Docosahexaenoic Acid for Selective Prevention of Posttraumatic Stress Disorder Among Severely Injured Patients: A Randomized, Placebo-Controlled Trial

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ABSTRACT

Objective: Docosahexaenoic acid (DHA) might help prevent or attenuate posttraumatic stress disorder (PTSD) symptoms. We examined the efficacy and safety of DHA for preventing PTSD (*DSM-IV*) after severe accidental injury.

Method: From December 2008 to August 2013, we conducted a randomized, double-blind, placebo-controlled trial of 110 accident-injured patients consecutively admitted to an intensive care unit of the National Disaster Medical Center in Tokyo, Japan. All patients were taught about their psychological reactions to accidental injury for 20 minutes and were randomly assigned to receive 1,470 mg/d of DHA plus 147 mg/d of eicosapentaenoic acid (EPA; n = 53) or placebo (n = 57) for 12 weeks. The primary outcome was total score on the Clinician-Administered PTSD Scale (CAPS) at 3-month follow-up. Secondary outcomes included PTSD diagnosis (full-blown or partial PTSD). Adherence to the interventions was assessed by erythrocyte fatty acid composition.

Results: At 3 months, the CAPS total score revealed no differences between the 2 groups (10.78 in the DHA group vs 9.22 in the placebo group; n = 100; $P = .572$). We found that 11.1% of the DHA group and 5.5% of the placebo group developed PTSD. The erythrocyte level of DHA and EPA in the DHA group was significantly elevated compared to the placebo group ($P < .01$).

Conclusions: Docosahexaenoic acid supplementation was not superior to placebo for the secondary prevention of PTSD symptoms at 3 months after severe accidental injury. The efficacy of a different ratio of DHA and EPA and higher doses of omega-3 fatty acids as secondary prevention of PTSD remains to be determined.

Trial Registration: ClinicalTrials.gov Identifier: NCT00671099

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Significant numbers of accident-injured individuals worldwide who are admitted to intensive care units (ICUs) or emergency departments develop posttraumatic stress disorder (PTSD), and comorbidity between PTSD and major depressive disorder is also highly prevalent.[1–4] Approximately 1 in every 4 patients develops full-blown or partial PTSD after accidental injury. Posttraumatic stress disorder is associated with suicide attempts, subsequent other mental disorders, work impairment, and adverse life course.[5] Developing a preventive intervention strategy for PTSD that is easy to use and disseminate is a pressing public health need.

Preclinical approaches to PTSD are examining the mechanism of memory consolidation and how this consolidation process could be interrupted to prevent the development of trauma-related disorder.[6] The hippocampus is crucial for converting short-term memory into long-term memory,[7] and it can process and temporarily store new memory during the transition period before labile memory is transferred to the cortex for permanent storage.[8] In the pathogenesis of PTSD, fear memory becomes excessively consolidated and extinction learning does not progress.[9] Kitamura et al[10] found that the period of hippocampus-dependent fear memory is longer in mice with decreased hippocampal neurogenesis and shorter in mice with active hippocampal neurogenesis. The possibility arises then that the fear memory characteristic of PTSD can be controlled by properly regulating hippocampal neurogenesis.[6]

Omega-3 polyunsaturated fatty acids (PUFAs) are critical for the normal development and function of the mammalian brain. Basic experimental research has revealed that docosahexaenoic acid (DHA, 22:6[n-3]) promotes hippocampal neurogenesis in the adult brain.[11,12] Moreover, He et al[13] have shown that fat-1 transgenic mice, which have enriched levels of DHA in the brain because they can endogenously convert omega-6 to omega-3 PUFAs, exhibited increased hippocampal neurogenesis compared to wild-type mice. Although the specific mechanisms of DHA action on neurogenesis are not yet known, it is plausible that higher consumption of DHA might promote hippocampal neurogenesis. Thus, Matsuoka[6] proposed that promoting adult neurogenesis by omega-3 PUFA supplementation early in the posttrauma period might facilitate the clearance of fear memory from the hippocampus and consequently minimize PTSD symptoms.

