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Effect of three different doses of arginine enhanced enteral nutrition on nutritional status and outcomes in well nourished postsurgical cancer patients: a randomized single blinded prospective trial

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Abstract. – OBJECTIVE: Patients with head and neck cancer undergoing surgery have a high occurrence of postoperative complications. The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using an enhanced enteral formula with three different doses of arginine could improve nutritional variables as well as clinical outcome, depending of arginine dose.

PATIENTS AND METHODS: A population of 84 patients with oral and laryngeal cancer was enrolled. At surgery patients were randomly assigned to three different treatment groups, each one containing at less 28 patients. Group I (28 patients) received an enteral diet supplements with a low physiological dose of arginine (5.7 g per day), group II (28 patients) received an isocaloric, isonitrogenous enteral formula with a medium dose of arginine (12.3 g per day) and group III (28 patients) received an isocaloric, isonitrogenous enteral formula with a high dose of arginine (18.9 g per day).

RESULTS: The length of postoperative stay had a trend to be better with high dose of arginine received (31.9 ± 17.2 days in group I vs 27.8 ± 15.2 days in group II vs 24.8 ± 18.3 days in group III: $p = 0.034$). No differences were detected in postoperative infections complications and diarrhea. Fistula was less frequent in groups II and III than I (10.7% group I vs 3.6% group II vs 3.6% group III: $p = 0.033$), The length of postoperative stay had a trend to be better with high dose of arginine received (31.9 ± 17.2 days in group I vs 27.8 ± 15.2 days in group II vs 24.8 ± 18.3 days in group III: $p = 0.034$).

CONCLUSIONS: Our results suggest that these patients could benefit from a high dose of arginine enhanced enteral formula to decrease length of hospital stay and fistula wound complications.

Key Words:
Argnine, Head and neck cancer, Surgery.

Introduction

Malnutrition is reported in approximately 35% of all head and neck patients[1]. Despite available treatments, the survival of head and neck cancer patients remains disappointing due to persistent or recurrent disease. The incidence of postoperative complications within this population is 20-50%, leading to prolonged hospital stay and poorer prognosis[1]. Malnutrition is one of the factors contributing to this morbidity rates. Patients with head and neck cancer have a high occurrence of postoperative complications including major wound infections, fistula formation, septicaemia and pneumonia. Many patients with head and neck cancer are malnourished because of mechanical obstruction, tumour induced cachexia, poor dietary habits and excessive alcohol consumption[2].

Plasma arginine concentrations are reduced in patients with cancer, indicating that arginine metabolism is disturbed in the presence of a malignancy[3-6]. Arginine enriched nutrition is known to improve outcome, like local wound complications, fistula rates and hospital stay in postoperative head and neck cancer patients[7,8]. Arginine is the most common immunonutrient given to patients with head and neck cancer. It is a non-essential amino acid with a role in the synthesis of nucleotides, polyamines, nitric oxide and proline. Poor nutrition is known to have an adverse impact on outcome in this patient group[9]. These defects combined with the immune suppressive effects of surgery contribute to increased postoperative complications, such as poor wound healing. There is evidence suggesting that enteral nutrition, supplemented with different agents includ-

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ing arginine, improve immune function and reduce postoperative complications[7,8]. The highest dose of arginine used in these clinical studies was 20 g per day with an improvement in wound complications[10]. This high dose has been compared with a medium dose of arginine (12.3 g per day) and fistula was less frequent in high dose of arginine group.

The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using an enhanced enteral formula with three different doses of arginine could improve nutritional variables as well as clinical outcome, depending of arginine dose. As far as we know any protocol has compared three diferent doses of arginine supplementation in this type of patients such as a low physiological dose (4.3 g/day), a medium dose (11.1 g/days) and a high dose (19.6 g/day)

Patients and Methods

Patients

The study was a randomized, single-blinded, prospective trial that was carried out between 2009 and 2011. The study was approved by the local ethics committee. Eighty four patients with head and neck cancer eligible for surgery that entered the Departament of Otolaryngology of our Universitary Hospital were recruited in this nutritional intervention study. In all cases, there was a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharyns or hypopharynx and required major ablative surgery. Patients were excluded from the study if they were previous radiotherapy or chemotherapy, impaired renal function (serum creatinine concentration > 2 mg/dl) or hepatic function (total bilirubin concentration > 3 mg/dl and serum alanine aminotransferase > 100 UI/l), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months and no severely malnourished (weight loss < 10% of body weight). Baseline studies on all patients consisted of complete history taking and physical examination. General assessment of nutritional status included measurements of height, body weight, body mass index (kg/m^2).

