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Original

Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomyzed clinical trial

P. Casas-Rodera*, C. Gómez-Candela**, S. Benítez**, R. Mateo**, M. Armero**, R. Castillo** and J. M. Culebras***

*Department of Otorhinolaryngology. La Paz University Hospital. Madrid. Spain. **Department of Clinical Nutrition. La Paz University Hospital. Madrid. Spain. ***Department of General Surgery. Complejo Asistencial de León. Spain.

Abstract

Introduction: **Significant malnutrition exists in a high percentage of patients with head and neck cancer. Malnutrition is associated with defects in immune function that may impair the host response to malignancy. Malnutrition and immunosupression make patients highly susceptible to postoperative infections and complications.**

Objectives: **Compare two immunoenhanced enteral nutritions with a control diet, and evaluate the effect in postoperative infections, length of stay and inflammatory markers.**

Patients: **A population of 44 patients with oral and laryngeal cancer was enrolled in a randomized trial. At surgery, patients were randomly allocated to three groups: (group I); patients receiving an arginine-enhanced formula (group II); patients receiving a standard polymeric formula, and (group III) patients receiving an arginine, RNA and omega-3 fatty acids enhanced formula, in an isonitrogenous way.**

Results: **The duration of enteral nutrition in the three groups was similar with an average duration of 14,5 ± 8 days. The length of postoperative stay was similar, with an average of 19,8 ± 8,5 days. Wound infections and general infections were more frequent in the control group. Fistula rates were not improved in the enhanced diet groups. No significant intergroup differences in the trend of the two plasma proteins (albumin, transferrin), lymphocytes, weight, IL-6, CPR and TNFα were detected. The control group showed the highest levels of TNFα at the fourteenth postoperative day. Gastrointestinal tolerance and diarrhoea rate were similar in all the patients.**

Correspondencia: Dr. Pablo Casas Rodera.
Servicio de Otorrinolaringología del Hospital de León.
C/ Altos de Nava, s/n.
24701 León. España.
E-mail: pablocasas@clinicasas.es

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FÓRMULAS DE NUTRICIÓN ENTERAL INMUNO-ENRIQUECIDAS EN LA CIRUGÍA DEL CÁNCER DE CABEZA Y CUELLO. ENSAYO PROSPECTIVO Y ALEATORIZADO

Resumen

Introducción: **Un alto porcentaje de pacientes con cáncer de cabeza y cuello presentan un importante grado de malnutrición. Esta malnutrición está asociada defectos de la función inmune. Tanto la malnutrición como la inmunosupresión hacen a estos pacientes susceptibles de padecer complicaciones infecciosas en el postoperatorio.**

Objetivos: **Comparar 2 inmunonutriciones enterales con una dieta control, y evaluar el efecto en las infecciones postoperatorias, duración de la estancia hospitalaria y marcadores de inflamación.**

Pacientes: **Se realizó un estudio aleatorizado en un grupo de 44 pacientes con cáncer de cavidad oral y laringe. En el momento de la cirugía los pacientes fueron aleatoriamente asignados a 3 grupos diferentes: (grupo I), pacientes que recibieron una nutrición enriquecida con arginina (grupo II); pacientes que recibieron una nutrición isocalórica, isonitrogenada, y (grupo III), pacientes que recibieron una nutrición enriquecida con arginina, nucleótidos y ácidos grasos omega 3.**

Resultados: **La duración de la nutrición enteral fue similar en los 3 grupos, con una media de 14,5 ± 8 días. La duración de la estancia hospitalaria fue similar, con una media de 19,8 ± 8,5 días. Las infecciones de la herida quirúrgica y las infecciones generales fueron más frecuentes en el grupo control. El porcentaje de fístulas no mejoró en los grupos con nutriciones enriquecidas. No se observaron diferencias significativas entre los grupos en cuanto a la tendencia de las proteínas plasmáticas (albúmina y transferrina), linfocitos, peso, ni IL-6, CPR y TNFα. El grupo control mostró los niveles más altos de TNFα al decimocuarto día del postoperatorio. La tolerancia gastrointestinal (diarrea) fue similar en todos los pacientes.**

