European Review for Medical and Pharmacological Sciences 2013; 17: 1090-1094

A randomized clinical trial with two doses of a omega 3 fatty acids oral and arginine enhanced formula in clinical and biochemical parameters of head and neck cancer ambulatory patients

D.A. DE LUIS, O. IZAOLA, L. CUELLAR, M.C. TERROBA, B. DE LA FUENTE, G. CABEZAS

Institute of Endocrinology and Nutrition, Medicine School and Hospital Rio Hortega, University of Valladolid, Valladolid, Spain

Abstract. – INTRODUCTION: Postsurgical patients with head and neck cancer could have a high rate of ambulatory complications. The aim was to investigate whether oral ambulatory nutrition of head and neck cancer patients with recent weight loss, using two different doses of an omega 3 fatty acids and arginine enhanced diets could improve nutritional parameters.

DESIGN: At Hospital discharge post surgical head and neck cancer patients (n=37) were asked to consume two or three cans per day of a designed omega 3 fatty acid and arginine enhanced supplement for a twelve week period.

RESULTS: Albumin, prealbumin, transferrin and lymphocytes levels improved in both groups. Weight, fat mass and fat free mass improved during supplementation in group II (3 bricks per day). No differences were detected in anthropometric parameters in group I. Gastrointestinal tolerance with both formulas was good, no episodes were reported. There are no differences between both formulas on postsurgical complications rates.

CONCLUSIONS: Omega 3 and arginine enhanced formulas improved blood protein concentrations and lymphocyte levels in ambulatory postoperative head and neck cancer patients. A high dose of arginine and omega 3 fatty acids formula improved weight, too.

Key Words:
Arginine, Omega 3 fatty acids, Head and neck cancer, Surgery.

Introduction

Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications, based on dysfunction of host homeostasis, inflammatory response and defense mechanisms[1].

Although immune impairment in these cases is multifactorial, the immune system may be modulated by specific nutritional substrates such as ω3 fatty acids and arginine[2].

This immune system may be modulated by specific nutritional substrates, such as omega 3 fatty acids[3]. ω3 fatty acids are long-chain polyunsaturated acids that appear to have anti-inflammatory effects. They influence the production of prostanoids from dienoic to the trienoic variety, they alter of which are less immunosuppressive. Administration of omega 3 fatty acids or high purity eicosapentaenoic acid (EPA) capsules has been associated with weight stabilization in patients with pancreatic cancer[4].

Arginine is a semiessential amino acid that may become essential in catabolic situations. Arginine is known to promote T-cell proliferation and generation of lymphokine-activated killer celss[5]. Beneficial effects on wound healing have been reported, making arginine a potential therapeutic agent. Previous studies have demonstrated in head and neck cancer patients an improvement in weight and complications rate with enteral arginine enhanced formulas after surgery[6-7]. Both immunonutrients could produce benefits in these patients.

The aim of our study was to investigate whether oral ambulatory nutrition of head and neck cancer patients with recent weight loss, using two different doses of an omega 3 fatty acids and arginine enhanced diets could improve nutritional parameters.

Material and Methods

Design

The study was a randomized, prospective trial that was carried out between 2009 and 2011. The

Corresponding Author: Daniel A. de Luis, MD; e-mail: dadluis@yahoo.es

study was approved by Ethics Committee of HURH and an informed consent was obtained from each patient prior to the study.

A population of 37 ambulatory post surgical patients with oral and laryngeal cancer with recent loss weight (>5% during previous 3 months) were enrolled and randomized (sealed envelops). In all cases, there was a histologically proven diagnosis of squamous cell carcinoma of head and neck. Exclusion criteria included; severely impaired hepatic function (total bilirubin concentration >3.5 mg/dl) and/or renal function (serum creatinine concentration >2.5 mg/dl), autoimmune disorders and steroids treatment. After Hospital discharge and surgery consisted of complete history taking and physical examination, a general assessment of nutritional status was performed. Measurements of height, body weight, body mass index (BMI: kg/m^2), circumferences and tricep skin fold of the midarm and an additional bioimpedance were measured.

Patient Evaluation

At the initial assessment body weight was measured to an accuracy of 0.01 kg and BMI computed as body weight (kg)/height (m^2). Bipolar body electrical bioimpedance was used to determine body composition[9] (Akern EFG, Florence, Italy). Regional changes in body mass were estimated by measuring the circumferences and tricep skin fold of the midarm.

