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Effect of ω-3 Fatty Acids Supplementation on Inflammatory Factors of Gastric Cancer Patients During Chemotherapy

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Abstract: Supplementing of ω-3 fatty acid has a large impact on anti-inflammatory and immune-modulating. These effects may be beneficial to cancer patients. In this study, the effects of ω-3 fatty acid intakes on inflammatory factors of gastric cancer patients were investigated during chemotherapy. This double blind clinical trial study was conducted on 30 adult patients (15 cases and 15 controls) with different pathologic type of gastric cancer during chemotherapy in Ardebil city, Iran 2010-2011. A 3 g of ω-3 fatty acid (1.8 g EPA and 1.2 g DHA per 10 g fish oil) and placebo were given for patient grouped randomly as omega and control. Blood samples were taken to measure IL-1β, IL-2, IL-6, hs-CRP and TNF-α at the beginning, 4 and 6 weeks after intervention. According to previous reports in current study, elevated serum concentrations of IL-1β, hs-CRP and TNF-α have been found in cancer patients with reduce in weight. While weight was significantly increased but IL-1β, IL-6 and TNF-α were decreased after consumption of ω-3 fatty acid, time dependently ($p<0.05$). Supplementation of ω-3 fatty acid can reduce the inflammatory effects and hence, it may have beneficial effects for gastric cancer patients during chemotherapy.

Key words: Inflammatory factors, gastric cancer, ω-3, Ardebil, chemotherapy, Iran

INTRODUCTION

After cardiovascular diseases and accidents, cancer is the third cause of deaths in Iran (Naghavim, 2005). Globally, it is the second leading cause of cancer-related death with 738,000 deaths annually all over the world (Ferlay *et al*., 2010). The gastric cancer incidence in Iran is around 7,300 cases year^{-1} which is most common in men (Sadjadi *et al*., 2002), mortality from stomach cancer is also the first cause of death due to cancer in both sexes (Naghavi, 2005). Ardabil province, Northwestern Iran has the highest incidence of gastric cancer in Iran (Sadjadi *et al*., 2003).

At the time of diagnosis, 80% of patients with upper gastrointestinal cancers have already experienced substantia weight loss. The cachexia prevalence is 50 to >80% in gastric cancer patients before death which is the main cause of death (Bruera, 1997). Cancer cachexia is a multifactorial event and inflammation plays a relevant pathogenesis role (Preston *et al*., 1998; Wigmore *et al*., 2000a). One of the common biochemical denominator contributing to cachexia in cancer and other chronic diseases is increase in IL-1, IL-2, IL-6 and TNF-α production (Plata-Salaman, 2000) and hence, increases energy expenditure and reduces dietary intake of nutrients leading to negative energy balance and weight loss. Elevated serum concentrations of IL-1, IL-6 and TNF-α have been found in cancer patients and their concentrations correlate with tumor progression (Mantovani *et al*., 2000).

The presence of an inflammatory response has been correlated with poor outcome in cancer and inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) have been proposed as important factors in the development of cancer-associated malnutrition (Argiles, 2005). With administration of ω-3 fatty acids, changes in leukotriene pattern is well tolerate which is suggesting favorable anti-inflammatory effects and further clinical benefits (Grimm *et al*., 2006). Study was showed; there were no significant changes in CRP, IL-6 and TNF-α following ω-3 fatty acids supplementation (Mori *et al*., 2003).

In some study reported in cancer patients, the production of pro-inflammatory cytokines such as IL-6, IL-1 and TNF-α can be down-regulated by the ω-3

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polyunsaturated fatty acid (Giacosa and Rondanelli, 2008). The aims of the present study were to examine the effect of ω-3 fatty acids supplementation on inflammatory factors and food intake in gastric cancer patients during chemotherapy.

MATERIALS AND METHODS

Study design: A double blind clinical trial study was conducted in Nutrition Research Center of Tabriz University of Medical Sciences in Iran in 2010-2011. The study was approved by Medical Ethical Committee of the Tabriz University of Medical Sciences and recorded with identification code of IRCT201011095144N1 in Iranian Registry of Clinical Trials. Thirty adult patients with pathologic type of gastric cancer undergoing chemotherapy in Imam and Fatemi Hospitals of Ardabil city were randomly selected. They were divided in two groups; omega and placebo.

