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Original Article

The Effects of EPA, GLA, and Antioxidant-Enriched Enteral Nutrition on Oxidative Stress and Oxygenation in Patients With ARDS: A Prospective, Randomized, Controlled Trial

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ABSTRACT

Objective: The aim of this study was to determine the effects of eicosapentaenoic acid (EPA), gamma linolenic acid (GLA), and antioxidant-enriched enteral nutrition on oxidative stress and oxygenation in patients with acute respiratory distress syndrome (ARDS).

Methods: This prospective randomized controlled clinical trial included 41 patients suspected of having of ARDS. Group C received high-carbohydrate enteral nutrition, and group E received enteral nutrition enriched with EPA, GLA, and antioxidants. The control group included 10 healthy volunteers used to compare basal enzyme levels. Oxidative stress was evaluated via measurement of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), xanthine oxidase (XAO), and malonaldehyde (MDA) levels in blood samples. Patients were followed-up for 7 d, and on d 1, 4, and 7 blood samples were collected. Ventilatory settings, including the PaO_2:FiO_2 ratio, positive-end expiratory pressure (PEEP), peak inspiratory pressure (PIP), and minute ventilation volume (MV), were recorded daily.

Results: In total, 31 of the 41 patients completed the study. Findings for d 1 showed that the ARDS patients had antioxidant enzyme deficiency, as compared to the healthy controls. XAO and GPx levels in group E increased daily and the difference between successive days were significant ($p<0.05$). CAT and SOD levels in groups C and E did not differ between days. In group E the MDA level decreased significantly over time ($p<0.05$). There weren't any significant differences in PEEP, PIP, MV, or the PaO_2:FiO_2 ratio between baseline and d 7 of the study. Oxygenation in group E did improvement during the study.

Conclusion: EPA, GLA, and antioxidant-enriched enteral nutrition in patients with ARDS increased antioxidant enzyme levels and reduced lipid peroxidation, which decreased oxidative stress, but did not improve gas exchange or oxygenation.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by neutrophilic inflammation, increased membrane permeability, and alveolar deposition.[1-3] The cause of ARDS' primary clinical symptoms is proinflammatory mediators and uncontrolled oxygen-free radical production. Insufficient levels of non-enzymatic antioxidants (ascorbate, alpha tocopherol, and beta-carotene) or antioxidant enzymes (catalase [CAT], superoxide dismutase [SOD], glutathione peroxidase [GPx], and xanthine oxidase [XAO]) can increase oxidative tissue injury.[4,5]

Earlier studies reported that nutrition enriched with omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) and antioxidants modulates the inflammatory response, reduces proinflammatory mediator production, and results in the production of less active and potentially anti-inflammatory mediators.[6-8] Preclinical studies have shown that the combination of the omega-6 fatty acids gamma linolenic acid (GLA) and EPA reduces proinflammatory neutrophil leukotriene synthesis and stimulates the vasodilator prostoglandin E1.[9,10] Based on these findings, it is suggested that EPA and GLA in combination supports antioxidant systems and decrease oxidative stress.

Metnitz et al.[11] studied the antioxidant defense system in patients with ARDS that received micronutrient supplementation and reported that the ARDS patients had low non-enzymatic antioxidant levels and increased lipid peroxidation products, which were indicative of oxidative stress. Based on these findings, we think ARDS patients require antioxidant supplementation, might be achieved via enteral nutrition. Earlier randomized controlled trials reported inconsistent findings regarding the effectiveness of EPA, GLA, and antioxidant-enriched dietary supplementation.[12-15] As such, the present study aimed to determine the effects of EPA, GLA, and antioxidant-enriched enteral nutrition on oxidative stress and oxygenation in patients with ARDS, based on comparison of antioxidant enzyme levels (CAT, SOD, GPx, and XAO) and lipid peroxidation products (malonaldehyde [MDA]) in ARDS patients and healthy controls.

