

# High dose of arginine enhanced enteral nutrition in postsurgical head and neck cancer patients. A randomized clinical trial

D.A. DE LUIS, O. IZAOLA, L. CUELLAR, M.C. TERROBA, T. MARTIN, R. ALLER\*

Institute of Endocrinology and Nutrition, Medicine School and Hospital Rio Hortega;

\*Hospital Clinico, University of Valladolid, Valladolid (Spain)

**Abstract. – Objective:** Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications. The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using a higher dose of arginine (20 g per day) could improve nutritional variables.

**Materials and Methods:** A population of 72 patients with oral and laryngeal cancer was enrolled. At surgery patients were randomly allocated to two groups: a) patients were receiving an enteral diet supplements with arginine and fiber (group I); b) patients were receiving an isocaloric, isonitrogenous enteral formula (group II).

**Results:** No significant intergroup differences in the trend of the three serum proteins and lymphocytes were detected. Gastrointestinal tolerance (diarrhea) of both formulas was good (7.89% group I and 5.88% group II: ns). The postoperative infections complications were similar in both groups (23.6% group I and 20.6% group II: ns). Fistula was less frequent in enriched nutrition group (5.2% group I and 17.6% group II:  $p=0.026$ ). The length of postoperative stay was better  $24.3\pm 14$  days in the immunonutrition group than  $36.1\pm 27$  days in the control group ( $p=0.036$ ).

**Conclusions:** Enriched formula improves local wound complications in postoperative head and neck cancer patients and decreases length of stay.

*Key Words:*

Enteral nutrition, Head and neck cancer, surgery.

## Introduction

Each year, 500,000 new cases of head and neck cancer are diagnosed world-wide, with

over 40,000 new cases in the United States alone. In addition to mortality, head and neck cancer causes significant morbidity related to problems with poor nutrition, decreased communication, pain and decreased general functional. Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications<sup>1</sup>. These complications include anastomotic fistula, wound infection, major complications such as septicemia, and may lead a prolonged hospital stay.

It is known that immune system is frequently affected in these patients. Also, surgery and malnutrition have been found to depress the immune system<sup>2</sup>. The alterations in the host defense mechanism make the patients susceptible to above-mentioned complications. Although immune dysfunction could be multifactorial, the immune system may be modulated by specific nutritional substrates, such as arginine<sup>3</sup>. There is evidence suggesting that enteral nutrition, supplemented with different agents including arginine, improve immune function and reduces postoperative complications, in different groups of patients such as surgery of stomach and colon-rectum cancer<sup>4,5</sup>, pancreatic surgery<sup>6</sup>, postsurgical head and neck cancer patients<sup>7-10</sup> and critically ill patients<sup>11</sup>. The highest dose of arginine used in these clinical studies was 17 g per day. However, gastrointestinal tolerance of higher dose of arginine than 17 g per day could be a problem and the potential benefits could be minors.

The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using a higher dose of arginine (20 g per day) could improve nutritional variables as well as clinical outcomes, when compared with an isonitrogenous and isocaloric control enteral diet.

## Material and Methods

### Patients

A population of 72 patients with oral and laryngeal cancer was enrolled. Exclusion criteria included: severely impaired renal function (serum creatinine concentration >2.5 mg/dl) and hepatic function (total bilirubin concentration >3.5 mg/dl and serum glutamic pyruvate >150 UI/l), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months and severely malnourished (weight loss <10% of body weight). The study was a prospective randomized trial carried out from January 2006 to December 2007. The study has been approved by the local Ethics Committee. Baseline studies on all patients consisted of complete history taking and physical examination. General assessment of nutritional status included measurements of height, body weight, BMI (kg/m<sup>2</sup>).

### Nutrition

At surgery patients were randomly allocated to two groups: a) 38 patients received an enteral diet supplements with arginine (group I); b) 34 patients received an isocaloric, isonitrogenous enteral formula (group II). Main investigator and patients remained blind to the treatment group. Table I shows the composition of the two enteral diets. Enteral feeding was started within 24 hours of surgery at a rate of 30 ml/h, via an intraoperatively placed nasogastric tube. The infusion rate was progressively increased every 24 hrs until the daily nutritional goal (32 total kcal/kg; 1.7 g

protein/kg) was reached, on postoperative day 4. All patients reached 100% of calculated requirements. Any drop outs were present in the study. The end point to discontinuing nutritional support was a minimum oral intake of 1700 cal day and 1 g/kg/day of protein with supplementation with a minimum of 10 days of enteral support.