The aims of current investigation were explained to the subjects and a written consent was taken prior to fill in a questionnaire. Only patients >30 years old were selected to participate in the study. Subjects with diseases causing cachexia such as heart, lung and renal disease, AIDS, acute leukemia, diabetes, multiple myeloma and individuals undergoing surgery were excluded. Staging procedure based on imaging results of cancer was used for patients with gastric cancer and only stages II and III were included in the study. Blood samples were collected three times at weeks 0, 4 and 6 weeks by venipuncture and sera separated immediately. Sera were kept frozen at 80°C until analyzed. Anthropometric indices and inflammatory parameters were measured at beginning, 4 and 6 weeks after supplementation with ω-3 and placebo. Omega group were taken 10 capsules day^{-1} each containing 180 mg Eicosapentaenoic Acid (EPA) and 120 mg Docosahexaenoic Acid (DHA) in 1 g fish while the placebo group were given.

Treatment schedule: The chemotherapy regimen consisted of: Once every 3 weeks docetaxel (Taxotere; Sanofi-aventis, Bridgewater, NJ) 75 mg m^{-2} (day 1) plus cisplatin 75 mg m^{-2} (day 1) and fluorouracil 750 mg/m^2/day continuous infusion (days 1-5; DCF) according to Ajani's protocol (Ajani *et al*., 2007).

Measuring of inflammatory factors: Fasting venous blood samples were taken for measurement of hs-CRP, IL-1β, IL-2, IL-6 and TNF-α at the beginning and the end of 4 and 6 weeks. Inflammatory factors such as IL-1β, IL-2, IL-6 and TNF-α were measured using appropriate Enzyme Linked Immunosorbent Assay (ELISA) kits were purchased from Bender Med Systems (Vienna, Austria) according to the manufacturer instructions. For the accuracy of assessment, duplicate assay were performed. Quantification of immunoreactive IL-1β, IL-2, IL-6 and TNF-α was carried out on 96 well microtiter ELISA plates using standard protocols. The color formation was measured at 450 and 630 nm (Anhos 2000 microplate reader) and the sample concentration of IL-1β, IL-2, IL-6 and TNF-α was estimated using Multicalc program (Wallac, Turku, Finland). Serum hs-CRP was determined immunoturbidimetric assay by Azemon kit.

Dietary method: The food intake was estimated for energy and other nutrients by 24 h recalls method for 3 days in week at the beginning, 4 and 6 weeks. Mean daily dietary intake and food composition were estimated using Iranian Food Processor software (Rafiei *et al*., 2003).

Statistical methods: Repeated measures, Paired sample t-test and Independent sample t-test were used for data analysis. $p<0.05$ was considered as significant differences.

RESULTS AND DISCUSSION

The mean of age in omega group and placebo group was 62.2±13.9 and 66.1±11.7 years old, respectively. About 67% of the participants were male and 33% comprised women. There were no significant differences regarding to age, weight, inflammatory factors and calorie intake between the omega and placebo groups in beginning study (Table 1 and 2).

Table 1: The comparison of inflammatory factors in placebo and omega groups during study

