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ORIGINAL ARTICLE

Clinical and biochemical outcomes after a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer patients

DA de Luis[1], O Izaola[1], L Cuellar[1], MC Terroba[1], T Martin[1] and R Aller[2]

[1]*Medicine School and Unit of Investigation, Institute of Endocrinology and Nutrition, Hospital Rio Hortega, University of Valladolid, Valladolid, Spain and* [2]*Hospital Rio Hortega, Hospital Clinico, University of Valladolid, Valladolid, Spain*

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-enhanced diet (17 g/day) than previous studies, could improve nutritional variables as well as clinical outcomes, when compared with a control enteral diet.
Design: Randomized clinical trial.
Setting: Tertiary care.
Subjects: A population of 72 patients with oral and laryngeal cancer was enrolled.
Interventions: At surgery, patients were randomly allocated to two groups: (a) 35 patients receiving an arginine-enhanced formula with arginine (group I) and (b) 37 patients receiving an isocaloric, isonitrogenous enteral formula (group II).
Results: No significant intergroup differences in the trend of the three plasma proteins (albumin, transferrin, prealbumin) and lymphocytes were detected. Episodes of diarrhea rate were equal in both groups (22.8% group I and 21.6% group II: NS). The postoperative infections complications were equal in both groups (5.7% group I and 5.4% group II: NS). Fistula (wound complication) was less frequent in enriched nutrition group (2.8% group I and 18.9% group II: $P<0.05$), whereas wound infection was similar in both groups. The length of postoperative stay was similar in both (27.9 ± 21 vs 28.2 ± 12 days; NS).
Conclusions: At this dose, arginine-enhanced formula improves fistula rates in postoperative head and neck cancer patients without a high rate of diarrhea.
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Introduction

Patients with head and neck cancer undergoing surgery have a high incidence of local postoperative complications (anastomotic fistula) and wound infections (Arriaga *et al*., 1990) and have a lot of problems in swallow function and perception of dysphaghia (De Luis *et al*., 2000; Pauloski *et al*., 2002).

Correspondence: Dr DA de Luis, Medicine School and Unit of Investigation, Institute of Endocrinology and Nutrition, Hospital Rio Hortega, Valladolid University, C/Los perales 16 (Urb Las Aceñas), Simancas, Valladolid 47130, Spain. E-mail: dadluis@yahoo.es
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It is known that immune system is frequently affected in these patients. Also, surgery and malnutrition have been found to depress the immune system (Van Bokhorst-de van der Schueren *et al*., 1998). The alterations in the host defence mechanism make patients susceptible to above-mentioned complications. A role for nutrition therapy in the regulation of wound healing has been predicted on two concepts. The first is that malnutrition increases the risk of wound-related complications. The second is that dietary intervention can improve or accelerate the wound-healing response. Although immune dysfunction could be multifactorial, this immune system may be modulated by specific nutritional substrates, such as arginine (Daly *et al*., 1998). There is evidence suggesting that enteral nutrition (Weil *et al*., 2005), supplemented with different agents including arginine and dietary fiber, improves immune function and reduces postoperative complications, in different groups of patients such as pancreatic surgery (Di Carlo *et al.,* 1999), surgery of stomach and colorectum cancer (Gianoti *et al.,* 1999; Wu *et al.,* 2001) and critically ill patients (Caparros *et al.,* 2001). Our group has demonstrated, in a previously randomized clinical trial, a decrease in local complications of postsurgical patients with head and neck cancer (de Luis *et al.,* 2002, 2004). In the first study, differences in formulas were arginine and dietary fiber contents, perhaps fiber had a role in detected differences. In the second study, the design did not have differences in fiber amount, an arginine-enhanced formula (12 g/day of arginine) was better than an isocaloric formula in local complications. However, gastrointestinal tolerance of arginine could be a problem with high doses of arginine.

The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using a higher dose of arginine (17 g/day)-enhanced diet than previous studies, could improve nutritional variables as well as clinical outcomes, when compared with a control enteral diet.

Materials and methods

Patients

A population of 72 patients with oral and laryngeal cancer was enrolled. Exclusion criteria included: severely impaired hepatic function (total bilirubin concentration >3.5 mg/dl and serum glutamic pyruvate >150 UI/l) and renal function (serum creatinine concentration >2.5 mg/dl), 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 October 2003 to December 2005. Baseline studies on all patients consisted of complete history taking and physical examination. General assessment of nutritional status included measurements of height, body weight and body mass index (BMI) (kg/m^2).

