Effect of Nutritional Supplement Enriched with Eicosapentaenoic Acid in Lean Mass of Subjects with Oral Cavity Cancer in Oncologic Pretreatment: a Clinical Trial

doi: https://doi.org/10.32635/2176-9745.RBC.2021v67n1.868

Efeito do Suplemento Nutricional Enriquecido com Ácido Eicosapentaenoico na Massa Magra de Indivíduos com Câncer de Cavidade Oral em Pré-Tratamento Oncológico: um Ensaio Clínico

Efecto del Suplemento Nutricional Enriquecido con Ácido Eicosapentaenoico en Massa Magra de las Personas con Cáncer de cavidad oral en el Pretratamiento Oncológico: un Ensayo Clínico

Bruna Cristina dos Santos Cruz[1]; Thayana Calixto de Carvalho[2]; Danúbia da Cunha Antunes Saraiva[3]; Adriana dos Santos[4]; Patrícia Fonseca dos Reis[5]

ABSTRACT

Introduction: Oral cavity cancer is considered a public health problem worldwide. Malnutrition is prevalent in this population, increasing morbidity and mortality. Supplementation with eicosapentaenoic acid has been proposed to reverse protein catabolism and modulate inflammatory processes. **Objective:** Assess the effect of supplement with eicosapentaenoic acid in the weight and lean mass of patients with oral cavity cancer. **Method:** Clinical trial conducted with patients in oncologic pretreatment. The patients were randomized to receive nutritional supplement with eicosapentaenoic acid (2 g/day) or placebo. Nutritional parameters (weight, height, body composition and food intake) were assessed at baseline (T0) and after 4 weeks of supplementation (T1). The paired t-test or Wilcoxon test were used in intragroup comparisons. Associations between categorical variables were verified using the χ^2 or Fisher Exact test. Logistic regression was applied to identify the chance of weight loss. Differences were considered significant at p <0.05. **Results:** It was not observed significant difference on nutritional parameters between the groups after intervention. However, considering each group at the beginning and at the end of the study, it was observed that patients in the control group presented significant weight loss (T0: 57.2 kg *x* T1: 56.4 kg), reduction in the body mass index (T0: 22.6 kg/m^2 *x* T1: 22.0 kg/m^2), fat mass (T0: 17.3 kg *x* T1: 15.3 kg) and arm circumference (T0: 27.4 cm *x* T1: 26.8 cm). Those who received supplement with eicosapentaenoic acid had 80% less chance of losing weight (95% CI: 0.045-0.860; OR: 0.19). **Conclusion:** This trial yielded data suggesting that patients with oral cavity cancer can benefit from eicosapentaenoic acid-containing nutritional supplement in oncologic pretreatment. Registration number: U1111-1177-3678.

Key words: Neoplasms/drug therapy; Dietary Supplements; Eicosapentaenoic Acid/administration & dosage; Body Composition/drug effects; Nutritional Status.

RESUMO

Introdução: O câncer de cavidade oral é considerado um problema de saúde pública no mundo. A desnutrição é prevalente nessa população, aumentando a morbimortalidade. A suplementação com ácido eicosapentaenoico tem sido proposta para reverter o catabolismo proteico e modular processos inflamatórios. **Objetivo:** Avaliar o efeito do suplemento nutricional enriquecido com ácido eicosapentaenoico no peso corporal e massa magra de pacientes com câncer de cavidade oral. **Método:** Ensaio clínico realizado com pacientes em pré-tratamento oncológico. Os pacientes foram randomizados para receber suplemento nutricional com ácido eicosapentaenoico (2 g/dia) ou placebo. Os parâmetros nutricionais (peso, estatura, composição corporal e ingestão alimentar) foram avaliados no início (T0) e após quatro semanas de suplementação (T1). O teste-t pareado ou de Wilcoxon foram usados nas comparações intragrupos. As associações entre as variáveis categóricas foram verificadas por meio do teste do χ^2 ou Exato de Fisher. A regressão logística foi aplicada para identificar a chance de perder peso. As diferenças foram consideradas significativas quando p<0,05. **Resultados:** Não foi observada diferença significativa nos parâmetros nutricionais entre os grupos após a intervenção. No entanto, considerando cada grupo no início e no final do estudo, observou-se que os pacientes do grupo controle apresentaram perda de peso significativa (T0: 57,2 kg *x* T1: 56,4 kg), redução no índice de massa corporal (T0: 22,6 kg/m^2 *x* T1: 22,0 kg/m^2), massa gorda (T0: 17,3 kg *x* T1: 15,3 kg) e circunferência do braço (T0: 27,4 cm *x* T1: 26,8 cm). Aqueles que receberam suplemento com ácido eicosapentaenoico tiveram 80% menos chance de perder peso (95% IC: 0,045-0,860; OR: 0,19). **Conclusão:** Este estudo produziu dados que sugerem que pacientes com câncer de cavidade oral podem se beneficiar com o uso de suplemento nutricional contendo ácido eicosapentaenoico no pré-tratamento oncológico. Número de Registro: U1111-1177-3678.

Palavras-chave: Neoplasias Bucais/tratamento farmacológico; Suplementos Nutricionais; Ácido Eicosapentaenoico/administração & dosagem; Composição Corporal/efeitos dos fármacos; Estado Nutricional.