Variables	Measurement stage	Omega group	Placebo group	p-values
Weight (kg)	Before	56.7±10.2	56.2±6.9	0.86
	After 4 weeks	58.3±9.4^{+}	54.3±6.6^{+}	0.18
	End of week 6	59.2±8.9^{+*}	52.6±5.6^{+*}	0.02*
TNF-α (ng mL^{-1})	Before	24.4±4.4	25.8±3.8	0.92
	After 4 weeks	21.7±3.0	26.1±2.9^{+}	0.68
	End of week 6	12.8±2.8^{+*}	27.5±3.0	0.12*
IL-1β (ng mL^{-1})	Before	5±1.6	4.0±1.2	0.85
	After 4 weeks	3.4±1.4^{+}	4.2±1.6	0.16
	End of week 6	2.6±1.6^{+*}	4.5±0.8	0.00*
IL-2 (ng mL^{-1})	Before	47.6±24.4	45.7±32	0.85
	After 4 weeks	41.6±17	42.7±21.6	0.87
	End of week 6	36.2±13^{+}	45.6±20	0.14
IL-6 (ng mL^{-1})	Before	5.9±0.9	5.6±1.2	0.99
	After 4 weeks	5.8±1.5	5.5±3.6	0.70
	End of week 6	5.6±0.5	4.3±3.7	0.48
hs-CRP (g m mL^{-1})	Before	3.1±3.0	2.7±2	0.92
	After 4 weeks	3±2.8	3.4±3.2^{+}	0.85
	End of week 6	2.4±2.0^{+*}	3.7±3.5^{+*}	0.27

Values are mean±SD. $^{+}$ and * indicate significant differences in comparison to baseline and 4th week in repeated measures, respectively. *Indicates significant differences between two groups based on results of independent sample t-test

Table 2: The comparison of inflammatory factors and nutritional factors in placebo and omega groups during study

Variables	Measurement stage	Omega group	Placebo group	p-values
Calorie (k cal day^{-1})	Before	1651±183	1734±164	0.200
	After 4 weeks	1692±180^{+}	1597±183^{+}	0.160
	End of week 6	1793±130^{+*}	1408±255^{+*}	0.000*
CHO (g day^{-1})	Before	232±40	247±33	0.100
	After 4 weeks	259±30^{+}	258±35	0.900
	End of week 6	269±37^{+}	218±48^{+*}	0.003*
Fat (g day^{-1})	Before	49±11	50±16	0.810
	After 4 weeks	42±11	37±11^{+}	0.160
	End of week 6	44±14	38±12^{+}	0.250
Pr (g day^{-1})	Before	73±22	58±19	0.055
	After 4 weeks	74±22	57±15	0.020*
	End of week 6	74±14	48±18	0.000*
Saturated fatty	Before	2±3	11±6	0.710
acids	After 4 weeks	10±4	9±4	0.580
(g day^{-1})	End of week 6	11±5	8±3	0.040*
Plyunsaturated	Before	7±3	6±3	0.070
fatty acids	After 4 weeks	6±2	5±1.7	0.490
(g day^{-1})	End of week 6	6±2	5±2	o.220
Monounsaturated	Before	15±4	12±4.5	0.060
fatty acids	After 4 weeks	12±4	11±4	0.800
(g day^{-1})	End of week 6	14±5	11±4	0.060
Cal CHO	Before	56±7	61±8	0.060
	After 4 weeks	61±7	64±5	0.700
	End of week 6	59±7	61±6	0.490
Cal fat	Before	26±6	25±7	0.700
	After 4 weeks	23±4	19±6	0.059
	End of week 6	25±5	24±6	0.780
Cal pro	Before	15±3	14±4	0.920
	After 4 weeks	16±4	14±3	o.850
	End of week 6	17±4	13±3.8	0.008*

CHO = Carbohydrate; Pr = Protein, Cal CHO = Calorie percent from carbohydrate, Cal fat = Calorie percent from fat and Cal pro. = Calorie percent from protein. Values are mean ±SD. $^{+}$ and * indicate significant differences in comparison to baseline and 4th week in repeated measures, respectively. *Indicates significant differences between two groups based on results of independent sample t-test

As shown in Table 1, increment of weight and decrement of IL-1β and TNF-α were time dependently significant by intaking of ω-3 fatty acids in comparison to placebo group ($p<0.05$).

The serum levels of IL-1β, IL-2 and hs-CRP of omega group were decreased significantly at the end of 6 weeks ($p<0.05$). The serum levels of IL-1β, TNF-α and hs-CRP in gastric cancer patients supplemented with placebo were increased but just the increment of hs-CRP was significant at week 6 ($p<0.05$). As shown in Table 2, the mean intake of calorie, carbohydrate and protein in omega group were significantly higher than placebo group after intervention ($p<0.05$). About 67% of patients were in stage II and remaining are in stage III.