MATERIALS AND METHODS

This prospective, randomized, controlled clinical trial was conducted at the medical ICU. The study included 41 ARDS patients aged >18 years that were mechanically ventilated and 10 healthy controls. ARDS was diagnosed based on observation of acute onset of diffuse bilateral pulmonary infiltrates via chest radiography and a partial pressure of arterial oxygen:fraction of inspired oxygen (PaO_2:FiO_2) ratio <200 without clinical evidence of fluid overload.[16] Exclusion criteria included patients with a Glasgow Coma Scale score <5, head trauma, pulmonary malignancy, cerebral hemorrhage, active bleeding, immunosuppressive medication use, pregnancy, total parenteral nutrition, and a leukocyte count ≤5000 cells mm–3. A low-volume ventilation strategy (tidal volume <6 mL kg–1 and P plateau <30 mmHg) was administered with the ventilator in volume control mode, along with a conservative hemodynamic management protocol.[17,18]

Group C included ARDS patients that were given standard carbohydrate-enriched enteral nutrition (Ensure, 500 mL, 1 kcal mL–1, Abbott Laboratories, Inc., Netherlands) and group E included ARDS patients that were given EPA, GLA, and antioxidant (vitamin E, vitamin C, and B-carotene)-enriched enteral nutrition (Oxepa, 500 mL, 1.5 kcal mL–1, Abbott Laboratories Inc., Netherlands). Patients were divided into groups C and E randomly via the sealed envelope technique. The control group included 10 healthy volunteers that were used for comparison of baseline enzyme levels. All patients were fed via nasogastric tube and an enteral feeding pump (Kangaroo Enteral Feeding Pump, Covidien, USA). Caloric intake was calculated according to the Schofield formula.

Patients received enteral nutrition within 6 h of meeting entry criteria. Nutrition was started at 10 mL h–1 and increased to 20 mL h–1 over the course of 8 h. Patients were considered well-tolerated to feeding based on a GRV <500 mL d–1 and lack of diarrhea. Patients that achieved ≥750 mL of enteral nutrition with a GRV <500 mL d–1 were included in the study. Upon study enrollment, patient age, gender, weight, height, comorbidities, diagnosis, APACHE II (Acute Physiology and Chronic Health Evaluation) score, SOFA (Sequential Organ Failure Assessment) score, mean blood pressure (MBP), and central venous pressure (CVP) were recorded. The day on which each patient fulfilled all study criteria was considered d 1. Patient blood samples were collected on d 1, 4, and 7 for analysis of arterial blood gases, plasma MDA, and erythrocyte antioxidant enzyme activity (CAT, SOD, GPx, and XAO). Serum and plasma were prepared following centrifugation for 15 min at 4000 rpm and 4 °C and were then stored at -80 °C until analyzed.

MDA was used as a marker of oxidative stress. Plasma MDA (nmol mL–1) was measured spectrophotometrically using the TBARs (thiobarbituric acid reactive substances) method, as described by Dahle.[19] Antioxidant enzymes were assayed as follows: CAT (IU mL–1) was measured based on the decrease in absorbance due to disappearance of H_2O_2 at 240 nm;[20] GPx (IU mL–1) and XAO (mIU mL–1) were measured via the spectrophotochemical method;[21,22] SOD (IU mL–1) was measured via the photochemical method.[23] Clinical assessment was based on recorded ventilator settings, including positive-end expiratory pressure (PEEP), peak inspiratory pressure (PIP), and minute ventilation volume (MV). Oxygenation status was determined via the PaO_2:FiO_2 ratio, and $PaCO_2$, PaO_2, and pH values in arterial blood samples were recorded daily.

Data were analyzed using SPSS v.15.0 for Windows (SPSS, Inc., Chicago, IL). All values are expressed as mean ± SD. Demographic variables (age, weight, and height) were

compared using Student's t-test. Qualitative data were analyzed using the chi-square test and quantitative data were analyzed via analysis of variance (ANOVA) or the Mann-Whitney U-test. Differences in parameters according to time were assessed via repeated measures ANOVA. The level of statistical significance was set at P≤0.05.

RESULTS

In all, 4 patients died (group C: n=2; group E: n=2) and 6 others did not reach the nutritional target (group C: n=3; group E: n=3). Data obtained from the remaining 31 patients (group C: n=15; group E: n=16) were assessed. There weren't any significant differences in age, gender, weight, height, APACHE II score, SOFA score, MBP, or CVP between groups C and E (P>0.05) (Table 1).

On d 1 of the study GPx and XAO levels were significantly higher (P<0.05), and the MDA level was significantly lower (P<0.05) in the control group than in groups C and E, but there wasn't a significant difference in SOD or CAT levels between the patients (groups C and E) and controls (Table 2). In group C the GPx level did not change significantly over time, but in group E the GPx level did increase significantly over time (P<0.05). The GPx level was significantly higher in group E than in group C on d 4 and d 7 (P<0.05). CAT and SOD levels did not differ significantly between days in groups C and E, or between the 2 groups. In group E the XAO level increased significantly over time (P=0.001). The XAO level on d 4 and d 7 was higher in group E than in group C (P=0.001). The MDA level in group E decreased significantly over time; on d 4 and d 7 the MDA level in group E was significantly lower than in group C (P<0.05) (Table 3).