Conclusiones: **Las inmunonutriciones enterales disminuyeron el número de infecciones generales en el postoperatorio de pacientes con cáncer de cabeza y cuello. En cuanto al porcentaje de fístulas faringocutáneas no obser-**

Conclusions: **Immunoenhanced enteral nutrition formulas improved the infection rate in the postoperative of head and neck cancer patients. In the fistula rates, we observed that technical problems and nutritional status might have played an equally important role, and therefore the positive effect of immunonutrition in this parameter might have been overestimated.**

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Key words: *Arginine. RNA. Omega-3 fatty acids. Head and neck cancer. Enteral nutrition. Inflammatory markers.*

vamos disminución en los grupos con nutriciones enriquecidas. Por lo que pensamos que la técnica quirúrgica y el estado nutricional tienen una importancia similar y por ello en este parámetro el efecto positivo de la inmunonutrición puede estar sobrevalorado.

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Palabras clave: *Arginina. Nucleótidos. Ácidos grasos omega-3. Cáncer de cabeza y cuello. Nutrición enteral. Marcadores de inflamación.*

Introduction

Significant malnutrition exists up to 35-50% of patients with cancer of the head and neck.[1-3] Many factors contribute to malnutrition in this patient population, including poor dietary practices, alcoholism, local tumor effects, anorexia, cancer-induced cachexia, and treatment effects.[4] Patients undergoing surgery because of a head and neck malignancy have a 20-50% incidence of postoperative complications.[5] These complications include major wound infections, fistula, anastomotic leakage, respiratory insufficiency, and septicaemia and may lead to not only a prolonged hospital stay but also a poorer prognosis. Several factors may contribute to this morbidity, one of which is malnutrition.[6]

Malnutrition is associated with defects in immune function that may impair the host response to malignancy. The alterations in the host defence mechanism make patients highly susceptible to postoperative infections. Multiple components of the diet may affect immune function. In particular, the important role of amino acids, dietary nucleotides, and lipids in modulating immune function has been recognized.[7,8] Arginine is a semi-essential amino acid and the store can become depleted in times of stress. It plays an important role in T- and B-cell immunity as well as in the production of nitric oxide. Dietary supplementation with arginine has positive effects on immune function and reparative collagen synthesis.[9] Nucleotides are the building blocks of DNA and RNA and are derived from RNA in the diet. Nucleotide restriction is associated with a significant increase in mortality in a murine model of Candida sepsis.[10] Diets high in n-6 polyunsaturated fatty acids (PUFA) such as linoleic acid are associated with the production of arachidonic acid metabolites (prostaglandin E2 and leukotriene B4) with adverse effects on immune function.[11] Diets high in n-3 PUFA derived from fish oils, however, result in the substitution of prostaglandins of the dienoic series (PGE2) by prostaglandins of the trienoic series, with different biological activities and physiological effects.[12]

We investigated whether postoperative feeding of head and neck cancer patients, using an enteral diet supplemented with arginine, and an enteral diet supplemented with arginine, RNA, and omega-3 fatty acids could improve selective immunological and nutritional variables, as well as clinical outcome, reducing postoperative infectious/wound complications and length of stay, when both of them were compared with an isocaloric and isonitrogenous control diet.

Materials and methods

A population of 44 patients with oral and laryngeal cancer was enrolled. Exclusion criteria included: severely impaired hepatic function (total bilirubin concentration over 43.5 mg/dl) and renal function (serum creatinine concentration over 42.5 mg/dl), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months. The study was a prospective randomized trial carried out for 12 months. Baseline studies on all patients consisted of a complete clinical history and physical examination. General assessment of nutritional status included measurements of actual height and body weight, and body mass index (kg/m^2).