RESUMEN

Introducción: El cáncer de la cavidad oral se considera un problema de salud pública en todo el mundo. La desnutrición prevalece en esta población, lo que aumenta la morbilidad y la mortalidad. Cuando la desnutrición se asocia con la anorexia, el aumento del gasto energético y la inflamación se denomina caquexia. Se ha propuesto la suplementación con ácido eicosapentaenoico para revertir el catabolismo proteico y modular los procesos inflamatorios. **Objetivo:** Evaluar el efecto de un suplemento nutricional enriquecido con ácido eicosapentaenoico sobre el peso corporal y la masa magra de pacientes con cáncer de cavidad oral. **Método:** Ensayo clínico realizado con pacientes sometidos a tratamiento previo al cáncer. Los pacientes fueron asignados al azar para recibir un suplemento nutricional con ácido eicosapentaenoico (2 g/día) o placebo. Los parámetros nutricionales (peso, altura, composición corporal e ingesta alimentaria) se evaluaron al inicio del estudio (T0) y después de 4 semanas de suplementación (T1). En las comparaciones intragrupo se utilizó la prueba t pareada o de Wilcoxon. Las asociaciones entre variables categóricas se verificaron mediante la prueba de la χ^2 o la prueba exacta de Fisher. Se aplicó regresión logística para identificar la posibilidad de perder peso. Las diferencias se consideraron significativas en p<0,05. **Resultados:** No hubo diferencias significativas en los parámetros nutricionales entre los grupos después de la intervención. Sin embargo, considerando cada grupo al principio y al final del estudio, se observó que los pacientes en el grupo de control tenían una pérdida de peso significativa (T0: 57,2 kg *x* T1: 56,4 kg), reducción en el índice de masa corporal (T0: 22,6 kg/m^2 *x* T1: 22,0 kg/m^2), masa grasa (T0: 17,3 kg *x* T1: 15,3 kg) y circunferencia del brazo (T0: 27,4 cm *x* T1: 26,8 cm). Aquellos que fueron suplementados con ácido eicosapentaenoico tenían 80% menos probabilidades de perder peso (95% IC: 0,045-0,860; OR: 0,19). **Conclusión:** Este estudio produjo datos que sugieren que los pacientes con cáncer de la cavidad oral pueden beneficiarse del uso de un suplemento nutricional que contenga ácido eicosapentaenoico en el tratamiento previo al cáncer. Número de registro: U1111-1177-3678.

Palabras clave: Neoplasias de la Boca/tratamiento farmacológico; Suplementos Dietéticos; Ácido Eicosapentaenoico/administración & dosificación; Composición Corporal/efectos de los fármacos; Estado Nutricional.

[1]Federal University of Viçosa (UFV). Viçosa (MG), Brazil. Email: brunacruz09@yahoo.com.br. Orcid iD: https://orcid.org/0000-0003-1248-7066
[2]Oswaldo Cruz Foundation (Fiocruz). Rio de Janeiro (RJ), Brazil. Email: thayanacalixto@hotmail.com. Orcid iD: https://orcid.org/0000-0002-4726-0630
[3,4,5]National Cancer Institute Jose Alencar Gomes da Silva (INCA). Nutrition and Dietetic Service. Rio de Janeiro (RJ), Brazil. Emails: danubiantunes@gmail.com; adriana.santos@inca.gov.br; patricia.reis@inca.gov.br. Orcid iD: https://orcid.org/0000-0003-1849-2894; Orcid iD: https://orcid.org/0000-0002-4494-6450; Orcid iD: https://orcid.org/0000-0001-6399-8718
Corresponding author: Bruna Cristina dos Santos Cruz. UFV. Av. Peter Henry Rolfs, s/n - Campus Universitário. Viçosa (MG), Brazil. CEP 36570-900. E-mail: brunacruz09@yahoo.com.br

INTRODUCTION

Malignant tumors in oral cavity form a significant part of the solid human tumors, corresponding to 30% of head and neck neoplasm cases[1,2]. Data from GLOBOCAN[3] indicate the occurrence of 354,864 new cases of oral cavity cancer in the world, and mortality reached 177,384 cases. In Brazil, the National Cancer Institute José Alencar Gomes da Silva[4] estimated the occurrence of 11,180 new cases of oral cavity cancer in men and 4,010 new cases in women in 2020.

About 35% to 60% of the patients with head and neck cancer are malnourished at the moment of the diagnosis due to tumor-related metabolic alterations, eating difficulties caused by obstructions or anorexia and cancer-associated cachexia[5-7]. Malnutrition severe condition is associated with progressive and involuntary weight loss, intense consumption of muscular and adipose tissue, expansion of extracellular water, immune dysfunctions, and metabolic alterations due to production of proinflammatory cytokines[8].

The alterations in body composition reflect on the patient's functionality and survival. Lean mass losses are associated with loss of strength, pulmonary, and cardiac function and varies across cancer types (5% to 89%) and in tumors of the respiratory and gastrointestinal tract these figures are higher[9]. The nutritional status of patients who start the treatment with malnutrition worsens even more along the treatment. This could cause increased toxicity and lower clinical response to the treatment, diminishing the survival and quality of life[10].

However, the clinical relevance of malnutrition in cancer patients is usually neglected, and only those in a more advanced stage received some kind of nutritional support. Nutritional evaluation must be part of the entire treatment and nutritional intervention should be initiated early[5,11,12]. Conventional nutritional support is efficient to increase food intake, however, it has not showed benefits regarding global survival[13,14].

Eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, has been receiving attention due to its potential effect as anti-inflammatory, capable of improving the nutritional status. EPA has anti-inflammatory properties, regulating the production of pro-inflammatory cytokines and the acute phase response negatively. In animal models, it inhibits tumor growth, reduces the production of proteolysis inducing factor, improves food ingestion and prevents anorexia[15,16]. However, these results remain contradictory in studies with humans.

EPA incorporation in tumor cells membranes and in the immune system alters their fluidity, expression of receptors, signal transduction, intracellular interaction, enzyme activity associated with membranes and production of pro-inflammatory eicosanoids[17,18]. EPA affects lean mass in different ways, including effects over proteolysis, protein synthesis, and through indirect mechanisms which can cause attenuation, maintenance and increase of lean mass[19,20].

The studies that assess the effects of EPA are usually performed with subjects during or after the oncologic treatment; however, information about its effects on pre-treatment when the disease presents intense metabolic activity are scarce. Considering the high prevalence of malnutrition and loss of muscle mass that occurs at the beginning of the treatment and the importance of nutritional status in clinical oncologic outcomes, this study aimed to assess the effect of nutritional EPA-enriched supplement in the lean mass and body weight of patients with oral cavity cancer before chemotherapy, radiotherapy or surgery.