Study Intervention

Patients were randomly assigned to three different treatment groups, each one containing at less 28 patients. Group I (28 patients) received an enteral diet supplements with a low physiological dose of arginine (5.7 g per day), group II (28 patients) received an isocaloric, isonitrogenous enteral formula with a medium dose of arginine (12.3 g per day) and group III (28 patients) received an isocaloric, isonitrogenous enteral formula with a high dose of arginine (18.9 g per day). Blinding of patients and dietitians involved in patient treatment was maintained.

Enteral feeding was started within 24 hrs of surgery at a rate of 30 ml/hour, via an intraoperatively placed nasogastric tube. Table I shows the composition of the three enteral diets. Postoperatively, all patients were tube-fed for approximately 10 days, as is the standard hospital procedure. The infusion rate was progressively increased every 24 hrs until the daily nutritional goal (35 total kcal/kg; 1.7 g protein/kg) was reached, on postoperative day 4. All patients reached 100% of calculated requirements. The end point to discontinuing nutritional support was a minimum oral intake of 1700 cal day and 1 g/kg/d of protein with supplementation with a minimum of 10 days of enteral support. No drop-outs were present in the study.

Table I. Composition of enteral diet (per 1000 ml).

	Group I (high dose)	Group II (mediun dose)	Group II (low dose)
Total energy (Kcal)	920	1020	1032
Protein (g)	50.7	49.8	54.9
Free L-arginine	1.7	4.4	8.5
Total lipid (g)	48.8	48.6	49.8
W6/w3	5/1	5/1	5/1
Linoleic acid	10.9	10.2	12.5
α-linolenic acid	2.4	2.3	2.5
Carbohydrate (g)	140.3	135.8	141.1
Dietary fiber (g)	13.8	13.8	14.4

Dietary fiber: (oligofructose, inulin, soy polysaccharide, resistant starch, arabic gum, cellulose).

Clinical and Biochemical Parameters

At basal time and on postoperative day 10, the following parameters were measured: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl), total number of lymphocytes (10^6/ml). The following events were monitored: general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive infiltration, temperature above 38.5ºC and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen) and local complications such as fistula and/or wound infection, assessed all complications with standard methods by the same investigator. Gastrointestinal problems related to enteral feeding were also recorded vomits, nausea and diarrhea (> 5 liquid tools in a 24-hour period or an estimated volume > 1500 mL/d).

Assays

Fasting serum samples were drawn for measurement of, albumin (3,5-4,5 g/dl), prealbumin (18-28 mg/dl), transferrin (250-350 mg/dl) with an autoanalyzer (Hitachi, ATM, Manheim, Germany). Lymphocytes (1.2-3.5.10^3/uL) were analyzed with an analyzer (Beckman Coulter Inc., Los Angeles, CA, USA).

Statistical Analysis

Sample size was calculated to detect differences of 20% on incidence of wound complication with 80% power and 5% significance. For descriptive purposes, we used median and standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with two tailed paired Student's *t*-test and ANOVA test, as needed. Non-parametric variables were analyzed with the H Kruskal-Wallis 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 under 0.05 was considered statistically significant.

Results

Sixty patients were enrolled in the study. The mean age was 61.9±10.7 years (21 females/63 males). There were 28 patients in the group I (high arginine-enhanced formula), 28 patients in the control diet group II (medium arginine-enhanced formula) and 28 patients in the control diet group II (low arginine-enhanced formula). Characteristics of the patients on enrolment were similar for the two groups, reflecting the homogeneity of the patient population under study (Table II).

Patients had the same % preoperatively weight loss (group I 4.4% vs 4.6% group II vs 4.5% group III; ns). Twenty seven patients underwent resection of a tumor located in the oral cavity with unilateral or bilateral neck dissection; 57 patients underwent laryngectomy (total or partial) or pharyngo-laryngectomy, with the same distributions of surgery in the three groups.

As shown in Table III, no significant intergroup differences in the trend of lymphocytes

Table II. Patients characteristics.

	Group I	Group II	Group III
Age (years)	63.1 ± 11.6	62.9 ± 10.4	62.7 ± 10.1
Men/women	19/9	22/6	22/6
Body weight (kg)	70.9 ± 15.1	71.3 ± 12.9	71.1 ± 11.8
Body mass index	25.4 ± 5.1	25.6 ± 4.1	25.2 ± 4.4
Disease Stage			
I	0	0	0
II	7	6	8
III	10	9	8
IV	11	13	12
Diagnosis of disease			
Oral cavity	10	8	9
Larynx	18	20	19

No statistical differences.

Table III. Visceral serum protein and anthropometric parameters.

