ORIGINAL ARTICLE

Role of omega-3 fatty acids in the prevention of delirium in mechanically ventilated patients

Taraneh Naghibi[1], Navid Shafigh[1], Saideh Mazloomzadeh[2]

[1]Department of Anesthesiology and Critical Care Medicine, School of Medicine, Mosavi Educational Hospital, Zanjan University of Medical Sciences, Zanjan, Iran, [2]Department of Epidemiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

Background: Inflammation is an important mechanism in the pathogenesis of delirium. Since delirium might reduce by anti-inflammatory effects of omega-3 fatty acids. Based on this respect, a study was conducted to indicate the effect of omega-3 fatty acids in the prevention of delirium in mechanically ventilated patients. **Materials and Methods:** This study is a randomized, double-blind, placebo-controlled clinical trial. One hundred and sixty-eight mechanically ventilated patients were selected in the investigation. Patients were randomly allocated to receive either 2 g of omega-3 syrup or placebo once a day. Twice daily delirium was assessed due to Confusion Assessment Method and the Richmond Agitation-Sedation Scale. The number of days with delirium during the first 10 days of admission was the primary outcome. Secondary outcomes had been included duration of mechanical ventilation, length of intensive care unit (ICU) stay, and mortality. **Results:** Patient-days with delirium ($P = 0.032$), the number of ICU stay ($P = 0.02$), and mechanical ventilation ($P = 0.042$) days in omega-3 group significantly were lower than control group. Mortality was not significantly different between two groups. **Conclusion:** Omega-3 fatty acids can reduce the risk of delirium in mechanically ventilated patients.

Key words: Delirium, inflammation, intensive care unit, mechanical ventilation, omega-3 fatty acids

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INTRODUCTION

One of serious and common disorders in the intensive care unit (ICU) is delirium. It is defined as an acute deterioration in mental status includes inattention, thought disorder, and loss of consciousness.[1] Every year, 20 million patients require mechanical ventilation.[2] Delirium occurs in 60%–80% of patients who are under mechanical ventilation.[3] It is concomitant with dangerous complications in this patient population. These complications include increased of ICU and hospital stay days, hospital costs, length of mechanical ventilation, and mortality.[4-7] Delirium decrease brain processing speed and cognition.[8] Pathophysiology and mechanisms of delirium are not well known.[9] A number of studies have shown correlation between inflammation and delirium.[10-12] Therefore, a drug that could reduce inflammation has been looking for to prevent delirium.[13]

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Several previous investigations have been shown in various diseases, the anti-inflammatory influence of omega-3. Various evidence has proven that omega-3 fatty acids (ω-3 FA) can influence on cytokine production, reduce inflammation markers, modify immunological, and inflammatory response.[14,15] Omega-3 effect on brain disorders has been investigated previously.[16,17] To determine the efficacy of omega-3 fatty acids in the prevention of delirium in patients who are under mechanical ventilation, a well-designed clinical trial was required. In this respect, a comparative clinical trial was intended to investigate the effect of omega-3 in the prevention of delirium in this patient population.

MATERIALS AND METHODS

Study design

This study is a randomized, double-blind, placebo-controlled clinical trial. After approval

Address for correspondence: Dr. Taraneh Naghibi, Department of Anesthesiology and Critical Care Medicine, School of Medicine, Mosavi Educational Hospital, Zanjan University of Medical Sciences, Zanjan, Iran. E-mail: tnaghibi@zums.ac.ir

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by the ethics committee (approval number: ZUMS. REC.1394.165) and registry with the Iranian Registry of Clinical Trials (IRCT2015095536N5), 168 patients were enrolled in this study. The research was conducted in a 21-bed of the ICU in a tertiary healthcare teaching hospital, in Zanjan University of Medical Sciences between December 2015 and October 2016. Valid informed written consent was obtained from the patient's relatives.

Patient population

Sample size was calculated 82 per group based on $P1 = 0.20$ (proportion with delirium in the intervention group), $P2 = 0.40$ (proportion with delirium in the placebo group), $\alpha = 0.05$, $\beta = 0.20$ using the formula of comparing two proportions.