The following events were monitored: general infections (respiratory tract infection and/or urinary tract infection) and local complications such as fistula and/or wound infection assessed all complications with standard methods by the same investigator. Tolerance of formula was evaluated. Gastrointestinal problems related to enteral feeding were also recorded (diarrhea, nauseas or vomiting episodes).

Nutritional Intervention

At Hospital discharge post surgical head and neck cancer patients were asked to consume two or three cans per day of a specially designed omega 3 fatty acids and arginine enhanced supplement for a twelve week period. Table I shows the composition of this supplement, in group I (2 bricks per day) and group II (3 bricks per day). Total dietary intake was calculated by adding oral supplement consumption to spontaneous food intake, asking to record the number of cans of supplements or parts therefore. One weekend day and two weekdays were studied to account for potential day of the week effects on dietary intake, at baseline (week 0), and weeks 12 were used to assess the patient's dietary intakes. A dietitian instructed patients on how to record food and beverage intake.

Biochemical Assays

Fasting blood samples were drawn for measurement of, albumin (3.5-4.5 g/dl), prealbumin (18-28 mg/dl), transferrin (250-350 mg/dl) (Hitachi, ATM, Mannheim, Germany), and lymphocytes (1.2-3.5.10^3/uL) (Beckman Coulter, Inc, Los Angeles, CA, USA).

Statistical Analysis

A power calculation based on albumin levels improvement was performed. Fifteen patients in each group were necessary to detect an improvement of 1 g/dl, with a p value <0.05 and a power of 80%. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with two tailed paired or unpaired Student's t-test. Non-parametric variables were analyzed with the Friedman and Wilcoxon tests. To minimize the potential for introducing bias, all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis). A p-value < 0.05 was considered statistically significant.

Results

Forty patients were enrolled in the study. There were 20 patients in the group I (two bricks per day of omega 3 fatty acid and arginine enhanced supplement) and 20 patients group II

Table I. Composition of supplement.

	Group I (2 units 227 ml)	Group II (3 units 227 ml)
Total energy (Kcal)	682.0	1023.0
Protein (g)	36	54.3
Free L-arginine (g)	8.4	12.6
Casein	27.8	41.7
Total lipid (g)	18.4	27.6
W6/w3	0.9	0.9
EPA	1.2	1.8
DHA	0.8	1.2
Acid linoleic	1.8	2.7
Carbohydrate (g)	89.4	134.1
Dietary fiber (g)	6.6	9.9

Dietary fiber source: guar gum.