Parameters	Baseline	Day 10
Albumin (g/dl)		
Group I	3.2 ± 0.4	3.0 ± 0.6
Group II	3.1 ± 0.6	3.1 ± 0.3
Group III	3.3 ± 0.7	3.1 ± 0.7
Prealbumin (mg/dl)		
Group I	17.7 ± 7.5	25.4 ± 5.3*
Group II	20.5 ± 8.3	22.0 ± 9.4*
Group III	20.2 ± 7.5	24.4 ± 9.8*
Transferrin (mg/dl)		
Group I	163.8±45.1	186.5 ± 39*
Group II	177.5±38.8	202 ± 38.2*
Group III	177.0±48.8	202 ± 38.2*
Lymphocytes (10^3 uL/mm^3)		
Group I	1191.7 ± 560.7	1647.8 ± 555.1*
Group II	1411.1 ± 849.8	1785.6 ± 807.7*
Group III	1415.6 ± 571.1	1910.9 ± 724.2*
Weight (kg)		
Group I	70.9 ± 15.1	70.8 ± 13.7
Group II	71.3 ± 12.9	71.2 ± 12.6
Group III	71.1 ± 11.8	71.0 ± 10.2

*($p < 0.05$) with baseline values.

and the three serum proteins were detected. Prealbumin, transferrin and lymphocytes count increased. No differences were detected in weight change.

Statistical differences were detected in local complications, fistula diagnosed by X-ray was less frequent in groups I and II than III (3.6% group I vs 3.6% group II vs 10.7% group III: $p = 0.033$), wound infection was equal in all groups (0% group I vs. 3.6% group II vs. group III 0%: ns). The postoperative infections complications (urinary tract and pneumonia with similar distribution) were similar in all groups (10.7% group I vs. 7.2% group II vs. group III 7.2%: ns).

The length of postoperative stay had a trend to be better with high dose of arginine received (24.8±18.3 days in group I vs 27.8 ± 15.2 days in group II vs 31.9 ± 17.2 days in group III: $p = 0.034$). No patients died in the hospital postoperative course.

Gastrointestinal tolerance (diarrhea) of three formulas was good, with no intergroup differences (7.1% group I vs. 10.7% group II vs. 7.1% group III: ns). There were no dropouts due to intolerance.

Discussion

The main result of our study is a significant decrease of fistula complications in patients treated with the high arginine dose enhanced formula and a reduced length of hospital stay. All formulas improved transferrin and prealbumin levels and were well tolerated.

Patients with head and neck cancer experience some degree of suppression of the cellular defense function following surgical stress. This alteration in the host defense mechanism makes these patients susceptible to infections, wound surgical complications and this remains an important factor to poorer clinical postoperative outcomes. Nutrients such as arginine, that stimulate the cellular defense system toward a more efficient defense response and, therefore, they may reduce postsurgical complications in these patients[11]. Casas-Rodera et al[12] compared postoperative arginine enhanced enteral formula with a control formula in head and neck cancer patients, and they found no significant intergroup differences in albumin and prealbumin. On the other hand, they demonstrated more frequent wound and general infections in the control group. Felekis et al[13] found a statistically significant difference in major complications between patients receiving an arginine ehnaced formula thatn other inmunoenhanced formula. Other group[14] reported that head and neck cancer patients with weight loss exceeding 10% during the last 6 month before surgery are at a great risk of the occurrence of major complications. De Luis et al[8] studied clinical outcomes in post postsurgical head and neck cancer patients after supplementation with a high dose of enteral arginine formula (20 g per day) and found that would be complications were less frequent in the enriched nutrition group compared to the controls.

Stableforth et al[15] examined 10 trials that investigated the effects of immunoenhanced enteral formula with arginine in patients treated surgically for head and neck cancer. A reduction in the length of postoperative hospital stay was seen, but the reason for this reduction is not clear. Length of hospital stay was reduced in all six studies where it was recorded[6,7,16-19]. Overall reduction corresponded to about a 3.5 day, which is clinically important. In our study, the decrease of the average stay of less arginine formula versus formula with more arginine was 7.1 days, and comparing the formula with arginine intermediate dose versus high dose of arginine, the reduc-

tion in the hospital stay was 4.2 days. The reduced length of hospital stay could not be explained by reduced clinical complications[16], the reason of this redution is not clear. The reduction of fistula formation could be a hypothesis[3,8,19], as our present data show. However, in two studies, fistula formation was more common in those patients receiving immunonutrition, yet length of hospital stay was reduced[17,18]. Many potential complications such as pneumonia, urinary infections or diarrhoea, could explain this relationship of arginine immunoenhanced formula and length of hospital stay, but in our study these complications were similar in all interventional groups.

This diversity of results could be explained by the heterogeneity of the interventions and the type and stage of cancers studied[20,21]. Different dietary interventions may not have an equal effect, or even the same direction of effect, for different cancer sites and stages or amount of arginine. The importance of this arginine immunoehnanced formula has recently demonstrated[22]. In this study[22], the group receiving arginine-enriched nutrition had a significantly better overall survival, better disease-specific survival and a significantly better locoregional recurrence-free survival.