METHOD

Selection of patients

Randomized, controlled clinical trial performed between July 2014, and November 2015 conducted in patients with diagnosis of oral cavity cancer, admitted in the Nutrition Ambulatory of the National Cancer Institute Jose Alencar Gomes da Silva (INCA). The inclusion criteria were patients of both genders with histopathological diagnosis of oral cavity cancer, aged between 40 and 75 years old, and nutritional diagnosis of malnutrition[21,22] or nutritional risk[23]. Patients with thinness (regardless of grade) in the body mass index (BMI) classification were classified as malnourished[21,22]. Nutritional risk was defined according to the presence of one or more of the following criteria: ≥ 10% weight loss at 6 months, dietary intake <75% of the daily requirements for a period of five consecutive days, and/or the presence of symptoms that could interfere with the food intake. Patients that met one or more of these criteria were classified as at nutritional risk[23]. Nutritional diagnosis of overweight (overweight or obese) does not invalidate the participation in the study, as long as the criteria adopted for nutritional risk are met. The exclusion criteria were presence of diabetes mellitus, liver and kidney diseases, and previous treatments as chemotherapy and/or radiotherapy for any kind of neoplasm.

Ethics

In compliance with the requirements of the Declaration of Helsinki and Resolutions number 466/2012[24] and number 510/2016[25] of the National Health Council for

research involving human beings, the study was submitted to the Institutional Review Board of the INCA, with favorable opinion on June 27th, 2014, under number 700,919. All the patients included in the study signed the informed consent form. This study was inscribed in the Brazilian Registry of Clinical Trials (ReBEC U1111-1177-3678).

DESIGN OF THE STUDY

The patients were randomized through Web-based randomization into two groups: a control group (C) received hypercaloric and hyperproteic supplement during 4 weeks; and an intervention group (EPA) received hypercaloric and hyperproteic EPA-enriched supplement from fish oil (2 g) for the same period. The nutritional supplements were isocaloric and isoproteic (Table 1).

Table 1. Nutritional composition of the supplements

Components	Hypercaloric and hyperproteic EPA-enriched supplement	Hypercaloric and hyperproteic supplement control
Calories (kcal)	562.0	595.3
Protein (g)	30.0	31.0
Carbohydrate (g)	80.0	75.6
Fiber (g)	9.2	-
Lipids (g)	11.4	18.9
EPA (g)	2.0	-
Polyunsaturated fatty acids (g)	5.2	3.5
Monounsaturated fatty acids (g)	2.2	4.7
Saturated fatty acids (g)	3.0	10.8

Diets were calculated individually at baseline and after 4 weeks, in order to meet the nutritional needs of each patient. Energy and protein requirement calculations were carried out in accordance with ESPEN Guidelines' Recommendation[26]. The energy and protein content from the nutritional supplement were considered in the calculation of the diet. The consistency of the prescribed diet was appropriate to each patient's tolerance.

The adherence to the supplementation was evaluated weekly through phone calls and in the return visits after 4 weeks of intervention, when the patients should return the supplement that had not been used. Clinical and sociodemographic data were collected from medical records and recorded in a specific form (gender, age, histological type, staging, comorbidities, and medical history). The patients were assessed in the first visit (T0) and 4 weeks after intervention (T1).

BODY COMPOSITION

Body composition was evaluated through bioelectrical bioimpedance analysis (BIA) on a tetrapolar equipment Biodynamics Model 450, according to a standardized technique[27]. The measurement of phase angle (PA) was given by BIA, and standard phase angle (SPA) was obtained through the equation SPA=PA-(average PA)/SD, in which PA is subtracted from the average PA of the healthy population and divided by the correspondent standard deviation[28].

Body compartments were evaluated through arm circumference (AC), triceps skinfold (TSF), and arm muscle circumference (AMC). AC was measured with an inelastic measuring tape in the middle point between the acromion of the scapula and the ulna olecranon. TSF was measured using the adipometer Lange Skinfold Caliper[29]. AMC was obtained through the equation: AMC(cm)=AC(cm)-πTSF(mm) and compared with the values established by Frisancho[30].

SAMPLE SIZE CALCULATIONS

The sample size was calculated for 90% of statistical power to detect a difference of body weight of 1.0 kg. It was assumed a standard deviation of 4.5 kg, based on Fearon et al.[31] investigation. The minimum sample size was 46 patients, with an increase of 15% for possible follow-up losses, resulting in 53 patients.

STATISTICAL ANALYSIS

Statistical processing and analysis were performed in the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (SPSS Inc., Chicago, USA). The primary analysis was conducted on an intent-to-treat principle (ITT), including every subject randomized according to randomized treatment assignment. It ignored noncompliance, protocol deviations, withdrawal, and anything that happens after randomization[32].

Shapiro-Wilk test was used to verify the normality of the variable's distribution. Categorical variables were expressed as absolute or relative frequencies, and continuous variables, as mean and standard deviation or median, minimum and maximum. The paired t-test was used for intragroup analysis at T0 and T1 for parametric variables. For nonparametric variables, the Wilcoxon Test was used. For the comparison between the C group and EPA, T-Test for parametric variables and Mann–Whitney test for nonparametric variables were used. χ^2 or Fisher

Exact Test was used to test the association of categorical variables. Logistic regression was applied to identify the possible confounding factors. Delta (Δ) was used to identify variations of weight and lean mass between the baseline and the end of the study. The results were considered significant when $\alpha \leq 0.05$, with a confidence interval (CI) of 95%.

RESULTS

Sixty-four (64) patients with oral cavity cancer in antineoplastic pretreatment were included and randomized to the study (n=32/group). From those, 11 were subsequently excluded: for not returning to the second visit (n=3), beginning of oncologic treatment (n=7), and transference to another unit (n=1). Fifty-three patients (n=24 group C; n=29 group EPA) concluded the study (Figure 1).