A preliminary open study[14] found that PTSD symptoms at the end of the trial were significantly alleviated in injured patients who took DHA compared with historical controls.

Clinical Points

- Developing an easy prevention strategy for posttraumatic stress disorder is a pressing public health need.
- Control of fear memory might become a fundamental strategy for overcoming posttraumatic stress disorder.
- The results of this clinical trial suggest that docosahexaenoic acid has no benefit in the prevention of posttraumatic stress disorder in frequent fish eaters such as the Japanese.

Another single-blind, randomized, parallel-group trial found that DHA was efficacious for attenuating PTSD symptoms in female rescue workers who were deployed during the acute disaster phase of the Great East Japan Earthquake.[15] Therefore, the present study aimed to examine the effectiveness of DHA for preventing PTSD in injured patients admitted to the ICU immediately after accidental injury.

METHOD

Trial Design

This double-blind, parallel-group, randomized controlled trial compares an intervention group receiving DHA supplementation with a parallel control group receiving placebo supplementation. This study was registered at ClinicalTrials.gov (NCT00671099). The full protocol[16] can be accessed at http://www.biomedcentral.com/1471-244X/13/8.

Participants

Participants were recruited solely from the ICU of the National Disaster Medical Center, Tokyo, Japan. The 110 injured patients were randomized to either the DHA group or the placebo group (1:1). The inclusion criteria applied to patients with accidental injury were as follows: (1) aged 18 years or older, (2) a native Japanese speaker, (3) contact with us within 240 hours after injury, and (4) physical and psychological ability to understand the scope of the present trial and to provide written consent for study participation. Exclusion criteria were the presence of the following: (1) acute brain parenchymal damage that is obviously irreparable, or subdural or subarachnoidal bleeding; (2) a score of < 24 on the Mini-Mental State Examination[17]; (3) a serious drinking problem; (4) a smoking habit of ≥ 40 cigarettes per day; (5) history and current suspicion of psychosis or bipolar I disorder; (6) suspicion of alcohol- or substance-related disorder or eating disorder; (7) a serious psychiatric condition such as suicidal ideation, self-harm behavior, or severe dissociation; (8) regular treatment with antiepilepsy medication, lithium, ethyl icosapentate, aspirin, or warfarin within the last 3 months; (9) regular preaccident consumption of PUFA supplements within the last 3 months; and (10) a habit of eating fish ≥ 4 times per week.

Procedure and Baseline Assessment

The ethics committee of the National Disaster Medical Center approved the study protocol on February 7, 2008. Eligible patients were screened through the daily conference records for patients newly admitted to the ICU. After a complete description of the study, participants provided written informed consent to take part in this study. We started participant recruitment on December 16, 2008, and ended on June 6, 2013. Follow-up assessment was completed on August 29, 2013.

Participants filled out the Peritraumatic Distress Inventory,[18,19] Connor-Davidson Resilience Scale (CD-RISC),[20] and Food Frequency Questionnaire[21,22] at baseline. Blood samples were obtained in the emergency room. All data were stored at the institution's data management section.

Interventions

Active treatment involved dietary supplementation with 300 mg of blackish-brown gelatin capsules containing concentrated marine fish oil. The daily dose of 7 capsules provided 1,470 mg of DHA, 147 mg of eicosapentaenoic acid (EPA, 20:5[n-3]), and 0.3% of α-tocopherol. We based the daily dose of approximately 1,600 mg of omega-3 PUFAs on our previous trial of university students who were under stress.[23] The content of the control oil was slightly modified from our previous study.[24] The present control oil was a mixture of rapeseed oil (47%), soybean oil (25%), olive oil (25%), fish oil (3%), and 0.3% α-tocopherol. The fatty acid composition of this mixture was similar to the average composition of fatty acid intake in Japan. We added a small amount of not fully deodorized fish oil to the base of the control oil to give it a fishy odor and make it indistinguishable from the active oil. Safety issues were monitored at least twice a week during hospitalization and once a week after discharge. Adherence to the study medication was monitored by bottle check and self-report as well as by erythrocyte fatty acid quantification.