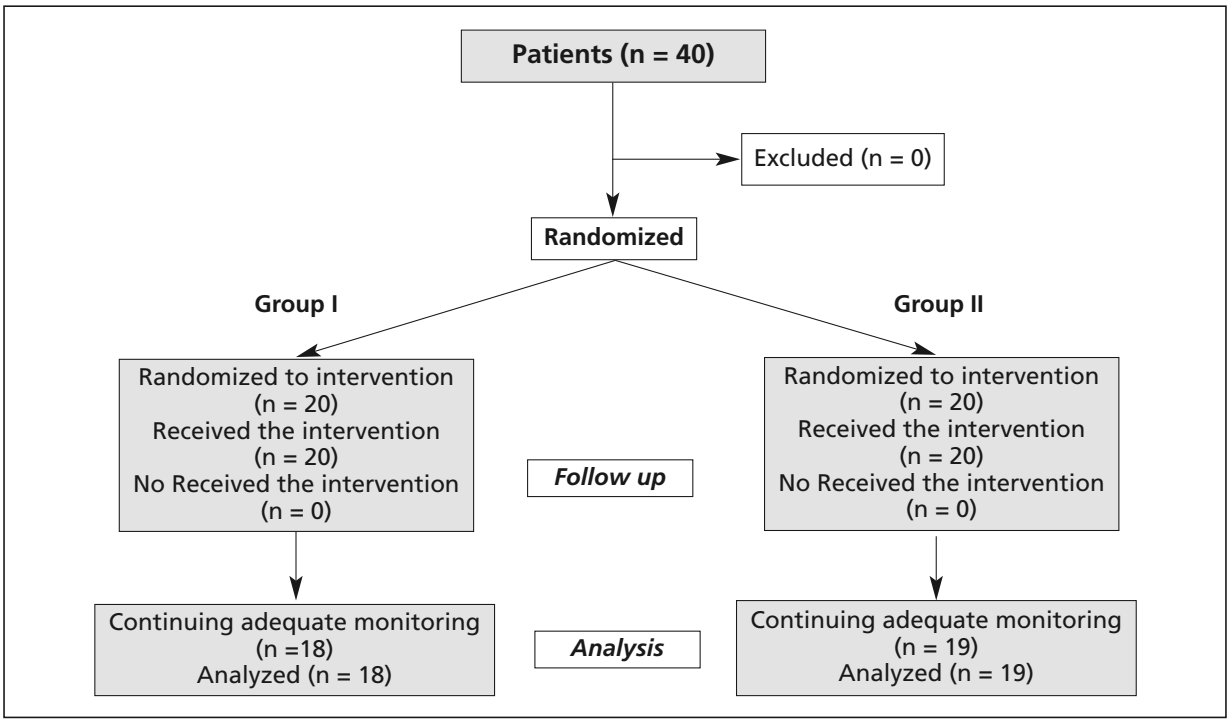

Figure 1. Flow chart.

(three bricks per day os the enhanced supplement), with 3 drop-outs during protocol (1 patients in group I and two patients in group II, due to not attend the scheduled visit (Figure 1, flow chart of protocol). The mean age of the total group was 67.4±13.1 years (7 females/30 males). Characteristics of the patients on enrollment were similar for the two groups. There were no significant differences with regard to gender, mean age, body weight, location and stage of tumor (Table II), reflecting the homogeneity of the analyzed patient. Toxic habits were similar in both groups. Alcohol habit were similar in both groups (group I 22.2% vs. group II 21.1%; ns), no differences were detected in smoking habit (group I 50.0% vs. group II 52.6%; ns).

To assure adherence to study supplementation program, we dispensed enough formula to our patients to provide 2 units per day. The consumption rates of the formula were (group I: 1.6±0.31 bricks/day) and (group II: 2.7 ± 0.22 bricks/day). Duration of supplementation in both groups was similar with an average duration of (group I: 84.2±23.1 days vs. group II: 87.6±20.6 days).

As shown in Table III, albumin, prealbumin, transferrin and lymphocytes levels improved in both groups. Prealbumin levels were lower in group II than group I. This difference was detected in basal and postreatment values.

Weight, fat mass and fat free mass improved during supplementation in group II (3 bricks per day). No differences were detected in anthropometric parameters in group I (Table IV).

There were no drop-outs due to intolerance. Gastrointestinal tolerance (diarrhea episodes) with both formulas was good, no episodes were reported. Oral tolerance (nausea episodes) with both formulas was good, without statistical differences (5.5% vs 10.5%: ns) (1 episode in each group). No vomiting episodes were reported.

Table II. Patients characteristics.

	Group I N = 18	Group II N =1 9
Age (years)	68.2 ± 13.4	66.1 ± 13.5
Women/men	3/15	4/15
Body weight (kg)	71.1 ± 5.8	69.4 ± 9.4
Body mass index	24.7 ± 2.5	25.4 ± 3.3
Disease Stage		
I	0	0
II	2	2
III	6	7
IV	10	10
Diagnosis of disease		
Oral cavity	3	3
Larynx	15	16

No statistical differences.

Table III. Changes in biochemical parameters.

Parameters	Basal	3 months
Albumin (g/dl)		
Group I	3.5 ± 0.4	4.3 ± 0.1*
Group II	3.7 ± 0.4	4.2 ± 0.6*
Prealbumin (mg/dl)		
Group I	31.4 ± 7.1	35.0 ± 5.7*
Group II	22.8 ± 3.4$	26.6 ± 6.2*$
Transferrin (mg/dl)		
Group I	179.0 ± 18.8	231.0 ± 52.3*
Group II	177.7 ± 38.9	231.9 ± 59.2*
Lymphocytes (10^3 uL/$mm^{3)}$		
Group I	2250 ± 634	2625 ± 499*
Group II	1960 ± 598	2320 ± 847*

*($p < 0.05$) with basal values in each group. $($p < 0.05$) statistical differences between groups.