The most frequent tumors in the population were: tongue (49%), floor of the mouth (18.8%), and gum (13.2%). Most of the patients presented advanced staging (75% of C group; 79% of EPA group). As for the histopathological diagnosis, 96.6% were squamous cell carcinoma and 3.4%, adenoid cystic carcinoma.

Seventy nine percent of all patients had already changed the diet consistency in the first appointment, and 3.8% were using nasoenteral feeding catheter. The symptoms of nutritional impact, before and after intervention in both groups, were: odynophagia (64.2%), difficulty in deglutition (60.4%), sialorrhea (50.9%), intestinal constipation (41.5%) and difficulty in mastication (34%). The dietary supplements were well tolerated by both groups, since there were no adverse events associated with their use. Symptoms reported were considered due to the progression of the disease.

The groups were comparable, since it was not observed any significant difference between the evaluated variables at baseline (Table 2). Weight loss was found in the evaluated population. In the first appointment, 62.5% of the patients in C group reported some weight loss, whereas in EPA group, this complication was significantly greater (89.6% of the population). Groups C and EPA had a similar median initial weight loss, corresponding to 8.3 kg (4.3-14.5kg) and 6.9 kg (0.6-17.5kg), respectively. This loss corresponded to 14.2% of the usual weight in C group, and 13% in EPA group. Those who lost 10% or more of their usual body weight during six months were classified as severe weight loss. However, the groups did not present differences regarding the severity of weight loss. According to BMI, 50% of the patients in C group were initially classified as eutrophic, 25% presented some degree of underweight/malnutrition, and 25% were overweight; in EPA group, 48.3% of the patients were eutrophic, 44.8% had some degree of underweight/malnutrition, and 6.9% were overweight. Regarding the evaluation of AMC according to gender and age percentiles, 12.5% of the patients in C group presented depletion, and 37.5%, severe depletion. In EPA group, 20.7% of the patients had depletion, and 48.3% had severe depletion (non-significant difference).

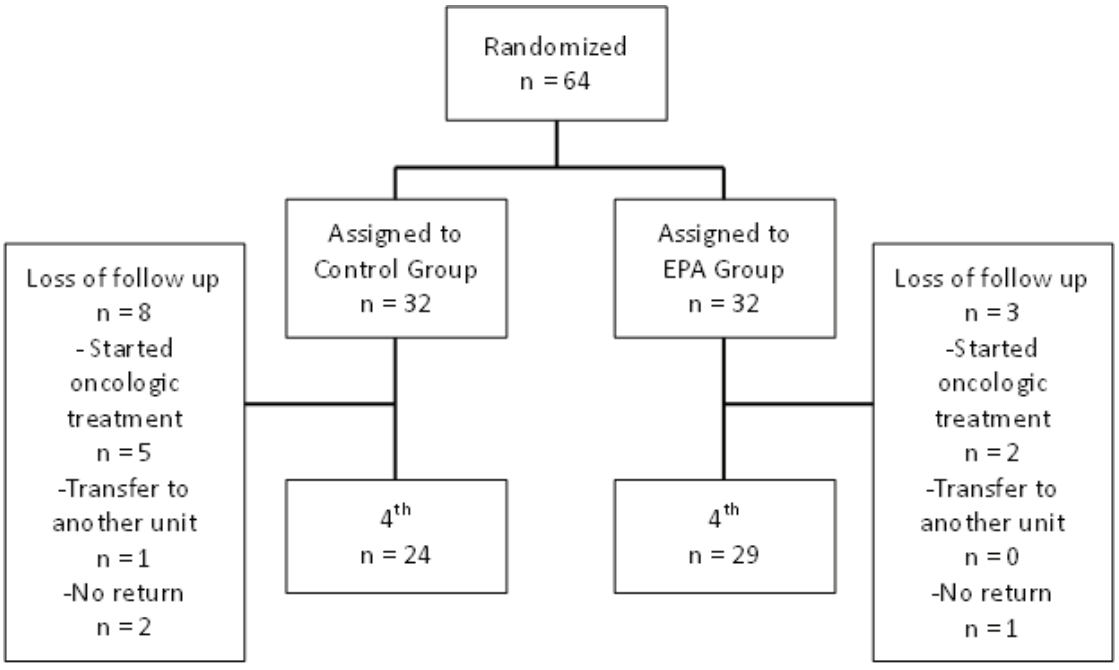

Figure 1. Patient assignment in groups and loss of follow up (baseline to fourth week)

Table 2. Baseline characteristics of groups C and EPA

Variables	C (n=24)	EPA (n=29)
Age (years)	53.3 ± 8.8	57.28 ± 9.1
Gender		
Male (n/%)	17 (70.8)	25 (86.2)
Female (n/%)	7 (29.2)	4 (13.8)
Stage of disease (n/%)		
I	3 (12.5)	1 (3.4)
II	3 (12.5)	5 (17.2)
III	1 (4.2)	7 (24.1)
IVa	15 (62.5)	12 (41.4)
IVb	2 (8.3)	4 (13.8)
Smoker (n/%)	19 (79.2)	28 (96.5)
Time (years)	32.8 ± 12.2	37.2 ± 10.6
Alcohol use (n/%)	19 (79.2)	28 (96.5)
Time (years)	31.3 ± 11.7	32.7 ± 12.7
Weight (kg)	57.2 (40.3 - 80.1)[1]	55.8 (37.5 - 100.0)[1]
BMI (kg/m²)	22.6 ± 4.3	20.7 ± 3.4
Weight loss (%)	14.2 ± 5.0	13.0 ± 8.9
LM (kg)	43.16 ± 9.3	42.48 ± 10.8
LM (%)	71.1 ± 5.2	73.3 ± 8.2
FM (kg)	17.6 ± 5.5	15.0 ± 4.8
FM (%)	28.8 ± 5.2	27.1 ± 9.6
PA°	6.4 ± 0.9	6.1 ± 1.1
SPA	-0.76 ± 1.0	-1.0 ± 1.1
BMR (kcal)	1347 ± 292	1325 ± 338
AC (cm)	27.4 ± 4.0	26.0 ± 4.0
TSF (mm)	10.5 (2.0 - 30.0)[1]	8.0 (3.0 - 28.0)[1]
AMC (cm)	23.5 ± 3.1	23.0 ± 2.8

[1]Values expressed in median (range). BMI: body mass index; LM: lean mass; FM: fat mass; PA: phase angle; SPA: standardized phase angle; BMR: basal metabolic rate; AC: arm circumference; TSF: triceps skinfold; AMC: arm muscle circumference.