There wasn't a significant difference in PEEP, PIP, MV, or the PaO_2:FiO_2 ratio between baseline and d 1, 4, and 7 of the study. Oxygenation—based on the PaO_2/:FiO_2 ratio—did not decrease in group C during the 7-d study period and did not improve in group E. There weren't any significant differences in daily pH, PaO_2, or $PaCO_2$ between groups C and E.

DISCUSSION

ARDS is characterized by production of oxygen-free radicals and arachidonic acid-derived inflammatory mediators from stimulated neutrophils, which causes tissue inflammation and alveolar damage. Secondary to this excessive oxidative stress, endogenous antioxidant functioning may be insufficient, and damage due to oxygen-free radicals can increase and lipid peroxidation can exacerbate. In con-

Table 1. Assessed data obtained from the remaining 31 patients

	Grup C (n=15)	Grup E (n=16)	p
Age (Year)	75±(8.5)	76±(8.2)	0.806
Gender (F/M)	7/8 (%46/54)	8/8 (%50/50)	0.743
APACHE II score (Mean±SD)	22.4±7.1	22.3±7.0	0.826
BMI kg/m2	26.5±5.2	25.1±5.4	0.612
SOFA score (Mean ±SD)	11.4±2.4	12.1±2.1	0.342
Vasopressor Using (n)	11 (%73)	12 (%75)	0.754
Tidal Volum ml/kg	7.0±(1.1)	7.2±(1.4)	0.355
Mean Blood Pressure (mmHg)	68.9±18.2	72.4±16.7	0.106
CVP (cmH2O)	10.4 (4.7)	11.0 (4.8)	0.287
Albumin g/dl	2.2±(0.4) g/dl	2.3±(0.3) g/dl	0.691
Pneumonia (n)	8 (%53)	8 (%50)	0.896
Sepsis (n)	3 (%20)	4 (%25)	0.619
Aspiration Pneumonia (n)	4 (%27)	4 (%25)	0.844

Table 2. GPx and XAO levels Groups C, E and K.

				P		
	Grup C	Grup E	Grup K	Grup S/EG	Grup SK	Grup EG/K
GSH-Px	11.63±2.5	10.41±2.2	18.12±2.0	0.586	0.003	0.004
SOD	585.16±23.77	580.90±14.21	573.23±19.25	0.342	0.102	0.130
CAT	45605±9340	43302±7687	48641±8781	0.282	0.367	0.116
XO	0.850±0.40	0.952±0.28	1.812±0.58	0.166	0.001	0.003
MDA	318.30±34.11	321.92±23.63	273.00±17.11	0.621	0.001	0.002

Table 3. The MDA levels in groups

	Days			P		
	1	4	7	1/ 4	1 /7	4 /7
GSH-PX Grup C	11.63±2.5	10.83±1.7	12.67±2.9	0.328	0.312	0.106
GSH-PX Grup E	10.41±2.2	13.88±4.3	21.40±4.2	0.006	0.001	0.004
p	0.586	0.008	0.002			
SOD Grup C	595.16±73.77	598.32±27.20	570.13±76.65	0.496	0.089	0.102
SOD Grup E	580.90±25.21	578.28±37.01	591.85±27.22	0.828	0.322	0.121
p	0.342	0.088	0.092			
CAT Grup C	45605±9340	47946±6283	45530±6958	0.074	0.064	0.157
CAT Grup E	43302±7687	41518±10045	43280±8523	0.439	0.990	0.181
p	0.282	0.062	0.429			
XO Grup C	0.850±0.40	1.228±1.04	1.363±0.76	0.183	0.101	0.672
XO Grup E	0.952±0.28	2.885±0.62	3.881±0.03	0.001	0.001	0.102
p	0.166	0.001	0.001			
MDA Grup C	318.3±34.11	313.45±34.27	324.48±28.63	0.443	0.421	0.102
MDA Grup E	321.92±23.63	293.28±22.84	285.96±18.91	0.001	0.001	0.136
p	0.202	0.002	0.001			

sideration of this pathophysiological mechanism, some researchers attempted to determine the benefits of omega-3 fatty acids in the treatment of ARDS. It was shown that omega-3 fatty acids can shift the synthesis of proinflammatory mediators to the synthesis of less inflammatory mediators, and that EPA/GLA-enriched nutritional support might decrease oxidative stress and lipid peroxidation and increase antioxidant enzyme levels.[6-8] These earlier studies indicated that enteral nutrition supplemented with EPA/GLA in ARDS patients improved clinical outcomes, including oxygenation, ventilation-free days, and the survival rate;[14,15,24] however, these studies did not measure antioxidant enzyme levels in both groups with ventilatory parameters. In the present study both cellular and clinical outcomes were assessed based on antioxidant enzyme levels and oxygenation parameters.

