Abstract. – Objectives: 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 an enteral high dose of arginine (20 g per day) vs a medium dose (12.3 g per day) could improve nutritional variables as well as clinical outcome.

Material and Methods: A population of 115 patients with oral and laryngeal cancer was enrolled. At surgery patients were randomly allocated to two groups: group I (58 patients) received an enteral diet supplements with a high dose of arginine (20 g per day) and group II (57 patients) received an isocaloric, isonitrogenous enteral formula with a medium dose of arginine (12.3 g per day).

Results: Gastrointestinal tolerance (diarrhea) of both formulas was good (3.44% group I and 3.51% group II: ns). The postoperative infections complications were similar in both groups (8.6% group I and 12.2% group II: ns). Fistula was less frequent in enriched nutrition group (3.4% group I and 10.5% group II; \( p=0.006 \)). The length of postoperative stay was similar in both groups (27.2±17.8 days in group I vs 25.7±18.8 days in group II: ns).

Conclusions: Enriched arginine formula improves fistula wound complications in postsurgical head and neck cancer patients. Our results suggest that these patients could benefit from a high dose of arginine enhanced enteral formula.

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

Introduction

Patients with head and neck cancer have a high incidence 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.

There is evidence that giving patients perioperative nutritional supplements with immunonutritional additives can favourably modulate the immune and inflammatory response both in vitro and in patients with trauma, burns or those undergoing oncological surgery. 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. Arginine stimulates lymphocyte function and improves wound healing. Poor nutrition is known to have an adverse impact on outcome in this patient group. 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 including arginine, improves immune function and reduces postoperative complications, in different group of patients such as surgery of stomach and colon-rectum cancer, pancreatic surgery and postsurgical head and neck cancer patients. The highest dose of arginine used in these clinical studies was 20 g per day with an improvement in wound complications. However, this high dose has not been compared with a medium dose of arginine, with a potential better tolerance.

The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using an enteral high dose of arginine (20 g per day) vs a medium dose (12.3 g per day) could improve nutritional variables as well as clinical outcome.
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Materials and Methods

Patients

One hundred and fifteen patients with head and neck cancer eligible for surgery that entered the Department of Otolaryngology of our University Hospital participated in a nutritional intervention study. All patients had a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx and required major ablative surgery. Patients were excluded from the study if they were impaired renal function (serum creatinine concentration >2.5 mg/dl) or 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 no severely malnourished (weight loss <10% of body weight). The study was a prospective randomized trial carried out from January 2007 to November 2009. The study has been approved by the local Ethics Committee [number of clinical registration trial (23/2007)]. 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/m²).

Nutritional Intervention

Patients were randomly assigned to one of the following treatment groups: group I (58 patients) received an enteral diet supplement with a high dose of arginine (20 g per day) and group II (57 patients) received an isocaloric, isonitrogenous enteral formula with a medium dose of arginine (12.3 g per day). Blinding of patients and dietitians involved in patient treatment was maintained.

Table I shows the composition of the two enteral diets. Postoperatively, all patients were tube-fed for approximately 15 days, as is the standard hospital procedure. Enteral feeding was started within 24 hrs of surgery at a rate of 30 ml/hour, via an intraoperatively placed nasogastric tube. 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. 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/d of protein with supplementation with a minimum of 10 days of enteral support. The patients had access to the dietitian for assistance if needed.

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

Patient Monitoring

At basal time 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 (10⁶/ml). Postoperative complications were registered as no complications, 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 10⁸ 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 >2000 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, Mannheim, Germany). Lymphocytes (1.2-3.5.10⁹/ul) were analyzed with an analyzer (Beckman Coulter Inc., Los Angeles, CA, USA).

<table>
<thead>
<tr>
<th>Table I. Composition of enteral diet (per 1000 ml).</th>
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<tbody>
<tr>
<td><strong>Group I (High dose)</strong></td>
</tr>
<tr>
<td>Total energy (Kcal)</td>
</tr>
<tr>
<td>Protein (g)</td>
</tr>
<tr>
<td>Free L-arginine</td>
</tr>
<tr>
<td>Total lipid (g)</td>
</tr>
<tr>
<td>W6/W3</td>
</tr>
<tr>
<td>Linoleic acid</td>
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<tr>
<td>α-linolenic acid</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
</tr>
<tr>
<td>Dietary fiber (g)</td>
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Dietary fiber: oligofructose, inulin, soy polysaccharide, resistant starch, arabic gum, cellulose.
Statistical Analysis

Sample size was calculated to decrease 20% of wound complication with 80% power and 5% significance. 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). 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 or unpaired Student’s t-test, as needed. Non-parametric variables were analyzed with the Friedman and Wilcoxon tests. A p-value under 0.05 was considered statistically significant.