The parameters assessed after the intervention (T1) did not differ between groups. However, when comparing each group separately at baseline and after intervention (T0 and T1), it was observed that the patients in C group presented significant weight loss, reduction of BMI, AC, and fat mass (Table 3). In contrast, subjects who received supplements containing EPA maintained weight and lean body mass for as long as four weeks of study; there was a significant reduction only in fat mass percentage.

Weight loss after supplementation was observed in 71% of patients in C group and 41.3 in EPA group. Analysis through logistic regression showed that patients in EPA group had 80% less chance of presenting weight loss when compared to C group (95% CI: 0.045-0.860; OR: 0.19), adjusted for gender, age, staging, and for the patients who had weight loss in the first appointment. However, the average variation of weight loss did not differ significantly between groups (Δ = -1.64 ± 2.7 kg in C group *x* Δ = -0.28 ± 2.7 kg in EPA group), as well as the variation of lean mass (Δ = -0.16 ± 3.2 kg in C group *x* Δ = -0.45 ± 4.3 kg in EPA group). During the intervention period, 47% of the patients in C group, and 33.3% in EPA group presented severe weight loss. The average weight gain did not differ between groups, with an increase of 1.3 ± 0.7 kg in C group and 1.6 ± 0.9 kg in EPA group. The number of meals consumed by the patients increased significantly in groups C and EPA after intervention.

Initially, it was verified that 16.7% of the patients in C group and 22.3% in EPA group presented SPA ≤ -1.65°. After intervention, this percentage increased to 19% in C group and reduced to 18.5% in EPA group (non-significant difference). Regarding the adherence to the supplementation, 70.8% of the patients in C group and 75.9% of the patients in EPA group reported they took the prescribed dose.

DISCUSSION

Data in literature regarding EPA supplementation in patients with oral cavity cancer before starting the oncologic treatment are scarce; most of the researches is limited to evaluating effects of supplementation during the treatment. The main results of this study suggest that the use of nutritional EPA-enriched supplement was able to stabilize body weight and lean mass in the period of 4 weeks, and reduce the chances of weight loss significantly compared to the use of the standard supplement. These findings indicate a promising role of EPA in improving nutritional status in individuals with oral cavity cancer in antineoplastic pretreatment.

These findings could be explained because EPA is able to reduce proteolysis intensity, due to reduction of levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α[33]. EPA is the only dietary component involved in ubiquitin-proteasome pathway regulation, the central focus of lean mass loss. Its administration attenuates the activation of nuclear factor-κ-B transcription, reducing the transcription of subunits of proteasome involved in protein degradation[34].

Among oral cavity cancers, most of them (90%) are squamous cell carcinomas, as highlighted in the present study. They are related to tobacco smoking, alcohol use, or human papillomavirus infections, and tend to affect

Table 3. Anthropometrical parameters and body composition of the C and EPA groups at baseline (T0) and after four weeks of supplementation (T1)

Variables		C (n=24)	Δ	EPA (n=29)	Δ
Weight (kg)	T0	57.2 (40.3 - 86.1)[I]	-1.63 ± 2.71	55.8 (37.5 - 100.0)[I]	-0.21 ± 2.13
	T1	56.4 (34.7 - 80.9)[I]		55.0 (38.7 - 101.1)[I]	
	p-value	**0.019**		0.983	
BMI (kg/m²)	T0	22.6 ± 4.3	-0.59 ± 0.97	20.7 ± 3.4	-0.08 ± 1.00
	T1	22.0 ± 4.7		20.6 ± 3.4	
	p-value	**0.006**		0.639	
LM (kg)	T0	43.1 ± 9.3	-0.16 ± 3.28	42.2 ± 10.8	0.45 ± 4.32
	T1	42.0 ± 9.3		41.7 ± 12.6	
	p-value	0.664		0.594	
LM (%)	T0	70.0 ± 5.5	3.01 ± 8.30	73.7 ± 8.2	0.41 ± 9.50
	T1	73.9 ± 9.6		73.7 ± 14.1	
	p-value	0.111		0.091	
FM (kg)	T0	17.3 ± 5.7	-2.10 ± 4.19	15.0 ± 4.8	-0.28 ± 5.07
	T1	15.3 ± 7.2		14.6 ± 7.4	
	p-value	**0.043**		0.104	
FM (%)	T0	29.0 ± 5.5	-3.00 ± 8.28	27.1 ± 9.6	-1.01 ± 9.79
	T1	26.0 ± 9.5		26.5 ± 14.3	
	p-value	0.112		0.050	
PA°	T0	6.4 ± 0.9	-0.15 ± 1.27	6.1 ± 1.1	-0.10 ± 0.85
	T1	6.3 ± 1.0		6.0 ± 1.0	
	p-value	0.219		0.540	
SPA	T0	-0.7 ± 1.0	-0.47 ± 1.32	-1.09 ± 1.1	0.09 ± 0.94
	T1	-0.8 ± 1.2		-1.1 ± 1.1	
	p-value	0.227		0.216	
AC (cm)	T0	27.4 ± 4.0	-0.63 ± 1.40	26.0 ± 4.0	-0.50 ± 1.42
	T1	26.8 ± 4.5		25.5 ± 3.9	
	p-value	**0.038**		0.068	
TSF (mm)	T0	10.5 (2.0 - 30.0)[I]	-0.45 ± 1.76	8.0 (3.0 - 28.0)[I]	-0.43 ± 2.28
	T1	9.0 (2.0 - 32.0)[I]		8.0 (3.0 - 26.0)[I]	
	p-value	0.217		0.457	
AMC (cm)	T0	23.5 ± 3.1	-0.46 ± 1.39	23.0 ± 2.8	-0.33 ± 1.30
	T1	23.0 ± 3.3		22.7 ± 2.9	
	p	0.118		0.180	

