of obvious traumatic stimuli (Pole, 2007). However, little is known about the effectiveness of drugs for the secondary prevention of these psychophysiological symptoms. To our knowledge, only one published clinical trial (Pitman et al., 2002) has reported a positive preventive effect on psychophysiological responses of beta-blockers administered immediately after a traumatic event. Obviously, effective agents other than beta-blockers must be explored.

As for possible alternatives, a leading candidate is omega-3 polyunsaturated fatty acids (PUFAs). Docosahexaenoic acid (DHA; 22:6)

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and eicosapentaenoic acid (EPA; 20:5), found in fish oil, and α-linolenic acid (18:3) are omega-3 PUFAs, essential fatty acids. They are involved in wide ranges of vital activities. Several possible mechanisms underlie the prevention of psychophysiological symptoms with omega-3 PUFAs. First, fish oil can facilitate fear-extinction learning by facilitating hippocampal neurogenesis (Beltz et al., 2007; Calderon and Kim, 2004; Kitamura et al., 2009; Matsuoka, 2011). In addition, omega-3 PUFAs maintain endocannabinoid-mediated neuronal functions (Lafourcade et al., 2011; Yamada et al., 2014) that facilitates extinction of fear memories (Marsicano et al., 2002). Such actions against fear memory are similar to those of beta-blockers (Brunet et al., 2008; Pitman et al., 2002). Second, fish oil can reduce sympathetic nerve activity (Ginty and Conklin, 2012; Hamazaki et al., 2005; Matsumura et al., 2012; Spence et al., 2003) that possibly plays a pivotal role in the development of PTSD (Charney et al., 1993). Third, intervention studies have shown effectiveness of fish oil in other psychiatric disorders (Freeman et al., 2006; Lin and Su, 2007). However, no evidence yet exists concerning psychophysiological symptoms.

In the present study, we examined the effectiveness of post-trauma supplementation of omega-3 PUFAs on reducing subsequent psychophysiological symptoms of PTSD in Japanese accident survivors. We adapted a script-driven imagery protocol (Brunet et al., 2008; McNally et al., 2004; Pitman et al., 2002) to measure psychophysiological symptoms in a randomized, double-blind, placebo-controlled trial. We hypothesized that patients who supplemented with omega-3 PUFAs would show reduced psychophysiological responses to trauma-related stimuli and/or decreased resting psychophysiological levels compared to those who supplemented with placebo.

2. Material and methods

2.1. Study design

This study was a single-center, stratified (gender, age, sense of threat), randomized (allocation ratio=1:1), double-blind, placebo-controlled, parallel-group trial. This study was conducted as part of the TPOP (Tachikawa project for prevention of posttraumatic stress disorder with polyunsaturated fatty acid) trial (registered at ClinicalTrials.com as NCT00671099). The full protocol is available as a published paper (Matsuoka et al., 2013).

2.2. Participants

Participants were a total of 83 severely accident–injured survivors who were recruited at the intensive care unit (ICU) of the National Disaster Medical Center, Tokyo, Japan. As part of the TPOP trial, we chose to follow the original guidelines of the TPOP trial. Inclusion criteria were (a) adult (≥18 years of age), (b) native Japanese language ability, (c) within 240 h of injury, and (d) physical and mental ability to understand the scope of the study and consent to trial participation. Exclusion criteria were (a) irretrievable acute brain parenchyma damage and subdural or subarachnoid bleeding, (b) cognitive impairment (mini-mental state examination score < 24), (c) heavy alcohol use or 100 IU/L≤γGTP, (d) heavy tobacco use (> 40 cigarettes per day), (e) history or current diagnostic suspicion of psychosis or bipolar I disorder, (f) diagnostic suspicion of alcohol or substance-related disorder or eating disorder, (g) existence of serious symptoms, such as suicidal ideation, self-harm behavior, and dissociation, (h) use of anti-epilepsy drugs, lithium, ethyl icosapentate, or anti-coagulant drugs at regular intervals within 3 months of injury, (i) regular use of polyunsaturated fatty acids supplements within 3 months of injury, and (j) a habit of eating fish (> 4 times per week). All patients provided written informed consent to participate in this study, which was approved by the appropriate ethics committees of the National Disaster Medical Center, Tokyo, Japan and other institutions.