Measures

The primary outcome measure was the total score on the Clinician-Administered PTSD Scale (CAPS)[25,26] at 3-month follow-up. Trained psychiatrists (Y.M. and D.N.), blinded to treatment assignment, conducted structured interviews to evaluate PTSD and other psychiatric morbidity at months 1 and 3. A diagnosis of full-blown PTSD required *DSM-IV* diagnostic criteria A (traumatic event) through F (impairment).[27] Participants were deemed to have partial PTSD if they fulfilled 2 of 3 symptom criteria (B [reexperiencing], C [avoidance], or D [hyperarousal]) and also at least 1 of the criteria A-1 (stressor), E (duration), or F (impairment). Interrater reliability of PTSD diagnosis was reported previously.[28]

We used several secondary measures. The Impact of Event Scale–Revised (IES-R)[29] provided an additional measure of PTSD severity. The Mini-International Neuropsychiatric Interview[30,31] was used to assess major depressive disorder. The Montgomery-Asberg Depression Rating Scale (MADRS)[32,33] provided a measure of depression severity. The Hospital Anxiety and Depression Scale (HADS)[34,35] was

used to measure severity of general distress. The CD-RISC[20] was used to measure resilience.

At baseline (ie, the time point before ICU admission) and 3-month follow-up (end of intervention), erythrocyte fatty acid composition was quantified. The detailed laboratory procedure was described elsewhere.[16] Eicosapentaenoic acid, DHA, and arachidonic acid (ARA) were used to index pretreatment to posttreatment fatty acid composition of the erythrocyte membrane as an objective measure of treatment adherence.

Sample Size

For sample size estimation, at least 49 cases per group were required given that the expected difference in CAPS score between the groups at 3 months was set at 10 (SD = 15) with an α level of .05 (2-tailed) and 90% power. The desired total number of participants was set at 140, with 70 cases per group based on our estimate that around 30% of the participants would discontinue or drop out of the study before it began. We stopped accumulating participants before the desired number was achieved due to a 10% dropout rate based on study monitoring reports of the blinded groups and because this trial became too difficult to continue for financial reasons and diminished numbers of injured patients admitted.

Randomization and Blinding

An independent statistician generated randomization lists with 3 stratification factors using a computer-generated random allocation sequence by block-randomization method. Stratification factors included sex (male or female), age (< 40 or ≥ 40 years), and sense of life threat (yes or no). The randomization list was sent to an independent pharmacist who securely kept the tables and prepared numbered supplement bottles according to the list. Both the research team and the participants were blinded to the randomization until the last participant completed the protocol and the spreadsheets of all results were finalized. Stratification by sex, age, and sense of life threat were justified in previous studies: prevalence of PTSD and major depressive disorder were higher in women than in men,[36,37] and our previous cohort study of survivors of motor vehicle accidents showed that sense of life threat was a strong predictor of subsequent PTSD.[4] Moreover, according to the National Health and Nutrition Survey on food group consumption by age group, the amount of meat products consumed, such as pork and beef, is higher for both sexes before age 40, but after age 40, seafood consumption increases.[38] Also, the omega-3 fatty acid content in red blood cells increases with age in the Japanese population.[39]

All members of the research team, including all authors, physicians, nurses, research assistants, and study participants, remained blinded to the actual intervention assignments until data collection was completed and confirmed and erythrocyte fatty acids were analyzed. An allocation Excel sheet file was blinded and securely kept under passcode protection by an independent pharmacist.

Statistical Analysis

All analyses were performed on an intent-to-treat basis using data from all randomized participants. Statistical tests were performed by 2-tailed tests and an α level of .05. We calculated proportions and 95% confidence intervals (CIs) for binary data and the median (minimum-maximum range) and mean (SD) for continuous grouped data. We calculated mean differences and 95% CIs for the primary and secondary outcomes of continuous data using analysis of covariance and regression models for adjustment. We calculated risk ratios and their 95% CIs for secondary outcomes of binary data using regression models for risk adjustment.[40] Randomized stratified factors and strong prognosis factors in previous reports were entered as covariates in the model-based analysis. To complement the primary analyses, we analyzed additional evaluations of secondary endpoints and subgroups. Because the analysis was exploratory, multiplicity was not controlled. All statistical analyses were performed using JMP software version 10.0 (SAS Institute Inc, Cary, North Carolina) and SAS software version 9.2 (SAS Institute).