[I]Values expressed in median (range). BMI: body mass index; LM: lean mass; FM: fat mass; PA: phase angle; SPA: standardized phase angle; BMR: basal metabolic rate; AC: arm circumference; TSF: triceps skinfold; AMC: arm muscle circumference.

swallowing and oral feeding[35]. It was observed high percentage of patients who used tobacco and/or alcohol, as well as difficulties in deglutition. These patients present high risk of developing malnutrition.

Stage of the disease is one of the factors that contribute to alterations in body composition and energy expenditure. Studies with patients with head and neck cancer in pretreatment verified that 80 to 100% of those subjects presented advanced staging (III or IV)[13,36,37]. In the current study, this prevalence was 77.3%. The causes of late diagnosis can be explained by poor awareness of self-care, patients unfamiliarity of injuries signs, late access to health services, and socioeconomic conditions.

The weight loss >10% over the 6-months period prior to diagnosis of cancer negatively impacts both short-term mortality and overall survival[38]. In this study, it was found that 45.8% of the patients in the C group and 44.8% in EPA group had lost ≥10% of body weight

within 6-months prior to the diagnosis. Therefore, it is recommended the implementation of the nutritional evaluation early to identify patients' nutritional status and body composition before starting treatment.

The BIA is a practical and non-invasive method of body composition evaluation. The analysis is based on the measurement of total body resistance to an electric current of low amplitude and high frequency, which shows properties such as impedance, resistance, reactance, and phase angle (PA)[39]. Preliminary studies have suggested that low PA obtained by BIA is related to survival in advanced digestive and respiratory cancers. It is used as an indicator of prognosis and survival predictor, and is able to assess the function of the cell membrane. Low values of PA are associated with reduction of cell integrity and lean mass, worse evolution of the disease and higher mortality[26,40].

In the current investigation it was not observed any significant change in PA after nutritional supplementation in both groups, corroborating the study of Sánchez-Lara et al.[15]. Paiva et al.[41] who evaluated populations with head and neck cancer found that PA was an independent predictive factor of mortality for patients under chemotherapy, with an average of 5.2 ± 0.89°.

A limitation found in the use of PA is absence of reference values for specific clinical situations. Thus, Barbosa-Silva et al.[28] proposed the use of standardized phase angle (SPA), which transforms the measurement of PA into a z-score and turns its measurements comparable. In a study with 195 cancer patients in pre-chemotherapy, it was observed that patients with SPA < -1.65° presented higher mortality rates[37,41].

The analysis of SPA evidenced that the percentage of subjects with SPA < -1.65° increased in C group and decreased in EPA group after intervention, however, this difference was not significant. Because it is a prognosis indicator, the impact of the supplementation should be assessed prospectively considering possible outcomes, such as increase of survival or death rates.

Previous studies have reported improvement in nutritional parameters in cancer patients with EPA[13,31]. Although the patients of the EPA group have been able to maintain weight and lean mass during the intervention period, it was not observed lean mass gains. Weed et al.[13] verified that, in patients with pre-surgical head and neck cancer, supplementation with 2.16g EPA for two weeks was able to promote weight and lean mass gains. However, the percentage of initial weight loss experienced by this group of patients was lower than that observed in the present study, which may explain the absence of lean mass gain. Nevertheless, patients in the C group had significant weight loss even after intervention, whereas patients in EPA group maintained their weight.

One of the factors that should be considered when analyzing the results of the present study is the duration of the nutritional intervention, since researches conducted by longer periods have shown satisfactory effects on body composition, especially lean mass gain. Patients supplemented with 1.8g of EPA for three months had significant gains in weight, lean and fat mass, as well as improved levels of albumin, prealbumin, transferrin and lymphocytes[42].

Adherence to the supplementation and intake of the recommended dose should also be considered. It is suggested that intake of 2g/day of EPA is sufficient to promote their anti-inflammatory and anti-cachexia effect[41]. Approximately 24% of the patients in EPA group reported taking less than 80% of the daily recommended dose. In a pilot study by Barber et al.[42], weight and lean mass gains were observed with a dose of 2.1g/day of EPA.

In clinical practice, it is not always possible to reach the recommended dose. Fearon et al.[43] obtained an average consumption of 1.5g/day of EPA which, according to the author, would be insufficient to reach the desired physiological effect. In spite of the lack of expected results, the use of EPA-enriched supplement was positively correlated with weight and lean mass gains in the same study. A study conducted by Bruera et al.[44] has also failed to show significant improvement in weight or body composition after intervention with an average dose of 1.8g of EPA for two weeks.

In order to solve the intake issue, Fearon et al.[31] performed a second, controlled, randomized and double-blind clinical trial to assess the response to two doses of EPA (2g/day and 4g/day) for eight weeks. The results were weight gain in patients who received 2g/day of EPA in comparison to placebo; no additional benefit was found in the supplementation of 4g/day of EPA, ratifying the lack of response to doses superior to 2g/day.

Limitations of the present study include the low number of patients in the sample and non-assessment of plasma EPA incorporation. On the other hand, one of the strengths of this study is that to our knowledge, it is the first to assess the effect of nutritional supplementation with EPA-enriched hypercaloric and hyperproteic formula on the nutritional profile of patients with oral cavity cancer in antineoplastic pretreatment.