In all patients, prophylactic antibiotic treatment was given for 7 days postoperatively (cef-tazidime, 500 mg tid i.v. and clyndamicine 300 mg tid i.v.).

### Patient Monitoring

Perioperatively and on postoperative day 10, the following parameters were recorded: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl), total number of lymphocytes (10<sup>6</sup>/ml). Postoperative complications were registered as none, general infections (urinary tract infection was diagnosed if the urine culture showed at least 10<sup>5</sup> colonies of a pathogen and/or respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive infiltration, temperature above 38,5°C and isolation of pathogens from the sputum or blood culture) 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 (diarrhea, >5 liquid stools in a 24-hour period or an estimated volume >2000 mL/d).

### Assays

Fasting serum samples were drawn for measurement of albumin (3,5-4,5 gr/dl), prealbumin (18-28 mg/dl), transferrin (250-350 mg/dl) with an autoanalyzer (Hitachi, ATM, Mannheim, Germany). Lymphocytes (1.2-3.5.10<sup>3</sup>/μL) were analyzed with an analyzer (Beckman Coulter Inc., LA, CA).

### Statistical analysis

Sample size was calculated to decrease 20% of wound complication with 80% power and 5% significance. The results were expressed as mean ± SD. 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, as needed and analysis of variance (ANOVA). Non-parametric variables were analyzed with the Friedman and Wilcoxon tests. To minimize the potential for introducing bias, all ran-

**Table I.** Composition of enteral diet (per 100 ml).

	Group I (immunonutrition)	Group II (standard)
Total energy(Kcal)	125	125
Protein (g)	6.22	6.25
Free L-arginine	0.85	–
Casein	5.595	6.25
Total lipid (g)	4.86	4.86
W6/w3	5/1	5/1
Linoleic acid	1.18	1.25
α-linolenic acid	0.23	0.25
Carbohydrate (g)	13.58	14.11
Dietary fiber (g)	0.9	–

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

domized 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

Seventy two patients were enrolled in the study. The mean age was 62.3±11.3 years (15 females/57 males). There were 38 patients in the group I (arginine-enhanced formula) and 34 patients in the control diet group II. Epidemiological data of the patients on enrollment were similar for the two groups, reflecting the homogeneity of the patients. There were no significant differences with regard to gender, mean age, body weight, location and stage of tumor (Table II).

Patients had the same % preoperatively weight loss (group I 4.3% vs 4.7% group II; ns). Twelve patients underwent resection of a tumor located in the oral cavity with unilateral or bilateral neck dissection. Fifty patients underwent laryngectomy (total or partial) or pharyngo-laryngectomy, with the same distributions of surgery in group I and II.

As shown in Table III, no significant intergroup differences in the trend of the three serum proteins and lymphocytes were detected. No differences were detected in weight.

Gastrointestinal tolerance (diarrhea) of both formulas was good, with no intergroup differences (7.89% group I and 5.88% group II: ns). There were no drop outs due to intolerance.

**Table II.** Patients characteristics.

	Group I	Group II
Age (years)	63.1 ± 13	61.2 ± 9.9
Men/women	30/8	27/7
Body weight (kg)	72.6 ± 13.7	70.9 ± 12.1
BMI	26.5 ± 5.1	26.4 ± 4.6
Disease stage		
I	0	0
II	4	3
III	5	5
IV	29	26
Diagnosis of disease		
Oral cavity	7	5
Larynx	31	29

No statistical differences.

**Table III.** Visceral serum protein and anthropometric parameters.

Parameters	Baseline	Day 10
Albumin (g/dl)		
Group I	2.6 ± 0.53	2.9 ± 0.6*
Group II	2.7 ± 0.6	3.1 ± 0.5*
Prealbumin (mg/dl)		
Group I	15.9 ± 7.8	21.6 ± 8.6*
Group II	14.9 ± 6.5	20.7 ± 6.5*
Transferrin (mg/dl)		
Group I	161.1 ± 44	192.4 ± 51*
Group II	163.6 ± 44	201 ± 40.2*
Lymphocytes (10 <sup>3</sup> µL/mm <sup>3</sup> )		
Group I	1179 ± 408	1658 ± 756*
Group II	1253 ± 61	1592 ± 613*
Weight (kg)		
Group I	72.6 ± 13.7	71.8 ± 13.4
Group II	70.9 ± 12.1	70.8 ± 12.6

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

The postoperative infections complications (urinary tract and pneumonia with similar distribution) were similar in both groups (23.6% group I and 20.6% group II:ns). Statistical differences were detected in local complications, fistula diagnosed by X-ray was less frequent in enriched nutrition group (5.2% group I and 17.6% group II: *p*=0.026), wound infection was equal in both groups (2.63% group I and 2.9% group II:ns)

The length of postoperative stay was better 24.3±14 days in the immunonutrition group than 36.1±27 days in the control group (*p*=0.036).