Results

One hundred and fifteen patients were enrolled in the study. The mean age was 62.6±11.7 years (25 females/90 males). There were 58 patients in the group I (high arginine-enhanced formula) and 57 patients in the control diet group II (medium arginine-enhanced formula). Characteristics of the patients on enrolment were similar for the two groups, reflecting the homogeneity of the patient population under study. There were no significant intergroup 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). Thirty patients underwent resection of a tumor located in the oral cavity with unilateral or bilateral neck dissection; 95 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 (3.44% group I and 3.51% group II: ns). There were no drop-outs due to intolerance.

The postoperative infections complications (urinary tract and pneumonia with similar distribution) were similar in both groups (8.6% group I and 12.2% group II: ns). Statistical differences were detected in local complications. Fistula diagnosed by X-ray was less frequent in enriched nutrition group (3.4% group I and 10.5% group II: p=0.006). Wound infection was equal in both groups (3.4% group I and 3.5% group II: ns)

The length of postoperative stay was similar in both groups (27.2±17.8 days in group I vs 25.7±18.8 days in group II: ns). No patients died in the postoperative course.

Discussion

Two major factors characterize head and neck cancer patients: malnutrition and immunosuppression13,14. There is a body of evidence suggest-
ing that enteral feeding supplemented with immunomodulatory agents including arginine reduces postoperatively complications. The main result of our study is a significant decrease of fistula complications in patients treated with the high arginine dose enhanced formula.

Van Bokhorst-de van der Schueren et al.\textsuperscript{15} 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\textsuperscript{16}.

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 early use of enteral feedings during head and neck cancer treatment reduces weight loss, malnutrition, dehydration and the associated need for hospitalization or treatment interruption\textsuperscript{17,18}. There is some evidence that arginine enhanced formulas can reduce the incidence of postoperative infectious complications compared with standard formulas\textsuperscript{19}. Riso et al.\textsuperscript{20} confirmed that an enteral diet supplemented with arginine in the early postoperative period improved postoperative immunological status and speed up recovery from the immunodepression following surgical trauma. On malnourished patients of this study, administration of an enriched formula reduced major postoperative complications and length of hospital stay significantly. In our study, length of stay was similar in both groups, the presence of arginine in both branches could explain this fact.

Snyderman et al.\textsuperscript{21} demonstrated 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. In our study with better nourished patients than reported in previous studies, no differences were detected in postoperative infections complications and serum proteins improved with both arginine immune-enhancing formulas. We don’t have a clear explanation to this early improvement in serum proteins in both groups. In other study with an arginine supplemented formula\textsuperscript{22} did not significantly improve nutritional status, reduce the immune suppression, or affect clinical outcome in head and neck cancer patients. However, only nine days of postoperative tube feeding was used in this study.

In a recent systematic review\textsuperscript{19}, 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. Occurrence of wound infection was reported in three trials. The risk of wound infection ranged from 0% (0/45) to 9% (2/23) in immunonutrition fed groups and from 0% (0/45) to 14% (3/21) in control groups without statistical differences. The effects of immunonutrition in malnourished patients reduced wound infections when given immunonutrition, only in one study\textsuperscript{20}. Occurrence of fistula formation was reported in five trials; in 3 trials\textsuperscript{8,9,11} a decrease in fistula rate was detected and no effect was detected in 2 trials\textsuperscript{20,21}. The pooled data did not show a significant improvement. Our present study shows a low rate of fistula formation in the group with the high dose of arginine. Perhaps, these differences in the literature could be explain by the different doses of arginine used.

The length of postoperative hospital stay was equal in both groups. Length of hospital stay was reduced in all six studies where it was recorded\textsuperscript{8,9,11,20-22}. Overall reduction corresponded to about a 3.5 day, which is clinically and economically important. The length of stay was similar in our groups, this data could be secondary to the presence of arginine in both branches.

In conclusion, enriched arginine formula improves fistula wound complications in postoperative head and neck cancer patients. Our results suggest that these patients could benefit from a high dose of arginine enhanced enteral formula. 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.

\textbf{Acknowledgements}

D.A. de Luis designed the protocol and wrote the article Olatz Izaola, realized nutritional evaluation Luis Cuellar, realized nutritional evaluation Maria Concepcion Terroba, realized nutritional evaluation Tomas Martin, realized nutritional evaluation Marta Ventosa realized nutritional evaluation.
References