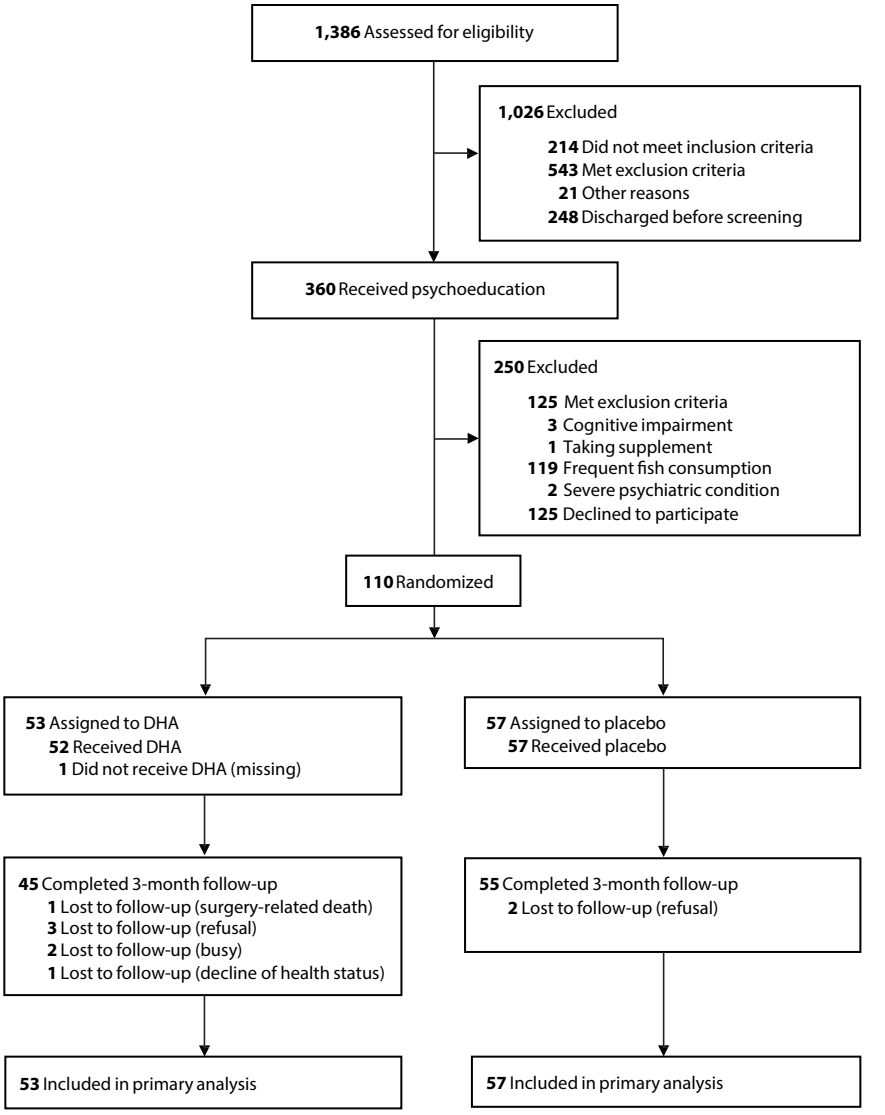
We reported the factors affecting dropouts from this study in a prior report.[41] Therefore, we determined that sex, IES-R score, injury severity score, subjective loss of consciousness, education, and interventions were potential prognostic factors for dropout, and we assumed data were missing at random according to the Rubin missing data mechanism.[42] For sensitivity analysis under the missing-at-random assumption, we performed multiple imputations with those factors to impute outcomes after the motor vehicle accident for participants who dropped out. Multiple imputation for missing data was performed using PROC MI and MIANALYZE in SAS software version 9.1.3 (SAS Institute).