Sample was taken from all surgical patients who were on mechanical ventilation. Other inclusion criteria were as follows: patients who were older than 18 years, acute physiology and chronic health (APACHE) II score under 25, Glasgow Coma Scale (GCS) higher than 9, no history of Dementia, Parkinson's and Alzheimer's disease or other Brain diseases, no allergy to ω-3 or sea foods, no history of sedative medications use, no pregnancy, and no evidence of head injury.

Patients were excluded from the analysis for the following reasons: delirium screening could not be performed; patients died before 48 h after admittance; and patients who were extubated before 72 h after admittance. Moreover, those who have electrolyte imbalance.

For screening, delirium confusion-assessment method-ICU (CAM-ICU) was used. Based on the previews studies, CAM-ICU had sensitivities of 93%–100% and specificities of 98%–100%.[18]

Randomization and blinding

This study was double-blind, in which both the clinician (investigator) and the patient were blinded to the intervention allocated.

Patients who had the inclusion criteria, were randomly divided (1:1) to drug or placebo group. According to the study statistician randomization code list, the ventilated patients were selected to one of the investigation groups. A computer program (random number generator V 1.4) to permute block design generated was used to permute block design generated.

Patients in the drug group received 2 g of omega-3 fatty acids syrup (VITABIOTICS-England) once a day at 6 a.m. and in the other group, the placebo was gavaged once a day at 6 am. Patients received 2 g of omega-3 fatty acids syrup as this dosage had been shown to be safe and effective in previous studies. Placebo syrup was prepared by pharmaceutics group of Zanjan University of Medical Sciences with methylcellulose. Its shape, color, and packaging were quite similar to omega-3 syrup and without any effective substances.

Clinical assessments

At the time of admission, patient's demographic data included age and sex, as well as APACHE score II has been recorded.

In this study, the Richmond Agitation-Sedation Scale (RASS)[19] and the CAM-ICU[20] were assessed twice daily at 8:00 a.m. and p.m. by the resident of anesthesiology who was not aware of the group of patients. Delirium was defined as positive results for CAM-ICU when RASS scores were between −2 and +4. Interruption of sedation drugs made daily at 06:00 a.m. and p.m. In The first step RASS score was evaluated for patients' consciousness. If patient's RASS score was from −2 to +4 the CAM-ICU was assessed for the diagnosis of delirium. If RASS score was <−2, all sedative agents were avoided for 2 h and patients were evaluated once more. For 10 days from the 1st day of admission in the ICU, patients were followed up.

Treatment with the study drug was initiated at the 1st day of intubation and they were discontinued according to the following conditions:

After a maximum of 10 days' treatment, when patients were discharged from the ICU, or death.

If delirium was detected by the CAM_ICU, Haloperidol was used to manage episodes of agitation (RASS +2 and above) according to the following protocol:

Patients received 2.5–5 mg Haloperidol (EXIR-IRAN) intravenously according to age and weight. After 30 min of drug administration, if patient was still agitated, drug administration was repeated.

Outcome

Primary outcomes had been included the number of days without delirium during the first 10 days of admission.

Secondary outcomes had been included mortality during admission, number of days in which the patient was separated from the ventilator, and number of ICU admittance days.

Statistical analysis

To evaluate the distribution of quantitative variables, the Kolmogorov–Smirnov test was used. The Mann–Whitney

test for nonnormally distributed and independent *t*-test for normally distributed were performed. The Chi-square test was used for categorical variables. Values were shown as mean ± standard deviation, number (percentage), and median (Inter Quantile Range), where appropriate. The SPSS PC version 16.0 computer software program for Windows (SPSS, Chicago, IL, USA) was performed for analyzing. $P < 0.05$ has been defined as statistically significant.