### Discussion

The main result of our study is a significant decrease of fistula complications and length of stay in patients treated with the arginine enhanced formula.

Malnutrition and immunosuppression were two characteristics of head and neck cancer patients<sup>12</sup>, malnutrition is reported in 50% of these patients<sup>13</sup>. Malnutrition is due to reduced dietary intake secondary to dysphagia and alcohol consumption<sup>14</sup> and secondary to interleukins secreted by tumor with catabolic action played a dominant role<sup>15</sup>. Immunosuppression is related with surgery and immunosuppressive capacity of the tumor<sup>16</sup>. For example, Van Bokhorst-de van der

Schueren et al<sup>17</sup> have reported that patients with head and neck cancer and weight loss exceeding 10% during the six months before surgery are at great risk of the occurrence of major complications. Patients may be malnourished because of the disease and their pre-morbid lifestyle, while the adverse effects of treatment almost always exacerbate the problem<sup>18</sup>.

Nutritional support is an essential component of head and neck cancer management and enteral feeding is the method of choice<sup>19</sup>. Polymeric formulas are suitable for head and neck cancer patients, considering that the gastrointestinal tract distal to the oropharynx is usually normal and the digestion and absorption functions are intact. Various studies demonstrate that the early use of enteral feedings during the head and neck cancer treatment reduces the weight loss, malnutrition, dehydration and the associated need for hospitalization or treatment interruption<sup>20-22</sup>. Newer, so-called immune enhancing nutritional formulas incorporate substances such as arginine, nucleic acids and fish-oil derived n-6 polyunsaturated fatty acids (PUFA). There is some evidence that this type of supplement can reduce the incidence of postoperative infectious complications compared with standard formulas<sup>23</sup>. However, only a few studies have analyzed the immunonutrition formula with arginine used in our study. Rios et al<sup>24</sup> confirmed that an enteral diet supplement with arginine in the early postoperative period improved postoperative immunological status and speed up recovery from the immunodepression following a surgical trauma. On malnourished patients of this study, the administration of an enriched formula reduced major postoperative complications and length of postoperative stay significantly. In our study, length of stay was better in enriched formula group and wound complications (fistula) were also improved in our patients. Snyderman et al<sup>23</sup> showed that a perioperative nutritional supplementation with an immune-enhancing formula was superior to standard formula in the prevention of postoperative infectious complications. There was no significant difference in wound healing problems or duration of hospitalization. Higher serum of albumin was demonstrated in enriched formula group compared with standard formula. Caparros et al<sup>11</sup> observed in critically ill patients with a diet enriched with arginine and fiber a decrease in catheter-related sepsis rate. In our study with better nourished patients than reported in previous studies, no differences were detected in postoper-

ative infections complications and serum proteins improved with standard and immune-enhancing formula without differences. We don't have a clear explanation to this early improvement in serum proteins in both groups. In other study an arginine supplemented formula<sup>25</sup> did not significantly improve nutritional status, reduce the immune suppression, or affect clinical outcome. However, only nine days of postoperative tube feeding was used in this study, whereas our patients received an average of 30 days of enteral nutrition.

Arginine stimulates anabolic hormone release, improves survival in gut-derived sepsis and peritonitis by modulating bacterial clearance and has been demonstrated to enhance natural killer cell cytotoxicity, increase T-cell proliferation, and accelerate wound healing<sup>26</sup>. Arginine-supplemented enteral formulas may have a beneficial effect on wound healing as a primary therapy. Other strategies to decrease fistula rates have been demonstrated poor results. Primary tracheoesophageal puncture after total laryngectomy with primary pharyngeal closure showed similar rate for fistula rate than other strategies<sup>27</sup>.

In conclusion, enriched formula improves local wound complications in postoperative head and neck cancer patients and decreases length of stay. Our results suggest that these patients could benefit from an arginine enhanced enteral formula.

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