RESULTS

Details of the method have been published elsewhere.[16] Briefly, 1,386 patients with high-energy accidental injury were assessed for first-step eligibility screening. Among them, 360 injured patients were taught about their psychological reactions to accidental injury for 20 minutes; of these, 110 met the inclusion criteria and consented to participate (Figure 1). One hundred five participants (95%) were retained at the 1-month follow-up, and 100 (91%) were retained at the 3-month follow-up (Figure 1).

Baseline demographic, medical, psychosocial, and nutritional data are presented in Table 1. No significant differences were seen between the 2 groups. The 110 injured patients were randomly assigned to an intervention group to receive either DHA (n = 53) or placebo (n = 57) capsules. Treatment began a mean 3.4 days (SD = 2.1 days) after accidental injury. Ten participants (9%) dropped out of the study before the end of the treatment period. No clear between-group differences existed for these variables. Most participants (98%) had no past history of psychiatric illness before their accidental injury.

Figure 1. Flowchart of Enrollment and Intervention in a Randomized Controlled Trial of Docosahexaenoic Acid (DHA)[a] in Patients With Severe Accidental Injury



[a]Participants received 1,470 mg/d of docosahexaenoic acid and 147 mg/d of eicosapentaenoic acid or placebo capsules daily.

Primary and Secondary Outcome Measures

Table 2 summarizes the effect of DHA on outcome measures at 3 months. No difference existed between the 2 groups in the total CAPS score (10.78 [SD = 16.71] in the DHA group vs 9.22 [SD = 10.57] in the placebo group, mean difference = 1.56; 95% CI, −3.90 to 7.01; $P = .572$). Imputed and per-protocol data sets continued to show no difference between the groups. Also, no differences existed between the groups in the incidence proportion of full-blown PTSD and that of partial PTSD. No difference existed between the groups in mean total scores on the IES-R, MADRS, HADS, and CD-RISC at 3 months (Table 2). Also, no difference existed between the groups in the diagnosis of major depressive disorder (Table 2). Subgroup analyses stratified by sense of life threat and sex revealed no differences between the 2 groups. However, subgroup analysis for age < 40 years showed that the CAPS total score in the DHA group was higher than that in the placebo group at 3 months (Table 3).

Treatment Adherence and Adverse Events

The proportion of adherence with supplementation based on self-report and bottle check was 88.7% (n = 47) in the DHA group and 93.0% (n = 53) in the placebo group ($P = .517$). There was no difference in days of supplementation between the 2 groups (77.3 [SD = 2.43] vs 80.2 [2.34]; $P = .40$).

Table 4 shows mean changes in erythrocyte PUFAs from baseline to 3 months in the 2 groups. There were significant increases in EPA and DHA in the DHA group and a significant decrease in ARA in the DHA group compared with the placebo group. One participant in the placebo group