The present study showed the antioxidant enzyme levels of the ARDS patients according to healthy volunteers before study begin and the response of the patients to the EPA, GLA and antioxidants enriched enteral nutrition with continue infusion. In comparison to the healthy controls the ARDS patients had significantly higher MDA levels (indicative of high lipid peroxidation), significantly lower GPx and XAO levels, and lower (not significantly) SOD levels. The observed low level of activity of antioxidant defense enzymes in the present study's ARDS patients was indicative of oxidative stress. In addition, high lipid peroxidation (according to MDA levels) was another indicator of oxidative stress and a cause of cellular membrane instability in the ARDS patients, as previously reported.[11,25-27]

In the present study antioxidant enzyme levels (GPx, SOD, and XAO) increased and the lipid peroxidation product (MDA) decreased daily in group E. Metnitz et al.[11] and Kumar et al.[28] reported oxidative stress in ARDS patients, as in the present study, and Nelson et al.[13] reported the positive effect of EPA/GLA and antioxidant-enriched nutrition on antioxidant status in ARDS patients; however, these earlier studies did not analyze clinical outcomes. Although the present study's pathophysiological findings are similar to those of earlier studies,[11,13,28] clinical improvement in the present study's ARDS patients, such as improved oxygenation, was observed in response to EPA, GLA, and antioxidant-enriched enteral nutrition. Rice et al.[12] was criticized due to a lack of clinical improvement following bolus administration of nutritional support, whereas in the present study enteral nutrition was administered via continuous infusion in groups C and E, but clinical improvement in oxygenation was not achieved; the PaO_2:FiO2 ratio did not differ between groups C and E at all time points it was measured.

Grau-Carmona et al.[29] did not obtain better clinical outcomes with EPA and GLA supplementation in mechanically ventilated patients. Singer et al.,[14] Gadek et al.,[15] and Pontes-Arruda et al.[30] suggested that the combination of EPA and DHA results in significantly better clinical outcomes—in terms of survival and length of ICU stay, but we could not show the same benefit even at oxygenation level so we do not agree with better clinical outcomes. Differences in outcome between earlier studies and the present study might be due to differences in group C characteristics; earlier studies administered formulations with a high fat ratio for calorie to group C. Some studies have reported that high-fat ratio nutrition can result in production of inflammatory leukotrienes.[7,8] In contrast to studies that reported improved clinical outcomes,[14,15,30] in the present study an isocaloric nutrition product containing mostly carbohydrate calories was used in an effort to avoid false clinical improvement. Rice et al.[12] administered

high-carbohydrate ratio nutrition to their group C, as in the present study, and did not observe any clinical improvement, including oxygenation. Some clinicians may be concerned about hypercapnia in patients fed high-carbohydrate nutrition. Al-Saady et al.[31] reported that high-fat, low-carbohydrate nutrition lowers the $PaCO_2$ level, but in both Rice et al.[12] and the present study elevated $PaCO_2$ was not observed in group C.

The cause of the observed cellular benefits of EPA and GLA without any clinical improvement in the present study is not clear, but we think it might have been due to the rapid onset of ARDS; however, as Weaver et al.[32] observed cellular response to EPA treatment within 1-3 d, it may be most important to initiate nutritional support before the onset of ARDS. We thought that dosage and timing studies with larger sample sizes may be helpful to prove better clinical outcomes.

Not to comprise the research of the ventilatory free days, days of critical care stay and mortality as clinical outcomes may be seen as the limitations of the present study but we thought that as a first step in ARDS treatment, improvement of gas exchange which was showed with PaO_2/FiO_2 ratio may be enough to assess the clinical follow up of the patients. In addition, the primary aim of the present study was to determine the cellular benefits of EPA, GLA, and antioxidant-enriched enteral nutrition on oxygenation in ARDS patients. The benefits of enteral feeding with products enriched with EPA, GLA and antioxidants have not been clearly demonstrated in the studies. This may be due to differences in study designs, differences in laboratory and clinical parameters used in the evaluation, differences in etiology of ALI/ARDS development,[33] differences in control groups, and genetic polymorphism of patients.[34] It is controversial which component provides the beneficial effects of enteral feeding with EPA, GLA and antioxidant-enriched products and whether the positive effect of EPA occurs together with GLA or alone.