Conclusions

A high enriched arginine formula improves fistula wound complications in postoperative well nourished head and neck cancer patients compared with a low enriched formula. Our results suggest that these patients could benefit from a high dose of arginine enhanced enteral formula to decrease length of hospital stay. However, a suitable powered clinical trial is required before firm recommendations can be made on the use of immunonutrition in head and neck cancer patients postoperatively. Further studies to assess the financial impact of this type of enteral feeding are needed.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Linn B, Robinson D, Klimas N. Effects of age and nutritional status on surgical outcomes in head and neck cancer. Ann Surg 1988; 207: 267-273.

2) 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.

3) Chiarla C, Giovannini I, Siegel JH. Plasma arginine correlations in trauma and sepsis. Amino Acids 2006; 30: 81-86.

4) Lind DS. Arginine and cancer. J Nutr 2004; 134: 837S-2841S.

5) Vissers YLJ, Dejong CHC, Luiking YC, Fearon KCH, von Meyenfeldt MF, Deutz NEP. Plasma arginine concentrations are reduced in cancer patients: evidence for arginine deficiency? Am J Clin Nutr 2005; 81: 1142-1146.

6) Zea AH, Rodriguez PC, Atkins MB, Hernandez C, Signoretti S, Zabaleta J, McDermott D, Quiceno D, Youmans A, O'Neill A, Mier J, Ochoa AC. Arginase-producing myeloid suppressor cells in renal cell carcinoma patients: a mechanism of tumor evasion. Cancer Res 2005; 65: 3044-3048.

7) De Luis DA, Izaola O, Aller R, Cuellar L, Terroba MA. Randomized clinical trial with an enteral arginine-enhanced formula in early postsurgical. Eur J Clin Nutr 2004; 58: 1505-1508.

8) 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.

9) Zogbaum AT, Fitz P, Duffy V. Tube feeding may improve adherence toradiation treament schedule in head and neckncancer. Topics Clin Nutr 2004: 19: 95-106.

10) De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Aller R. High dose of arginine enhanced enteral nutrition in postsurgical head an neck cancer patients. A randomized clinical trial. Eur Rev Med Pharmacol Sci 2009; 13: 279-283.

11) Daly JM, Reynolds J, Thom A. Immune and metabolic effects of arginine in the surgical patients. Ann Surg 1998; 208: 521-523.

12) Casas-Rodera P, Gomez-Candela C, Benitez S, Mateo R, Armero M, Culebras JM. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. Nutr Hosp 2008; 23: 105-110.

13) Felekis D, Eleftheriadou A, Papadakos G, Bosinakou I, Ferekidou E. Effect of perioeprative innumo-enhanced enteral nutrition on inflammatory response, nutritional status, an outcomes in head and neck cancer patients indergoing major surgery. Nutrition and Cancer 2009: 62: 1105-1112.

14) Van Bokhorst-de Van Der Schueren M, Van Leeuwen P, Sauerwein H, Kuik D, Snow G. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. Head Neck 1997; 19: 419-425.

15) Stableforth WD, Thomas S, Lewis SJ. A systematic review of the tole of immunonutrition in patients undergoing surgery for head and neck cancer. Int J Oral Maxillofac Surg 2009; 38: 103-110.

16) Snyderman CH, Kachman K, Molseed L, Wagner R, D Amico F, Bumpous J, Rueger R. Reduced postoperative infections with an immne-enhancing nutritional supplement. Laryngoscope 1999; 109: 915-921.

17) Riso S, Aluffi P, Brugnani M, Farinetti F, Pia F, Dandrea F. Postoperative enteral immunonutrition in head and neck cancer patients. Clin Nutr 2000; 19; 407-412.

18) Van Bokhorst-de van der Schueren MA, Quak JJ, Von Blomberg-van der Flier ME, Kuik DJ, Langendoen SI, Snow GB, Green CJ, van Leeuwen PAM. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. Am J Clin Nutr 2001; 73; 323-332.

19) De Luis DA, Izaola O, Aller R, Cuellar L, Terroba MC. Postsurgery enteral immunonutrition in head and neck cancer patients. Eur J Clin Nutr 2002; 56: 1126-1129.

20) Buijs N, van Bokhorst-de van der Schueren M, Langius JAE, Rene Leemans C, Kuik DJ. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. Am J Clin Nutr 2010; 92: 1151-1156.

21) de Luis DA, Izaola O, Cuellar L, Terroba MC, de la Fuente B, Cabezas G. 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. Eur Rev Med Pharmacol Sci 2013; 17: 1090-1094

22) de Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Ventosa M. A randomized double-blind clinical trial with two different doses of arginine enhanced enteral nutrition in postsurgical cancer patients. Eur Rev Med Pharmacol Sci 2010; 14: 941-945.