Table 1. Baseline Characteristics of Participants

Characteristic	DHA (n = 53)	Placebo (n = 57)	*P* Value
Age, mean (SD), y	38.1 (13.5)	40.9 (17.3)	.34
Sex, n (%)			
Male	44 (83)	46 (81)	.75
Female	9 (17)	11 (19)	
Type of injury, n (%)			
Traffic accident	40 (75.5)	43 (75.4)	.99
Falling from a high place	9 (17.0)	10 (17.5)	
Workplace accident and other	4 (7.5)	4 (7.0)	
Glasgow Coma Scale, mean (SD)	14.6 (1.2)	14.8 (0.5)	.22
Injury Severity Scale, mean (SD)	9.6 (6.4)	9.0 (4.8)	.59
Heart rate, mean (SD), beats per minute	81.2 (15.3)	83.6 (15.6)	.42
Blood pressure, mean (SD), mm Hg			
Systolic	141.9 (24.0)	144.0 (18.4)	.61
Diastolic	86.3 (15.6)	84.1 (15.3)	.46
Body mass index, mean (SD)	22.9 (3.7)	23.4 (4.4)	.53
Sense of life threat, n (%)	11 (20.8)	14 (24.6)	.63
Mild traumatic brain injury, n (%)	28 (52.8)	20 (35.1)	.06
Current tobacco use, n (%)	21 (39.6)	15 (26.3)	.14
Alcohol consumption, n (%)			
≤Weekly	33 (62.3)	31 (54.4)	.18
1–6 Drinks per week	9 (17.0)	18 (31.6)	
Daily	11 (20.8)	8 (14.0)	
Marital status, n (%)			
Married or partnered	23 (43.4)	26 (45.6)	.88
Never married	26 (49.1)	28 (49.1)	
Divorced or widowed	4 (7.5)	3 (5.3)	
Education, mean (SD), y	13.1 (1.98)	12.4 (2.39)	.10
Employment status, n (%)			
Employed	41 (77.4)	41 (71.9)	.66
Student	6 (11.3)	7 (12.3)	
Homemaker	2 (3.8)	1 (1.8)	
Retired or unemployed	4 (7.5)	8 (14.0)	
Past history of psychiatric illness, n (%)	1 (1.9)	1 (1.8)	.96
Family history of psychopathology, n (%)	11 (21.2)[a]	5 (8.8)[b]	.11
Peritraumatic Distress Inventory, mean (SD)	13.7 (10.3)	13.7 (8.4)	.99
Food Frequency Questionnaire, mean (SD)			
Energy, kcal/d	2,249.8 (646.1)	2,346.1 (859.3)	.51
Carbohydrate, g/d	289.7 (89.4)	313.6 (120.9)	.24
Protein, g/d	74.1 (28.0)	77.4 (34.1)	.59
Lipid, g/d	71.5 (33.9)	72.9 (37.9)	.84
Omega-3 PUFAs, g/d	2.3 (1.1)	2.5 (1.3)	.45
Omega-6 PUFAs, g/d	11.5 (5.5)	12.3 (5.9)	.50

[a]n = 52. [b]n = 57.
Abbreviations: DHA = docosahexaenoic acid, PUFAs = polyunsaturated fatty acids.

was prescribed hypnotics and an antidepressant for insomnia after randomization. Almost one-third of participants complained of adverse events, with loose stool (10%) and constipation (3.6%) occurring frequently, but there were no significant differences between the 2 groups (32.0% in the DHA group vs 32.2% in the placebo group).

DISCUSSION

To our knowledge, this is the first randomized, placebo-controlled trial of traumatized patients at high risk of PTSD to test the preventive efficacy of DHA. Although DHA was well tolerated, it did not demonstrate an advantage over a placebo for secondary prevention of PTSD. The 2 groups also did not differ significantly on measures of symptoms of depression and resilience. This finding is inconsistent with our open-label pilot trial of injured patients in which DHA supplements reduced the development of PTSD symptoms.[14] Although another single-blind, randomized trial of disaster rescue workers also failed to find beneficial effects of DHA, it is suggested that DHA supplementation is associated with reduced PTSD symptoms, particularly in women.[15] Unfortunately, no other clinical trials have examined the effect of DHA on PTSD, so we cannot determine whether DHA has beneficial effects or not. Also, the generalizability of these negative findings to another country is uncertain.

The findings revealed that our original hypothesis was rejected. We presume that the negative findings were due to the use of DHA. A recent meta-analysis of depression found that EPA at ratios ≥ 60% of total EPA + DHA was effective against primary depression.[43–45] Sublette et al[45] suggested that supplements containing around 2,000 mg/d of EPA in excess of DHA were effective for depression. In addition, EPA rather than DHA has been used in prevention trials of several psychiatric disorders, including interferon-α–induced depression (3,500 mg/d of EPA)[46] and psychosis (700 mg/d of EPA and 480 mg/d of DHA).[47] The correct ratio and adequate dosage of omega-3 PUFAs in the prevention of PTSD remain unknown.

In our previous prospective cohort study, baseline serum levels of ARA and EPA immediately after the accident were inversely related to the risk of developing PTSD at 6 months after accidental injury, but we observed no significant association between DHA and PTSD.[48] Maekawa and colleagues[49] found that ARA supplementation to rat pups through mother's breast milk via an ARA-rich diet given to the mother rats promoted the proliferation of postnatal neural stem/progenitor cells in the hippocampus. On the other hand, oral administration of DHA promoted adult neurogenesis in the hippocampus of rats that were fed a fish oil–deficient diet over 3 generations.[12] It was also reported that feeding an omega-3 PUFA-rich diet to aged rats increased immature hippocampal neurons.[50] These results suggest that DHA is necessary but not sufficient for regulating postnatal neural stem/progenitor cells under physiological conditions but that ARA is sufficient to affect postnatal neural stem/progenitor cells even under physiological conditions.[51] Taken together, these results suggest that for patients with extremely low DHA levels, DHA might have a beneficial effect on preventing PTSD through hippocampal neurogenesis.