At surgery, patients were randomly allocated to three groups. Group I included patients receiving an enteral diet supplemented with arginine, group II included patients receiving a standard polymeric enteral formula, and group III included patients receiving an enteral diet supplemented with arginine, RNA and omega-3 fatty acids. The basal energetic waste was calculated with the Harris Benedict formula, with a stress factor correction of 1,4. The protein requirements were calculated to receive 1.5 g/kg adjusted body weight/day of proteins.

Table I shows the composition of the three enteral diets. Enteral feeding was started within 12 h of surgery, via an intraoperatively placed nasogastric tube. The infusion rate was progressively increased every 24 h until the daily nutritional goal was reached, on postoperative day 3. All patients reached 100% of the calculated requirements. No dropouts were present in the study. The end point to discontinuing nutritional support was a minimum oral intake of 1,500 cal/day and 1 g/kg/day of protein without supplementation with a minimum of 7 days of enteral support.

Perioperatively and on postoperative day 7 and day 14 the following parameters were evaluated: serum values of transferrin (mg/dl), albumin (g/dl), and total number of lymphocytes (10^6/ml), IL-6 (mg/dl), TNFα (pg/dl) and CPR (mg/dl). Postoperative complications

Table I
Composition of the enteral diets

Per 100 ml	*Group I (arginine-enhanced diet)*	*Group II (control group)*	*Group III (arginine, RNA, and omega-3 fatty acids enhanced diet)*
Total energy	131 kcal	122 kcal.	101 kcal
Total proteins	6.7 g	6.6 g	5.6 g
Nucleotids	0 g	0 g	0.12 g
Arginine	0.81 g	0 g	1,3
Carbohydrates	17.7 g	14.8 g	13.4 g
Total lipids	3.7 g	4 g	2.8 g
n ω6/ ω3 ratio	4.8	7	0.7 g
Osmolarity	308 mOsm/L	350 mOsm/L	298 mOsm/L
Energy density	1.3 kcal/ml	1 kcal/ml	1 kcal/ml

were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive infiltration, temperature above 38.5 ºC 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. All complications were assessed with standard methods by the same investigator. Gastrointestinal problems related to enteral feeding were also recorded (diarrhoea, > 5 liquid stools in a 24-h period or an estimated volume > 2,000 ml/day). The duration of hospitalization was based on the date that the patient was medically eligible for discharge.

The results were expressed as average ± s.d. ANOVA or Kruskall Wallis were used to compare the average of the length of stay with each of the different enteral diets. *T*-Student test or Mann-Whitney U test were used to compare the averages. Chi^2 or two-tailed Fisher exact test were performed to compare qualitative data. Pearson's correlation was performed to analyze the quantitative data. A P-value below 0.05 was considered statistically significant.

Results

Forty four patients were included in the study. There were 15 patients in group I (arginine-enhanced diet), 15 patients in group II (control group), and 14 patients in group III (arginine, RNA, and omega-3 fatty acids enhanced diet). The characteristics of the patients on enrolment were similar for the three groups, reflecting the homogeneity of patients. There were no significant differences with respect to gender, mean age, body weight, location, and stage of tumor (table II).

Totally, 18 patients underwent resection of a tumor located in the oral cavity with unilateral or bilateral neck dissection; 26 patients underwent laryngectomy or pharyngo-laryngectomy, with the same distributions of surgery in groups I, II and III.