The weight of gastric cancer patients in stage II were significantly higher than stage III patients as expected (73±11 kg vs. 65±9 kg) ($p<0.05$). However, comparing inflammatory factors between stage II and III patients displayed no significant differences during the study. Calorie and fat intake of patients at stage II were significantly higher than stage III patients (1815±144 vs. 1631±160 k cal day^{-1} and 59±13 vs. 44±12 g day^{-1}, respectively) ($p<0.05$). This study demonstrated efficiency of ω-3 fatty acids as an oral supplementation in patients with gastric cancer. We found that IL-1β, IL-2, TNF-α and hs-CRP increases in gastric cancer patients in accordance with previous studies (Ilhan *et al*., 2004; Mantovani *et al*., 2000) and ω-3 fatty acids can not only stop but also improve this changes. Animal experiments and clinical intervention studies indicate that ω-3 fatty acid have anti-inflammatory properties (De la Puerta *et al*., 2009; Simopoulos, 2002) as well as enhanc e the cytotoxic effect of chemotherapy and to offer protection to host tissues (Kapoor, 2009). For example, several interventional trials with administrating of ω-3 fatty acids have shown reduction in circulating levels of C-reactive protein, inflammatory cytokines including IL-6 (Grimble, 2003), IL-1 and TNF-α production (Barber and Fearon, 2001; Wigmore *et al*., 2000b).

This effect interested in scientists to treat cancer cachexia with ω-3 fatty acids supplementation. Clinical articles have reported improvements in appetite, body weight, nutritional parameters and clinical performance with ω-3 fatty acids supplementation (Barber *et al*., 1999; Wigmore *et al*., 2000b) although, the mechanism of improvement of food intake by ω-3 fatty acids in cancer anorexia was not well explained. Although, researchers believe that diminished food intake is a major reason for weight losing in cancer patients (Levine and Morgan, 1998; Parkinson *et al*., 1987; Staal-van den Brekel *et al*., 1994; Wigmore *et al*., 1997) but this idea is still under contravention (Cohn *et al*., 1981; Simons *et al*., 1998). It is believe that diminished dietary intake in placebo group could be accounted for weight loss, since energy intake was lower in this group in comparison to omega group. Low dietary intake is a good predictor for survive of patients (Fearon *et al*., 2006). Albeit the evaluation of survival rate was out of our scopes in current investigation but increased energy intakes in gastric cancer with consumption of ω-3 fatty acids could prevent weight loss and therefore may have role in improving of patient's survival. Cancer patients have a very variable response to underfeeding; some patients are able, at least for a period of time, to adapt with reduced energy consumption leading to cachexia and increment of inflammatory factors. Dietary as well as antioxidative, vitamin levels have been associated with altered cancer risk (Ziegler, 1989). ω-3 fatty acids show antioxidant action in various cells and tissues through inhibition of apoptotic gene expression and DNA fragmentation of gastric epithelial cells (Yu *et al*., 2009). Fish oil intake for 8 weeks reduce IL-1, IL-6 and TNF-α production at week 8 in animal (De la Puerta *et al*., 2009) and

human (Mantovani *et al*., 2004) but not all studies (Vega-Lopez *et al*., 2004). In the opinion, based on the results, consumption of ω-3 fatty acids supplements increases calorie and macronutrients intake and decreases IL-1β, IL2, TNF-α and hs-CRP in gastric cancer patients during chemotherapy. Reduced serum level of IL-1β, IL-2, TNF-α and hs-CRP may increase appetite and have effect on calorie and nutrients intake.

CONCLUSION

The study demonstrate that of ω-3 fatty acids supplementation reduces IL-1β, IL-2, hs-CRP and TNF-α which may be useful as complementary therapy for gastric cancer patients under chemotherapy. However, available evidence indicates that ω-3 fatty acids may be effect appetite and calorie and nutrients intake by reducing the cytokines resulting to better cancer outcome.

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