In the present study, around 7% of injured patients developed PTSD after accidental injury. The incidence proportion was consistent with previous observational studies in Japan.[4,52,53] The severity of PTSD in injured patients was generally lower than in those who were physically assaulted. Small effects might not be detected

Table 2. Effects of Intervention on Outcome Measures at 3 Months

Measure	DHA (n = 53)	Placebo (n = 57)	Effect(s)	95% CI	*P* Value
Primary outcome					
CAPS total score, mean (SD)	10.78 (16.71)[a]	9.22 (10.57)[b]	1.56 (MD)	−3.90 to 7.01	.572
Imputed			1.37	−3.65 to 6.39	.589
Per-protocol: compliance, mean (SD)	10.41 (16.72)[c]	8.89 (10.36)[d]	1.52	−3.99 to 7.03	.585
Secondary outcome					
Full-blown PTSD, n (%)	2 (4.4)[a]	1 (1.8)[b]	2.44 (RR)	0.23 to 26.10	.459
Imputed			2.15	0.20 to 23.04	.527
Per-protocol: compliance			2.25	0.21 to 24.08	.501
Full-blown and partial PTSD, n (%)	5 (11.1)[a]	3 (5.5)[b]	2.04 (RR)	0.52 to 8.07	.311
Imputed			1.79	0.45 to 7.14	.408
Per-protocol: compliance			2.01	0.51 to 7.94	.320
IES-R total score, mean (SD)	10.78 (13.59)[e]	8.98 (10.69)[f]	1.8 (MD)	−2.89 to 6.48	.449
MDD diagnosis, n (%)	2 (4.44)[a]	4 (7.27)[b]	0.73 (RR)	0.23 to 2.31	.688
MADRS total score, mean (SD)	4.78 (10.93)[e]	2.96 (6.44)[f]	1.81 (MD)	−1.67 to 5.30	.305
HADS total score, mean (SD)	6.90 (8.35)[e]	5.21 (5.36)[f]	1.69 (MD)	−0.99 to 4.36	.214
CD-RISC total score, mean (SD)	58.3 (18.45)[a]	61.4 (15.31)[g]	−3.16 (MD)	−9.89 to 3.39	.344

[a]n = 45. [b]n = 55. [c]n = 44. [d]n = 53. [e]n = 50. [f]n = 56. [g]n = 54.
Abbreviations: CAPS = Clinician-Administered PTSD Scale, CD-RISC = Connor-Davidson Resilience Scale, DHA = docosahexaenoic acid, HADS = Hospital Anxiety and Depression Scale, IES-R = Impact of Event Scale-Revised, MADRS = Montgomery-Asberg Depression Rating Scale, MD = mean difference, MDD = major depressive disorder, PTSD = posttraumatic stress disorder, RR = risk ratio.

Table 3. Effects of Intervention on PTSD and Depressive Symptoms at 3 Months and Subgroup Analyses