Pharyngo-cutaneous fistula was less frequent in group III, and wound infections were also less frequent in the groups with enriched diets (Groups I and III), although there were no statistical differences in these parameters. There was only one postoperative general infection (pneumonia), and this occurred in the control group (Group II). Gastrointestinal tolerance (diarrhoea) of the three formulas was similar in all the

Table II
Patients' characteristics

Characteristics	*Group I*	*Group II*	*Group III*
Age	59.67 ± 9.07	54.27 ± 13.04	50.07 ± 13.79
Weight	63.95 ± 9.82	66.49 ± 10.03	67.99 ± 14.96
Men/Women	13/2	15/0	14/0
Disease stage			
I	0	0	0
II	3	4	3
III	5	5	5
IV	7	6	6
Location of disease			
Oral cavity	6	6	6
Larynx	9	9	8

No statistical differences.

Table III
Patients' complications

Characteristics	*Group I*	*Group II*	*Group III*	*p*
Fistula of wound	3 (20%)	2 (13.3%)	1 (7.1%)	NS
Infection of wound	1 (6.7%)	2 (13.3%)	1 (7.1%)	NS
General infection	0	1 (6.7%)	0	NS
Diarrhea	1 (6.7%)	1 (6.7%)	0	NS

groups, without statistical difference. There were no dropouts due to intolerance (table III).

The duration of enteral nutrition in the three groups was similar with an average duration of 14.5 ± 8 days. The length of postoperative stay was similar, with an average of 19.8 ± 8.5 days (table IV).

As shown in table V, no significant intergroup differences in the trend of the two plasma proteins, lymphocytes and weight were detected. In the three groups there was a significant decrease of the transferrrin at the seventh postoperative day, in relation to preoperative levels, with a significant increase only in the enriched diet groups, at the fourteenth postoperative day. The control group showed the lower levels of lymphocytes at the seventh and fourteenth postoperative day.

No significant intergroup differences in the trend of IL-6, CPR and TNFα were detected. The control group showed the highest levels of TNFα at the fourteenth postoperative day.

Discussion

Two important factors characterize head and neck cancer patients: immunosuppression and malnutrition.[13] Patients with head and neck cancer are among the most malnourished of cancer patients.[14] This malnutrition is favoured by: a) catabolic factors secreted by the tumour, such as the cytokines tumour necrosis factor-a and interleukins;[15] b) reduced dietary intake due to dysphagia and odynophagia;[6] and c) poor dietary habits together with excessive alcohol consumption. Some studies report malnutrition in 30-50% of all head and neck cancer patients.[16]

Although immune dysfunction in surgical patients is multifactorial, recent studies suggest that the immune system may be modulated by the use of specific nutritional substrates ("immunonutrients"), like ariginine, omega-3 fatty acids and RNA which have the peculiar ability to improve the defence mechanisms and intestinal barrier function and to modulate the inflammatory response.[17]

There is evidence suggesting that enteral feeding, supplemented with immunomodulatory agents, improves postoperative immunological response and speeds up recovery from the immunodepression following surgical trauma and reduces the incidence of infectious complications.[18, 19]

In our study we compare two immunoenhanced enteral nutritions with a control diet, and we found that the only general infection appeared in the control group. Wound infections tended to be also less frequent in the groups with enriched diets. Snyderman,[14] in a group of patients with head and neck cancer, reported that postoperative infectious complications were significantly decreased in the patient groups that received the enriched diet with arginine, RNA and omega-3 fatty acids. They said that it was interesting to note that the increased number of infectious complications that were observed in the control group (standard formulas) was mostly due to infections at distant sites (lungs, urinary tract, etc.) rather than operative wound infections. This finding implies that most operative wound infections and fistulas have different risk factors and may be attributable to surgical technique rather than depressed immune function. This result may explain why in our study, fistulas were more frequent in one of the groups with enriched diet (Group I). Fistulas, do not seem to relate exclusively to infectious processes, and thus to immunosuppression. Indeed, technical problems and nutritional status might play an equally important role, even independent of the immune status, and therefore we might have overestimated the positive effect of immunonutrition.[20] In another study, De Luis et al[21] used an immunoenhanced formula supplemented with a high dose of arginine (17 g/day). They showed a decrease in fistula rate of wound healing without secondary effects in diarrhoea. They argued that this improvement could be due to an increase of hydroxi-