CONCLUSION

The use of nutritional EPA (2 g) enriched supplement for four weeks promoted maintenance of body weight and lean body mass in individuals with oral cavity cancer in antineoplastic pre-treatment. It was also observed that these individuals had 80% less chance of losing weight

compared to the control group, which suggests that these individuals may benefit from the use of EPA-enriched hypercaloric and hyperprotein supplements.

It is important to highlight that individuals from both groups showed a significant increase in the number of meals ingested per day, as well as energy and protein intake, demonstrating the need for nutritional guidance and early implementation of nutritional therapy, especially in this population at high risk of malnutrition.

CONTRIBUTIONS

Bruna Cristina dos Santos Cruz, Thayana Calixto de Carvalho and Patrícia Fonseca dos Reis participated of the conception, methodology, investigation, wording, review and editing of the manuscript, resources and supervision. Danúbia da Cunha Antunes Saraiva participated of the review and editing of the manuscript. Adriana dos Santos participated of the investigation. All the authors approved the final version of the manuscript.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

FUNDING SOURCES

This work was supported by the National Cancer Institute Jose Alencar Gomes da Silva.

REFERENCES

1. Cooper JS, Porter K, Mallin K, et al. National Cancer Database report on cancer of the head and neck: 10-year update. Head Neck. 2009;31:748-58. doi: https://doi.org/10.1002/hed.21022
2. Genden EM, Ferlito A, Silver CE, et al. Contemporary management of cancer of the oral cavity. Eur Arch Otorhinolaryngol. 2010;267(7):1001-17. doi: https://doi.org/10.1007/s00405-010-1206-2
3. World Health Organization; International Agency for Research on Cancer. World source: Globocan 2018 [Internet]. Lyon, France: IARC; Oct 2020 [cited 2020 Feb 11]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
4. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil [Internet]. Rio de Janeiro: INCA; 2019 [acesso 2020 fev 11]. Disponível em: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/estimativa-2020-incidencia-de-cancer-no-brasil.pdf
5. Alshadwi A, Nadershah M, Carlson ER, et al. Nutritional considerations for head and neck cancer patients: a review of the literature. J Oral Maxillofac Surg. 2013;71(11):1853-60. doi: https://doi.org/10.1016/j.joms.2013.04.028
6. de Pinho NB, Martucci RB, Rodrigues VD, et al. High prevalence of malnutrition and nutrition impact symptoms in older patients with cancer: results of a Brazilian multicenter study. Cancer. 2020;126(1):156-64. doi: https://doi.org/10.1002/cncr.32437
7. Ravasco P, Monteiro-Grillo I, Vidal PM, et al. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head Neck. 2005;27(8):659-68. doi: https://doi.org/10.1002/hed.20221
8. Bossola M, Pacelli F, Tortorelli A, et al. Cancer cachexia: it's time for more clinical trials. Ann Surg Oncol. 2007;14(2):276-85. doi: https://doi.org/10.1245/s10434-006-9179-5.
9. Rier HN, Jager A, Sleijfer S, et al. The prevalence and prognostic value of low muscle mass in cancer patients: a review of the literature. Oncologist. 2016;21(11):1396-1409. doi: https://doi.org/10.1634/theoncologist.2016-0066
10. Laviano A, Meguid MM, Inui A, et al. Therapy insight: cancer anorexia-cachexia syndrome - when all you can eat is yourself. Nat Clin Pract Oncol. 2005;2(3):158-65. doi: https://doi.org/10.1038/ncponc0112
11. Osland E, Hossain MB, Khan S, et al. Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: a systematic review and meta-analysis. JPEN J Parenter Enteral Nutr. 2014;38(1):53-69. doi: https://doi.org/10.1177/0148607112474825
12. Ottosson S, Zackrisson B, Kjellén E, et al. Weight loss in patients with head and neck cancer during and after conventional and accelerated radiotherapy. Acta Oncol. 2013;52(4):711-8. doi: https://doi.org/10.3109/0284186X.2012.731524
13. Weed HG, Ferguson ML, Gaff RL, et al. Lean body mass gain in patients with head and neck squamous cell cancer treated perioperatively with a protein- and energy-dense nutritional supplement containing eicosapentaenoic acid. Head Neck. 2011;33(7):1027-33. doi: https://doi.org/10.1002/hed.21580
14. Baldwin C, Spiro A, Ahern R, et al. Oral nutritional interventions in malnourished patients with Cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(5):371-85. doi: https://doi.org/10.1093/jnci/djr556
15. Sánchez-Lara K, Turcott JG, Juárez-Hernández E, et al. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. Clin Nutr. 2014;33(6):1017-23. doi: https://doi.org/10.1016/j.clnu.2014.03.006

16. Whitehouse AS, Smith HJ, Drake JL, et al. Mechanism of attenuation of skeletal muscle protein catabolism in cancer cachexia by eicosapentaenoic acid. Cancer Res. 2001; 61(9):3604-9. Cited in: PubMed; PMID: 11325828.

17. Mocellin MC, Pastore e Silva JA, Camargo CQ, et al. Fish oil decreases C-reactive protein/albumin ratio improving nutritional prognosis and plasma fatty acid profile in colorectal cancer patients. Lipids. 2013;48(9):879-88. doi: https://doi.org/10.1007/s11745-013-3816-0

18. Cockbain AJ, Toogood GJ, Hull MA. Omega-3 polyunsaturated fatty acids for the treatment and prevention of colorectal cancer. Gut. 2012;61(1):135-49. doi: https://doi.org/10.1136/gut.2010.233718

19. Murphy RA, Yeung E, Mazurak VC, et al. Influence of eicosapentaenoic acid supplementation on lean body mass in cancer cachexia. Br J Cancer. 2011;105(10):1469-73. doi: https://doi.org/10.1038/bjc.2011.391

20. Pappalardo G, Almeida A, Ravasco P. Eicosapentaenoic acid in cancer improves body composition and modulates metabolism. Nutrition. 2015;31(4):549-55. doi: https://doi.org/10.1016/j.nut.2014.12.002

21. World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva: WHO; 1995. (WHO Technical Report Series, no. 854).

22. Organización Panamericana de la Salud. División de Promoción y Protección de la Salud (HPP). Encuesta Multicentrica salud beinestar y envejecimiento (SABE) em América Latina el Caribe: Informe Preliminar. In: XXXVI Reunión del Comité asesor de investigaciones em Salud; 2001 jun 9-11; Kingston, Jamaica: OPAS, 2002.