RESULTS

Patient characteristics

In recent study, 168 ICU patients were enrolled. One patient was not included due to his brain tumor history. Two patients were excluded due to extubation <72 h of their admission. One patient was excluded due to death <48 h of his admission. Of the 164 patients, 82 received omega-3 fatty acids and 82 received placebo [Figure 1].

As shown in Table 1, patient characteristics were comparable in age, sex, and APACHE II score, RASS score, delirium on admission, and the type of reason admission ($P > 0.05$) [Table 1].

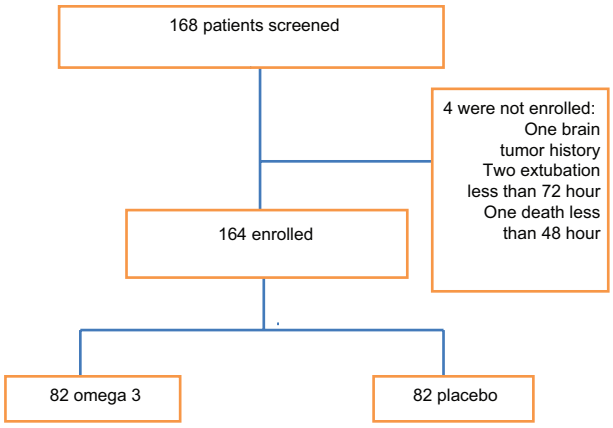

Figure 1: Flowchart of patients in the study

Table 1: Baseline characteristics of patients

	Omega-3 fatty acids group (*n*=82)	Placebo group (*n*=82)	*P*
Age[a]	47.15±12.62	45.57±14.53	0.147
Male gender[b], *n* (%)	42 (51.2)	40 (48.7)	0.211
APACHE II[a]	23.77±0.77	24.76±0.74	0.615
Type of admission[b], *n* (%)	-	-	0.31
Surgical elective	39 (47.5)	42 (51.2)	-
Surgical urgent	34 (41.4)	29 (35.3)	-
Medical	9 (10.9)	11 (13.4)	-

[a]Independent sample *t*-test was used for statistical analysis; [b]Chi-square test was used for statistical analysis. There was no statistically significant difference between groups ($P>0.05$). Data are shown as mean±SD or *n* (%).APACHE II=Acute physiology and chronic health; SD=Standard deviation

Outcome

Patient-days with delirium, the mechanical ventilation, and the length of ICU stay days in omega-3 group were lower than control group significantly. There were not significantly different in mortality in the ICU and the dose of Haloperidol for individual patients (mg/day) between groups [Table 2].

DISCUSSION

Based on our findings, this is the first study to examine the effect of omega-3 in the prevention of delirium in ventilated patients. The results of recent research showed that omega-3 is effective in reducing the delirium days in patients whom admitted to the ICU. Significant literature has considered the association between brain disorders and inflammatory elements in patients under mechanical ventilation.[10,21-23] Inflammation effect on the blood-brain barrier by change the microcirculation and neurotransmitter balance.[22] In this regard, various studies have shown the effect of inflammatory factors on the development of delirium.[24,25] In the critically ill patients, the unusual variations of lipid metabolism have in been noted, and many studies have shown that there is an association between nutritional intervention, lipid profile, and survival.[26] In recent years, enteral and parenteral omega-3 administrations have been considered to improve the immune response in critically patients. Eicosapentaenoic acid, docosapentaenoic acid , and docosahexaenoic acid are omega-3 polyunsaturated fatty acids (PUFAs). Fatty acid oxygenases, including cyclooxygenases, lipoxygenases, and cytochrome P450 monooxygenases, produce bioactive lipid mediators from PUFAs. These mediators have shown anti-inflammatory effects.[27] Martin and Stapleton have shown the role of omega-3 fatty acids compounds in reducing inflammatory factors in critically ill patients. Their research has proven the omega-3 fatty acids effect on cytokines, as well as eicosanoids, and hence, it can be helpful in this group of patients to reduce inflammation.[28] Reduction of the delirium days in the current study could be explained by these anti-inflammatory effects of omega-3 fatty acids.