Nutrition

At surgery, patients were randomly allocated to two groups: (a) 35 patients received an enteral diet supplements with arginine (group I) and (b) 37 patients received an isocaloric, isonitrogenous enteral formula (group II). Table 1 shows the composition of the two enteral diets. Enteral feeding was started within 8–12 h of surgery at a rate of 20 ml/h, via an intraoperatively placed nasogastric tube. The infusion rate was progressively increased every 24 h until the daily nutritional goal (32 total kcal/kg; 1.7 g protein/kg) was reached, on postoperative day 4 with 17 g/day of arginine. All patients reached 100% of calculated requirements. No drop-outs were present in the study. The end point to discontinuing nutritional support was a minimum oral intake of 1500 kcal/day and 1 g/kg/day of protein without supplementation with a minimum of 10 days of enteral support.

Table 1 Composition of enteral diet (per 100 ml)

	Group I (arginine-enhanced)	*Group II (standard)*
Total energy (kcal)	100	125
Protein (g)	5.5	6.25
Free L-arginine	0.85	—
Casein	4.1	6.25
Total lipid (g)	3.3	4.86
W6/w3	5/1	5/1
Linoleic acid	1.18	1.25
α-Linolenic acid	0.23	0.25
Carbohydrate (g)	12.5	14.11
Dietary fiber (g)	0.9	0.9

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

In all patients, prophylactic antibiotic treatment was given for 7 days postoperatively (ceftazidime, 500 mg t.i.d. intravenously (i.v.) and clyndamicine 300 mg t.i.d. i.v.).

Anthropometric measurements

Body weight was measured to an accuracy of 0.5 kg and BMI computed as body weight/(height^2). Bipolar body electrical bioimpedance was used to determine body composition. An electric current of 0.8 mA and 50 kHz was produced by a calibrated signal generator (Biodynamics Model 310e, Seattle, WA, USA) and applied to the skin using adhesive electrodes placed on right-side limbs. Resistance and reactance were used to calculate total body water, fat and fat-free mass.

Patient monitoring

Perioperatively and on postoperative day 12, the following parameters were evaluated: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl) and total number of lymphocytes (10^6/ml). Postoperative complications were recorded as none; general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38.5°C 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 wound complications, such as fistula and/or wound infection, assessed all complications with standard methods by the same investigator surgeon. Gastrointestinal problems related to enteral feeding were also recorded (diarrhea, >5 liquid tools in a 24-h period or an estimated volume >2000 ml/day).

Assays

Fasting blood samples were drawn for measurement of albumin (3.5–4.5 g/dl), prealbumin (18–28 mg/dl) and transferrin (250–350 mg/dl), with an autoanalyzer (Hitachi, ATM, Manheim, Germany). Lymphocytes ($1.2–3.5 \times 10^3/\mu l$) were analyzed with an analyzer (Beckman Coulter Inc., LA, CA, USA).

Statistical analysis

Sample size was calculated to decrease 25% of wound complication with 90% power and 5% significance. The results were expressed as average$\pm$s.d. 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 less than 0.05 was considered statistically significant.

Results

Seventy-two patients were enrolled in the study. The mean age was 61.8$\pm$13.3 years (7 females/65 males). There were 35 patients in the group I (arginine-enhanced diet) and 37 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 frequency, average age, body weight, location and stage of tumor (Table 2).

Patients had the same percentage of preoperative weight loss (group I 2.3 vs 1.8% group II; NS). Thirty patients underwent resection of a tumor located in the oral cavity with unilateral or bilateral neck disection; 42 patients underwent laryngectomy (total or partial) or pharyngolaryngectomy, with the same distributions of surgery in group I and II. Duration of enteral nutrition in both groups was similar with an average duration of 16$\pm$9 days.

As shown in Table 3, no significant intergroup differences in the trend of the three plasma proteins and lymphocytes were detected. No differences were detected in weight, fat free mass and fat mass.

Episodes of diarrhea with both formulas were equal without statistical differences. There were no dropouts due to intolerance.

Table 2 Patients characteristics

	Group I	*Group II*
Age (years)	62.1±12	61.5±11
Men/women	4/31	3/34
Body weight (kg)	68.4±11	68.5±17
Body mass index	24±4	25.1±5.3
Disease stage		
I	0	0
II	1	1
III	7	9
IV	27	27
Diagnosis of disease		
Oral cavity	14	16
Larynx	21	21