23. Instituto Nacional de Câncer José Alencar Gomes da Silva. Consenso nacional de nutrição oncológica [Internet]. 2. ed. rev. ampl. atual. Vol. 2. Rio de Janeiro: INCA; 2016 [acesso 2020 fev 23]. Disponível em: https://www.inca.gov.br/publicacoes/livros/consenso-nacional-de-nutricao-oncologica

24. Conselho Nacional de Saúde (BR). Resolução nº 466, de 12 de dezembro de 2012. Aprova as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Diário Oficial da União, Brasília, DF; 2013 jun. 13. Seção I, p. 59.

25. Conselho Nacional de Saúde (BR). Resolução nº 510, de 7 de abril de 2016. Dispõe sobre as normas aplicáveis a pesquisas em Ciências Humanas e Sociais cujos procedimentos metodológicos envolvam a utilização de dados diretamente obtidos com os participantes ou de informações identificáveis ou que possam acarretar riscos maiores do que os existentes na vida cotidiana, na forma definida nesta Resolução. Diário Oficial da União, Brasília, DF; 2016 maio 24. Seção I, p. 44.

26. Arends J, Bodoky G, Bozzetti F, et al. ESPEN Guidelines on enteral nutrition: non-surgical oncology. Clin Nutr. 2006;25(2):245-59. doi: https://doi.org/10.1016/j.clnu.2006.01.020

27. Guglielmi FW, Contento F, Laddaga L, et al. Bioelectric impedance analysis: experience with male patients with cirrhosis. Hepatology. 1991;13(5):892-5. Cited in: PubMed; PMID: 2029993.

28. Barbosa-Silva MC, Barros AJ, Wang J, et al. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr. 2005;82(1):49-52. doi: https://doi.org/10.1093/ajcn.82.1.49

29. Durnin JV, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Br J Nutr. 1967;21(3):681-9. doi: https://doi.org/10.1079/bjn19670070

30. Frisancho AR. New standards of weight and body composition by frame size and height for assessment of nutritional status of adults and the elderly. Am J Clin Nutr. 1981;40(4):808-19. doi: https://doi.org/10.1093/ajcn/40.4.808

31. Fearon KC, Barber MD, Moses AG, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J Clin Oncol. 2006;24(21):3401-7. doi: https://doi.org/10.1200/JCO.2005.04.5724

32. Gupta SK. Intention-to-treat concept: a review. Perspect Clin Res. 2011;2(3):109-12. doi: https://doi.org/10.4103/2229-3485.83221

33. Dewey A, Baughan C, Dean T, et al. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Cochrane Database Syst Rev. 2007;2007(1):CD004597. doi: https://doi.org/10.1002/14651858.CD004597.pub2

34. Whitehouse AS, Tisdale MJ. Increased expression of the ubiquitin - proteasome pathway in murine myotubes by proteolysis- inducing factor (PIF) is associated with activation of the transcription factor NF-*k*B. Br J Cancer. 2003;89:1116-22. doi: https://doi.org/10.1038/sj.bjc.6601132

35. Fonseca J, Santos CA, Brito J. Malnutrition and clinical outcome of 234 head and neck cancer patients who underwent percutaneous endoscopic gastrostomy. Nutr Cancer. 2016;68(4):589-97. doi: https://doi.org/10.1080/01635581.2016.1158297

36. Malecka-Massalska T, Smolen A, Morshed K. Body composition analysis in head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2014;271(10):2775-79. doi: https://doi.org/10.1007/s00405-013-2815-3

37. Carvalho TMR, Marin DM, Silva CA. Evaluation of patients with head and neck cancer performing standard treatment in relation to body composition, resting metabolic rate, and inflammatory cytokines. Head Neck. 2015;37(1):97-102. doi: https://doi.org/10.1002/hed.23568

38. Datema FR, Ferrier MB, Baatenburg de Jong RJ. Impact of severe malnutrition on short-term mortality and overall survival in head and neck cancer. Oral Oncol. 2011;47(9):910-4. doi: https://doi.org/10.1016/j.oraloncology.2011.06.510

39. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. Eur J Appl Physiol. 2002;86(6):509-16. doi: https://doi.org/10.1007/s00421-001-0570-4

40. Berbigier MC, Pasinato VF, Rubin BA. Bioelectrical impedance phase angle in septic patients admitted to intensive care units. Rev Bras Ter Intensiva. 2013;25(1):25-31. doi: https://doi.org/10.1590/s0103-507x2013000100006

41. Paiva SI, Borges LR, Halpern-Silveira D, et al. Standardized phase angle from bioelectrical impedance analysis as prognostic factor for survival in patients with cancer. Support Care Cancer. 2010;19(2):187-92. doi: https://doi.org/10.1007/s00520-009-0798-9

42. Barber MD, Fearon KC. Tolerance and incorporation of a high-dose eicosapentaenoic acid diester emulsion by patients with pancreatic cancer cachexia. Lipids. 2001;36(4):347-51. doi: https://doi.org/10.1007/s11745-001-0726-4

43. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut. 2003;52(10):1479-86. doi: https://doi.org/10.1136/gut.52.10.1479

44. Bruera E, Strasser F, Palmer JL, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. 2003;21(1):129-34. doi: https://doi.org/10.1200/JCO.2003.01.101

Recebido em 12/2/2020
Aprovado em 28/8/2020