Postoperative infectious complications and wound fistula were not detected. Wound infection was detected in (2 cases of group I (11.1%) and 2 cases of group II (10.5%), without statistical differences.

Discussion

Surgical head and neck cancer patients experience some degree of suppression of the immune function following surgical stress. This alteration makes these patients highly susceptible to infections, and this remains an important contributing factor to clinical and biochemical postoperative outcomes. Our finding shows that these two different doses of an omega 3 fatty acids and arginine enhanced diets improved blood protein concentrations and lymphocyte levels, with a weight improvement in the group with 3 bricks per day. Malnutrition and immunosupression were two factors of head and neck cancer patients[10]. The immune system may be modulated by the use of specific nutritional substrates. Nutrients such as omega-3 fatty acids and arginine that stimulate the cellular defense system may influence outcomes toward a more efficient defense response and, therefore, they may reduce complications in these patients.

There is evidence suggesting that oral nutrition, supplemented with omega 3 fatty acids, improves immune function and reduces postoperative complications, in different group of patients such as pancreatic surgery[11], surgery of stomach and colon-rectum cancer[12], bone marrow transplantation[13], cancer cachexia[14], critically ill patients[15] and head and neck cancer[6-8]. All these studies have been performed during hospital stance, with a short period of enteral nutrition. For example, the use of high dose of arginine enhanced enteral nutrition (20 g per day) in postsurgical patients with head and neck cancer[8] had a benefitial effect on wound complications with a decrease of fistulas. The present design evaluates the effect of these type of formulas on weight of ambulatory head and neck patiens as a supplementation of their oral diet. Both designs are complemtaries to obtain conclusions of this interventional trial with inmunoenhanced formulas.

In our investigation, we analyze ambulatory patients during three months of oral supplementation, with a significant improvement in albumin, prealbumin and transferrin concentrations with both doses (omega 3 fatty acids and arginine enhanced formula), with an improvement in weight with the high doses of omega 3 fatty acids (EPA+DHA 3 g/day) and arginine (12.6 g/day). Our data agree with previous studies in cachectic pancreatic patients suggested that EPA alone at a dose of 2 g/day was associated with weight stability (16), with net gain of lean body mass and an average can consumption of 1.9 cans/day (a dose of 2.1 g/day of EPA). Our average units consumption produced the next EPA intakes (0.95 g EPA in group I and 1.72 g EPA in

Table IV. Evolution of anthropometric parameters.

Characteristics	Group I		Group II	
	Baseline	3 month	Baseline	3 month
Weight (kg)	71.1 ± 5.8	71.3 ± 5.5	69.4 ± 9.4	74.6 ± 8.9*
Fat free mass (kg)	53.2 ± 11.2	52.9 ± 11.1	50.4 ± 11	53.0 ± 8.4*
Fat mass (kg)	19.2 ± 3.7	21.0 ± 4.5	19.3 ± 8.6	21.6 ± 4.5*
TS (mm)	14.1 ± 4.3	15.2 ± 5.6	15.5 ± 5.6	15.6 ± 3.9
MAC (cm)	27.4 ± 3.4	27.7 ± 4.4	27.8 ± 2.4	28.1 ± 1.5

*$p < 0.05$, differences between time 0 and at 3 months in each group. Tricipital skinfold. MAC: Midarm circumference.

group II), with a weight improvement in group II. It, therefore, remains to be tested whether if compliance can be improved there would be an increase in net anabolism with secondary increase in lean body mass and weight. In other study with head and neck cancer patients[17], an intake of an omega 3 enhanced supplements (0.6 g EPA per day) improved protein levels without effect on weight.

Arginine is a non-essential amino acid with a role in the synthesis of nucleotides, polyamines, nitric oxide and proline. Arginine stimulates lymphocyte function and improves wound healing[6]. Riso et al[14] confirmed that an enteral diet supplemented with arginine in the early postoperative period improved postoperative immunological status and speed up recovery from the imunodepression following surgical trauma. Our findings confirm this beneficial effect of an arginine enhanced formula on biochemical parameters at both doses (8.4 and 12.6 g per day).