Table IV
Lenght of nutritional support and stay

	Group I	*Group II*	*Group III*	*p*
Lenght of nutricional support	16 ± 9	14 ± 8	14 ± 8	NS
Lenght of stay	22.47 ± 9.94	18.27 ± 7.51	18.57 ± 7.75	NS

Table V
Anthropometric parameters, lymphocytes and biochemical parameters

	Basal	*Day 7*	*Day 14*	*p*
Weight (kg)				
Group I	62.75 ± 9.07	62.92 ± 8.64	60.98 ± 7.93	NS
Group II	66.06 ±10.74	64.63 ± 10.95	63.92 ± 10.39	NS
Group III	65.7 ±15.15	64.64 ± 13.64	64.82 ± 13.56	NS
Lymphocytes (10^6 /ml)				
Group I	2,181.6 ± 804	1,929.1 ± 771.6	1,862.5 ± 544.4	NS
Group II	1,818 ± 639.8	1503 ± 640.6	1597 ± 804.6	NS
Group III	2,550 ± 649.9	1,914.2 ± 756.3	1,972.8 ± 541.1	NS
Albumin (mg/dl)				
Group I	4 ± 0.4	3.3 ± 0.3*	3.4 ± 0.2	NS
Group II	4 ± 0.3	3.4 ± 0.2*	3.5 ± 0.1	NS
Group III	3.9 ± 0.3	3.1 ± 0.1*	3.3 ± 0.1	NS
Transferrin (mg/dl)				
Group I	230.6 ± 55.6	173.5 ± 43.9*	186.5 ± 38.6**	NS
Group II	210.3 ± 30.9	179.6 ± 27.7*	189.1 ± 21.1	NS
Group III	214.8 ± 47.3	170.1 ± 32.5*	190.5 ± 30.6**	NS
IL-6 (pg/dl)				
Group I	17.14 ± 14.83	30.66 ± 33.59	14.01 ± 6.66	NS
Group II	19.63 ± 11.31	17.57 ± 11.67	23.6 ± 13.50	NS
Group III	21.39 ± 12.45	20.26 ± 9.49	25.17 ± 26.70	NS
TNFα (pg/dl)				
Group I	35.33 ± 60.38	39.26 ± 35.02	35.57 ± 31.41	NS
Group II	55.09 ± 32.79	38.39 ± 21.11	87.11 ± 143.27**	NS
Group III	49.66 ± 46.96	46.29 ± 38.29	36.79 ± 23.11	NS
PCR (mg/dl)				
Group I	14.7 ± 20.57	80.92 ± 67.37	46.78 ± 30.93	NS
Group II	15.49 ± 18.28	58.86 ± 55.38	42.34 ± 35.55	NS
Group III	27.2 ± 45.21	122.23 ± 153.03	44.33 ± 37.23	NS

* $P < 0.05$ compared with basal values.
** $P < 0.05$ compared with day 7 values.

proline synthesis as detected in patients with gastric cancer.[22]

There was no significant difference in the length of stay between the enriched and standard patients. Snyderman,[14] De Luis,[19] Van Bokhorst-De Van Der Schueren[23] and Riso[18] did not find differences neither. No differences in weight were detected, similar results were found in other studies.[24,25]

De Luis[26] compared an arginine enhanced enteral nutrition with a standard diet, and showed that CRP and IL-6 improved in both groups without changes in TNFα levels and lymphocytes count. In our study, the enriched diets showed beneficial effects on the immunological and inflammatory response, as the control group had the lower levels of lymphocytes at the seventh and fourteenth postoperative day, and the highest levels of TNFα at the fourteenth postoperative day.

In conclusion, both enhanced diets used in our study showed beneficial effects on clinical outcome and immune status, without significant differences between them. The positive effect of immunonutrition might have been overestimated in the fistula rates.

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