Table 3 Blood protein levels, lymphocytes and anthropometric parameters

Parameters	*Basal*	*Day 12*
Albumin (g/dl)		
Group I	2.43±0.5	3.26±0.7[a]
Group II	2.37±0.5	3.3±0.55[a]
Prealbumin (mg/dl)		
Group I	12.1±7.2	21.8±7.6[a]
Group II	11.7±4.2	23.1±7.4[a]
Transferrin (mg/dl)		
Group I	135.1±29.3	180.6±55.7[a]
Group II	126.9±41.8	194±43[a]
Lymphocytes (10^3 $\mu l/mm^3$)		
Group I	1521±422	1678±1018[a]
Group II	1205±784	1552±830[a]
Weight (kg)		
Group I	68.4±11	67.6±10.2
Group II	68.5±17	67.4±10.8
Fat mass (kg)		
Group I	56.6±11.6	54.4±9.7
Group II	56.3±11.5	53.7±10.4
Fat-free mass (kg)		
Group I	12.1±7.4	14.1±7.5
Group II	11.9±8.7	13.4±7.4

[a]$P<0.05$, with basal values.

The postoperative infections complications (urinary tract and pneumonia with similar distribution) were equal in both groups (5.7% group I and 5.4% group II: NS). Statistical differences were detected in local complications, fistula of wound healing was less frequent in arginine-enhanced group (2.8% group I and 18.9% group II: $P<0.05$), and wound infection was similar in both groups (Table 4).

Table 4 Postsurgical patients complications

	Group I	*Group II*	
Fistula of wound (%)	2.8	18.9	$P<0.05$
Infection of wound (%)	0	0	NS
General infection (%)	5.7	5.4	NS
Diarrhea (%)	22.8	21.6	NS
Length of stay	27.9±21	28.2±12	NS

NS; not significant.

Discussion

Malnutrition is a typical characteristic of head and neck cancer patients (Riboli *et al.,* 1996: Martin Villares *et al.,* 2003), it is reported in 50% of these patients (Bassett and Dobie, 1990). Van Bokhorst-de van der Schueren *et al.,* (1997) has recently reported that patients with head and neck cancer and weight loss exceeding 10% during the 6 months before surgery are at great risk of the occurrence of major complications.

Nutritional intervention improves the caloric intake and protein ingestion of head and neck cancer patients under oncologic treatments (Goncalves Dias *et al.*, 2005). Few studies have analyzed the effect of immunonutrition formula enhanced with arginine in this type of patients. Riso *et al.* (2000) confirmed that an enteral diet supplementated with arginine in the early postoperative period improved postoperative immunological status and speed up recovery from the immunodepression following surgical injury. On malnourished patients' subgroup of this study, administration of an enriched formula reduced major postoperative complications and length of postoperative stay significantly. In our previous studies (de Luis *et al.,* 2002, 2004), wound complications (fistula) were improved. Snyderman *et al.* (1999) with a perioperative nutritional supplementation with an immune-enhancing formula showed better outcomes than a 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. In our study with better nourished patients than reported in previous studies, no differences were detected in postoperative infections complications, but wound complications were lower and plasma proteins improved with standard and immune-enhancing formula without differences. In other studies with an arginine-supplemented formula (Van Bokhorst-de van der Schueren *et al.,* 2001), nutritional status did not significantly improve, reduce the immune suppression or affect clinical outcome in head and neck cancer patients; however, only 9 days of postoperative tube feeding was used in this study. Our patients received an average of 16 days of enteral nutrition.

Arginine stimulates anabolic hormone release, improve survival in gut-derived sepsis and peritonitis by modulating bacterial clearance and accelerating wound healing (Reynolds *et al.,* 1988). In our previous study (De Luis *et al.,* 2002), two formulas were different in arginine and fiber. Fiber-supplemented enteral formulas may have a beneficial effect on components of the gut barrier, as well as the gut mucosa, and on bacterial translocation (Cummings, 1983). Soluble fiber is degraded by anaerobic colonic flora forming shorth-chain fatty acids, with a trophic effect on the mucosa of large bowel and metabolic effects on liver. In the next study (De Luis *et al.,* 2004), only arginine was the difference between formulas with the same amount of fiber, and with a dose of 12 g/day of arginine the improvement in fistula rate was equal. In normal individuals, markers of collagen synthesis have increased with daily oral doses ranging from 14 to 24.8 g of free arginine for 14 days (Wilmore, 2004). In our study, we decided to increase arginine to 17 g/day, showing a decrease in fistula rate of wound healing without secondary effects as diarrhea. This improvement in surgical wound healing in patients undergoing surgery for head and neck cancer could be due to an increase of hydroxyproline synthesis as detected in patients with gastric cancer (Farreras *et al.,* 2005).

In conclusion, at this dose (17 g/day), arginine-enhanced formula improves fistula rates in postoperative head and neck cancer patients without a high rate of diarrhea.

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