2.3. Interventions

All participants were instructed to take 300 mg×7 capsules per day for 12 weeks. Daily dose of omega-3 PUFAs capsules contained 1470 mg DHA (22:6) and 147 mg EPA (20:5), whereas that of placebo capsules contained 987 mg rapeseed oil, 525 mg soybean oil, 525 mg olive oil, and 63 mg fish oil. The composition of placebo oil was based on our previous study (Sawazaki et al., 1999).

2.4. Outcomes

We utilized the standardized practice of the script-driven imagery procedure to measure psychophysiological symptoms of PTSD at 3-month follow-up (i.e., end of intervention) as the primary outcome of the present study. In the script preparation procedure at 2-month follow-up, clinical psychologists conducted a 20-min semi-structured interview and summarized each traumatic experience using approximately 160 Japanese characters. Next, another researcher used a loud, slow, and tense voice to record a 30-s long "script." In the script-driven imagery procedure performed at 3-month follow-up, a 3-min adaptation period was followed by a 2-min script-driven imagery period. The script-driven imagery period consisted of four continuous 30-s periods (i.e., rest, read, imagery, and recovery). Participants were asked to sit quietly (rest), listen to the script (read), imagine the scene as realistically as possible (imagery), and relax (recovery). HR and SC were monitored during the entire laboratory session. Beat-by-beat HR was derived from the R-R interval of the lead II electrocardiogram recorded through disposable electrodes connected to a bioamplifier (ECG100C Monte system, Tokyo, Japan). SC was derived from an Ag/AgCl transducer, placed on the index and middle finger of the left hand, and connected to a bioamplifier (GSR100C Monte system, Tokyo, Japan). Mean values of HR and SC during rest and imagery phases were analyzed.

We also obtained self-reported measures to the imagery (displeasure, control, heart pounding, anger, and image vividness) immediately after the recovery period. Each item was rated using a 13-point Likert scale, ranging from 0 (*not at all*) to 12 (*extremely high*).

We measured erythrocyte DHA, EPA, and arachidonic acid composition at baseline and 3-month follow-up. Total lipids were extracted according to Bligh and Dyer (1959). Total phospholipid fractions were separated by thin-layer chromatography. After transmethylation with HCl-methanol, we analyzed fatty acid composition by gas chromatography (GC-2014 Shimadzu Corporation, Kyoto, Japan) equipped with a DB-225 capillary column (length, 30 m; internal diameter, .25 mm; film .25 μm; J & M Scientific, Folsom, CA). The entire system was controlled by gas chromatography software GC-solution version 2.3 (Shimadzu Corporation, Kyoto, Japan). We analyzed baseline data and delta values.

We also assessed PTSD severity using total scores of Clinician-Administered PTSD Scale (CAPS; Asukai et al., 2003; Blake et al., 1995) at 3-month follow-up. Trained psychiatrists (YM and DN), blind to the treatment, conducted structured interviews for this assessment.

All baseline data were measured before beginning supplementation. In particular, baseline HR and blood pressure were measured at ambulance transport or in the emergency room.

2.5. Randomization and blinding

We utilized three stratification factors for block-randomization: sex (male or female), age (< 40 or ≥40 years), and sense of life threat (yes or no). An independent pharmacist prepared sequentially numbered supplement bottles according to a computer-generated list of random numbers prepared by an independent statistician. The pharmacist securely kept the correspondence list blind to both participants and researchers until the trial was closed and all data were fixed. Identical capsules and bottles and the intentional addition of 63 mg fish oil to the