Burkhart *et al*. showed that inflammation factors, brain injury markers, and incidence of delirium could not be effected by n-3 fatty acids in critically ill septic patients. They investigated the properties of n-3 fatty acids on sepsis-associated delirium markers.[29] Their population study was septic patients who were at risk of hyper inflammatory reactions and changes of lipid profile. These reasons could be explained the difference between the results of two studies.

In the recent study, other clinical outcomes, such as length of ICU stay and mechanical ventilation days were different

Table 2: Outcome of the included patients

Outcome	Omega-3 fatty acids group (*n*=82)	Placebo group (*n*=82)	*P*
Patient-days with delirium[a]	2.71±2.01	4.72±2.19	0.032*
Duration of mechanical ventilation, days[a]	8.89±5.29	12.13±6.62	0.042*
Length of ICU stay, days[a]	12.94±5.09	15.87±6.05	0.02*
ICU mortality[b], *n* (%)	3 (3.7)	9 (11)	0.17
Haloperidol for individual patients (mg/day)[c]	5 (0-10)	7.5 (2.5-15)	0.21

*Statistically significant difference between groups ($P<0.05$); [a]Independent sample *t*-test was used for statistical analysis; [b]Chi-squre test was used for statistical analysis; [c]Mann-Whitney test was used for statistical analysis. Data are shown as mean±SD, *n* (%) or median (IQR). ICU=Intensive care unit; IQR=Interquartile range; SD=Standard deviation

significantly. Reduce in mortality rate was observed, but it was not statistically significant between two groups. The effect of omega-3 fatty acids on outcomes in critically ill patients have been shown by several clinical trials. Lu *et al*. have reported that in sepsis patients omega-3 fatty acids may reduce mechanical ventilation and length of ICU stay days, but this supplementation could not significantly reduce the mortality.[30] The results of their study were consistent with recent investigation.

In a systematic review and meta-analysis, Manzanares *et al*. have shown that intravenous fish oil lipid emulsions could reduce the duration of mechanical ventilation and hospital stay in critically ill patients.[31] These results are consistent with the present study, although the population of two studies was different.

Grau-Carmona *et al*. showed that n-3 PUFAs in surgical and medical critically ill patients is safe and well tolerated. Their investigation proven that risk of nosocomial infections could be reduced by n-3 PUFAs administration, but they could not detect differences between hospital and ICU mortality in patients significantly.[32] In another study, Hall *et al*. have demonstrated that treatment with the parenteral ω-3 could reduce mortality rate in critically ill septic patients.[33] This finding is in contrast with present data study. The route of administration and underlying disease could explain the reason for the difference.

Hamilton *et al*.[34] demonstrated that there are no significant independent associations between postoperative delirium and mortality. This is consistent with the present study that decrease days with delirium could not effect on mortality.

Level of consciousness could be evaluated by the GCS.[35] For this reason, we chose GCS higher than 9 that patient be cooperated to fill the ICU CAM sheets for evaluation of delirium.

APACHE II is a scoring system that is used to rule out the severity of illness. It provides objective discrimination between low- and high-risk groups of patients.[36] To make consistency between the two groups, we chose patients with APACHE score lower than 25.

Limitations of our study were heterogeneity in patients who were under mechanical ventilation and differences in the cause of hospitalization groups, which may have influenced the outcome of this study. Further important facts are that the study carried out in a single institute and small sample size was small. Moreover, assessment of delirium was twice a day in the present study, which is a transient and fluctuating disease. For this reasons, some positive cases might have been missed. In critical patients, the drug absorption may be impaired and we did not use a marker of fatty acids absorption.

The strength of our study was that, based on our findings it was the first investigation in the world that determine the efficacy of omega-3 in the prevention of delirium in patients who are under mechanical ventilation. On the other hand, study was well-designed in regard to its limitations.

CONCLUSION

The recent study outcomes showed the ability of omega-3 fatty acids in reduce the risk of delirium in patients undergoing mechanical ventilation.

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Conflicts of interest

There are no conflicts of interest.

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