	DHA	Placebo	Mean Difference	95% CI	*P* Value
Sense of life threat					
Threat (+)					
CAPS total score, mean (SD)	8.53 (12.05)[a]	8.07 (8.49)[b]	6.86	−12.48 to 26.19	.468
Imputed			6.00	−11.06 to 29.05	.475
Threat (–)					
CAPS total score, mean (SD)	19.78 (28.05)[c]	12.92 (15.39)[d]	0.46	−4.20 to 5.11	.846
Imputed			0.40	−3.89 to 4.68	.855
Sex					
Male					
CAPS total score, mean (SD)	9.70 (16.05)[e]	8.05 (10.78)[f]	1.65	−4.31 to 7.63	.582
Imputed			1.11	−4.28 to 6.49	.685
Female					
CAPS total score, mean (SD)	13.91 (8.56)[g]	15.75 (19.91)[h]	1.84	−12.24 to 15.92	.786
Imputed			3.46	−10.07 to 17.00	.597
Age					
Less than 40 y					
CAPS total score, mean (SD)	12.68 (14.58)[i]	5.71 (5.09)[j]	6.97	1.03 to 12.91	.0225
Imputed			5.37	0.12 to 10.63	.0453
40 y or more					
CAPS total score, mean (SD)	8.96 (18.67)[k]	12.85 (13.35)[l]	−3.89	−13.03 to 5.24	.395
Imputed			−2.89	−11.81 to 6.04	.519

[a]n = 9. [b]n = 13. [c]n = 36. [d]n = 42. [e]n = 37. [f]n = 44. [g]n = 8. [h]n = 11. [i]n = 22. [j]n = 28. [k]n = 23. [l]n = 27.
Abbreviations: CAPS = Clinician-Administered PTSD Scale, DHA = docosahexaenoic acid, PTSD = posttraumatic stress disorder.
Symbols: + = yes, – = no.

by our modest sample size. An earlier larger epidemiologic study found that traumas most commonly associated with PTSD were combat exposure and witnessing among men and rape and sexual molestation among women.[54] Had our trial been conducted with people traumatized by physical assault, our results might have been different. Although we failed to find benefits of DHA over placebo for PTSD prevention in accident-injured patients, further study would be meaningful.

The strengths of this study included the study design, use of reliable and standardized assessments, the application of an objective measure of treatment adherence, and a low attrition rate (9%). However, several caveats should be noted. First, because no other studies have examined the effect of DHA on PTSD, we estimated sample size with reference to previous data on omega-3 PUFAs for treating depression. Second, the results were obtained from only 1 teaching hospital in Tokyo. Third, because seafood consumption is prevalent in Japan, we excluded subjects who reported eating fish 4 times or more per week. However, the baseline erythrocyte omega-3 PUFA composition (about 7.6%) in the participants of the present study was still higher than

Table 4. Erythrocyte Fatty Acid Levels as a Percentage of Total Fatty Acids

Level	DHA (n = 53), % (SD)	Placebo (n = 57), % (SD)	Mean Difference	95% CI	*P* Value
Baseline					
Arachidonic acid	12.33 (1.051)	11.94 (1.157)			
Eicosapentaenoic acid	1.23 (0.590)	1.29 (0.585)			
Docosahexaenoic acid	6.40 (1.281)	6.29 (1.271)			
3 Months					
Arachidonic acid	10.90 (0.838)	11.58 (1.158)	−0.681	−1.095 to −0.268	.0015
Eicosapentaenoic acid	1.640 (0.641)	1.324 (0.492)	0.316	0.087 to 0.545	.0073
Docosahexaenoic acid	8.940 (1.130)	6.681 (0.942)	2.259	1.841 to 2.677	< .0001
Change between baseline and 3 months					
Arachidonic acid	−1.334 (0.848)	−0.343 (0.567)	−0.991	−1.278 to −0.703	< .0001
Eicosapentaenoic acid	0.381 (0.525)	0.056 (0.281)	0.325	0.159 to 0.492	.0002
Docosahexaenoic acid	2.521 (1.505)	0.438 (0.746)	2.083	1.614 to 2.552	< .0001

Abbreviations: DHA = docosahexaenoic acid.

that in people in Western countries. Thus, a ceiling effect might mask the results. Despite these limitations, this randomized, double-blind, placebo-controlled trial found no evidence for the superiority of DHA supplementation over placebo for the selective prevention of PTSD in patients with accidental injury. Related analyses of our patient sample are in progress to examine factors such as levels of serum brain-derived neurotrophic factor, neuropeptide Y, resolvins, and protectins as potential moderators of treatment response. Further studies are needed to determine the ratio and dosage of EPA and DHA and the indications for other traumatized and non-Japanese populations.

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Drug names: lithium (Lithobid and others), warfarin (Coumadin, Jantoven, and others).

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