In a recent systematic review[18], the Authors examined 10 trials that investigated the effects of immunonutrition in patients treated surgically for head and neck cancer. Where stated, all the studies looking at in-hospital postoperative nutrition used arginine as an immunonutrient and improvement in postsurgical complications are reported. Therefore, new studies are needed to evaluate the usefulness of these immunoenhanced formulas in outpatients. Our design has limitations as the lack of a control group receiving a standard isoenergetic and isonitrogenous oral nutrition supplement. Other limitation is the different levels of prealbumin in both groups. However, the data reported by our study are interesting to treat these high risk of undernutrition patients.

Conclusion

At dose taken, omega 3 and arginine enhanced formulas improved blood protein concentrations and lymphocyte levels in ambulatory postoperative head and neck cancer patients. A high dose of arginine and omega 3 fatty acids improved weight, too.

References

1) Arriaga MA, Johnson JT, Kanel KT, Myers EN. Medical complications in total laryngectomy: incidence and risk factors. Ann Otol Rhinol Laryngol 1990; 99: 611-615.
2) Braga M, Gianotti L, Radaelli G. Perioeperative immuno-nutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg 1999; 134: 428-433.
3) Meydani S. Effects of (N-3) polyunsaturated fatty acids on cytokine production and their biological function. Nutrition 1996; 12: 8-12.
4) Beck SA, Smith KL, Tisdale MJ. Anticachectic and antitumour effect of eicosapentaenoic acid and its effect on protein turnover. Cancer Res 1991; 51: 6089-6093.
5) Evoy D, Lieberman M, Fahey TR, Daly J. Immunonutrition, the role of arginine. Nutrition 1998; 14: 611-617.
6) De Luis DA, Izaola O, Aller R, Cuellar L, Terroba MC. Inmunoenhanced enteral nutrition, effect on inflammatory markers in head and neck cancer patients. Eur J Clin 2005; 59; 145-147.
7) De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Aller R. Clinical and biochemical outcomes after a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer patients. Eur J Clin Nutr 2007; 61: 200-204.
8) De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Aller R. High dose of arginine enhanced enteral nutrition in postsurgical head and neck cancer patients. A randomized clinical trial. Eur Rev Med Pharmacol Sci 2009; 13: 279-283.
9) Pichard C, Slosman D, Hirschel B and Kyle U. Bioimpedance analysis: an improved method for nutritional follow up. Clin Res 1993; 41: 53.
10) Riboli E, Kaaks R, Esteve J. Nutrition and laryngeal cancer. Cancer Causes Control 1996; 7: 147-156.
11) Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. Complications of pancreatic surgery and the role of perioperative nutrition. Dig Surg 1999; 16: 320-326.
12) Gianoti L, Braga M, Fortis C, Soldini L, Vignali A, Clombo S, Radaelli G, Di Carlo V. A prospective, randomized clinical trial on perioperative feeding with an arginine, omega-3 fatty acid, and RNA-enriched enteral diet. Effect on host response and nutritional status. J Par Ent Nutr 1999; 23: 314-320.
13) Coghlin-Dickson TM, Wong RM, Offrin RS, Shizuru JA, Johnston LJ, Hu WW, Blume KG. Efetc of oral glutamine suplementation during bone marrow transplantation. J Par Ent Nutr 2000; 24: 61-66.
14) Riso S, Aluffi P, Brugnani M, Farinetti F, Pia F, D'Andrea F. Postoperative enteral immunonutrition in head and neck cancer patients. Clin Nutr 2000; 19: 407-412.
15) Jones CD, Palmer TE, Griffiths RD. Randomized clinical outcome study of criticaly ill patients given glutamine-supplemented enteral nutrition. Nutrition 1999; 15: 108-115.
16) Wigmore SJ, Ross JA, Falconer JS. The effect of polyunsaturated fatty acids. Nutrition 1996; 12: 27-30.
17) Izaola O, de Luis DA, Cuellar L, Terroba MC, Ventosa M, Martin T, Aller R. Influence of an immunoenhanced formula in postsurgical ambulatory patients with head and neck cancer. Nutr Hospi 2010; 25: 793-796.
18) Stableforth WD, Thomas S, Lewis SJ. A systematic review of the role of immunonutrition in patients undergoing surgery for head and neck cancer. Int J Oral Maxillofac Surg 2009; 38: 103-110.