In addition, the answers to the questions of what the optimal dose, time of administration, duration of administration and route of administration should be for EPA and GLA are also controversial and further and comprehensive clinical studies are needed on this subject.

Conclusion

In conclusion, the present findings indicate that EPA, GLA, and antioxidant-enriched enteral nutrition in patients with ARDS increased antioxidant enzyme levels and reduced lipid peroxidation, and thereby decreased oxidative stress, but did not improve gas exchange or oxygenation. The cellular benefits of the described supplemental nutritional regimen must be studied further to more clearly elucidate its effect on clinical outcomes.

Ethics Committee Approval

The study was approved by the Ankara Numune Training and Research Hospital Ethics Committee (Date: 08/06/2011, Decision No: 2011-179).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.Y., H.Y.; Design: A.Y., H.Y.; Supervision: H.S.O., H.Y., B.D.; Fundings: A.Y., H.Y.; Materials: A.Y., H.Y., O.O., H.S.O.; Data collection &/or processing: A.Y., F.A., O.O., H.S.O.; Analysis and/or interpretation: A.Y.,O.O., H.Y., H.S.O., B.D.; Literature search: A.Y., H.Y., F.A.; Writing: A.Y., H.Y.; Critical review: H.Y., B.D.

Conflict of Interest

None declared.

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EPA, GLA ve Antioksidanla Zenginleştirilmiş Enteral Beslenmenin ARDS'li Hastalarda Oksidatif Stres ve Oksijenasyon Üzerindeki Etkileri: Prospektif, Randomize, Kontrollü Bir Çalışma

Amaç: Bu çalışmanın amacı, akut solunum sıkıntısı sendromu (ARDS) hastalarında eikosapentaenoik asit (EPA), gama linolenik asit (GLA) ve antioksidanlarla zenginleştirilmiş enteral beslenmenin oksidatif stres ve oksijenasyon üzerine etkilerini belirlemektir.

Gereç ve Yöntem: Bu prospektif randomize kontrollü klinik çalışmaya ARDS olduğundan şüphelenilen 41 hasta dahil edildi. Grup C, yüksek karbonhidratlı enteral beslenme aldı ve grup E, EPA, GLA ve antioksidanlarla zenginleştirilmiş enteral beslenme aldı. Kontrol grubu, bazal enzim seviyelerini karşılaştırmak için kullanılan 10 sağlıklı gönüllüyü içeriyordu. Oksidatif stres, kan örneklerinde katalaz (CAT), süperoksit dismutaz (SOD), glutatyon peroksidaz (GPx), ksantin oksidaz (XAO) ve malonaldehit (MDA) düzeylerinin ölçülmesiyle değerlendirildi. Hastalar 7 gün boyunca takip edildi ve 1, 4 ve 7. günlerde kan örnekleri toplandı. PaO_2:FiO_2 oranı, pozitif uç ekspiratuvar basınç (PEEP), tepe inspiratuvar basınç (PIP) ve dakika ventilasyon hacmi (MV) dahil olmak üzere ventilasyon ayarları günlük olarak kaydedildi.

Bulgular: Toplamda 41 hastanın 31'i çalışmayı tamamladı. d 1 bulguları ARDS hastalarının sağlıklı kontrollere göre antioksidan enzim eksikliğine sahip olduğunu gösterdi. Grup E'de XAO ve GPx düzeyleri gün geçtikçe arttı ve birbirini takip eden günler arasındaki fark anlamlıydı ($p<0.05$). C ve E gruplarında CAT ve SOD düzeyleri günler arasında farklılık göstermedi. Grup E'de MDA düzeyi zamanla önemli ölçüde azaldı ($p<0.05$). Çalışmanın başlangıç noktası ile 7. günü arasında PEEP, PIP, MV veya PaO_2:FiO_2 oranında anlamlı bir fark yoktu. E grubundaki oksijenlenme çalışma sırasında iyileşme gösterdi.

Sonuç: ARDS'li hastalarda EPA, GLA ve antioksidanlarla zenginleştirilmiş enteral beslenme, antioksidan enzim düzeylerini artırdı ve lipit peroksidasyonunu azalttı; bu da oksidatif stresi azalttı, ancak gaz değişimini veya oksijenasyonu iyileştirmedi.

Anahtar Sözcükler: Antioksidanlar; ARDS; EPA; GLA.