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Revisión

Immunoenhanced enteral nutrition formulas in head and neck cancer surgery; a systematic review

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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: **Some studies of patients receiving immunonutrition in the perioperative period in head and neck cancer have shown beneficial effects on clinical outcome and inmune status. The authors carried out a systematic review of randomised control trials to determine whether perioperative immunonutrition has a role in the treatment of head and neck cancer.**

Methods: **14 trials of polymeric nutritional supplementation with immunonutrition were identified. Two studies compared two types of immunonutrition.**

Results: **A reduction in the length of postoperative hospital stay was seen in some trials, but the reason for this reduction is not clear. Some studides showed statistical differences with less complications in arginine-enhanced group and also showed a significant decrease of fistula complications in patients treated with a high arginine dose enhanced formula, if compared with a medium dose of arginine.**

Conclussion: **Those planning future studies face challenges. 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.**

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Key words: *Immunonutrition. Arginine. Head and neck cancer. Enteral nutrition. Surgery.*

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FÓRMULAS DE INMUNONUTRICIÓN ENTERAL EN LA CIRUGÍA DEL CÁNCER DE CABEZA Y CUELLO; UNA REVISIÓN SISTEMÁTICA

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: **Algunos trabajos de pacientes que han recibido inmunonutrición en el postoperatorio de cirugía por cáncer de cabeza y cuello han mostrado un efecto beneficioso en la evolución clínica y el estado inmune. Los autores han llevado a cabo una revisión sistemática de los ensayos clínicos realizados hasta la fecha, para determinar el papel que tiene la inmunonutrición enteral postoperatoria en el tratamiento del cáncer de cabeza y cuello.**

Métodos: **Se identificaron 14 trabajos en los que se habían utilizado fórmulas de inmunonutrición. Dos trabajos compararon dos tipos de inmunonutrición. Resultados: En algunos trabajos se observó una disminución en los días de estancia hospitalaria, aunque la razón para ello no está clara. Algunos estudios mostraron diferencias significativas con menos complicaciones en los grupos que recibieron nutriciones enriquecidas, presentando una disminución significativa en el número de fístulas en pacientes tratados con nutriciones con altas dosis de arginina, si se compara con una nutrición con una dosis media de arginina.**

Conclusión: **Los futuros trabajos presentan retos. Es necesario un ensayo clínico extenso, para poder realizar recomendaciones firmes sobre el uso de la inmunonutrición en el postoperatorio de pacientes intervenidos de cáncer de cabeza y cuello.**

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Palabras clave: *Inmunonutrición. Arginina. Cáncer de cabeza y cuello. Nutrición enteral. Cirugía.*

Introduction

Significant malnutrition exists up to 35-50% of patients with cancer of the head and neck[1]. Many factors contribute to malnutrition in this patient population, including poor dietary practices, alcoholism, catabolic factors secreted by the tumor, such the cytokines tumor necrosis factor-α (TNF-α), interleukins (IL), and gamma-interferon, local tumor effects, anorexia, cancer-induced cachexia, and treatment effects[2]. Patients undergoing surgery because of a head and neck malignancy have a 20-50% incidence of postoperative complications[3]. 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[4].

Malnutrition is associated with defects in immune function that may impair the host response to malignancy[5]. The alterations in the host defence mechanism make patients highly susceptible to postoperative infections. Multiple components of the diet may affect immune function. 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[6]. In particular, the important role of amino acids, dietary nucleotides, and lipids in modulating immune function has been recognized[7]. 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. Arginine is able to reduce the production of inflammatory mediators such as IL-1 beta, IL-6, and TNF-α at the site of injury in rat septic models[8] and can accelerate tissue growth after trauma or infection[9]. Dietary supplementation with arginine has positive effects on immune function and reparative collagen synthesis[10]. 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[11]. RNA supplementation is essential for the proliferation of immune cells or cells involved in wound healing and greatly increases the survival rate of infected animals[12]. Dietary nucleotides, particularly the pyrimidine uracil, also appear to be essential to the normal lymphocytes maturation. 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[13]. 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[14].

Omega-3 fatty acids are long-chain polyunsaturated acids that appear to have anti-inflammatory effects, possibly by interference with macrophage eicosanoid production[15]. They play a role on the structural and functional integrity of the cell membrane, intercellular signal transduction, and synthesis of eicosanoids. In particular, they influence the production of prostanoids from the dienoic to the trienoic variety, the later of which are much less immunosuppressive[16]. By replacing other fatty acids with omega 3 fatty acids, membrane flexibility is enhanced, which is essential for phagocytes[17]. Decrease of proinflamatory cytokines, such as Il-1β, IL-6, IL-8, and TNF-α has been found in patients with sepsis[18].

Objectives

It is reported that cancer patients receiving immunonutrition perioperatively tended to have fewer postoperative complications[19].

Some studies of patients receiving immunonutrition in the perioperative period in head and neck cancer have shown beneficial effects on clinical outcome and inmune status. The authors carried out a systematic review of randomised control trials to determine whether perioperative immunonutrition has a role in the treatment of head and neck cancer.

Methods

Eligibility criteria and literature search

Clinical trials were eligible if patients undergoing head and neck surgery for cancer had been randomly allocated to be in a control group receiving either traditional care (i.v. fluids) or polymeric nutritional supplements and an interventional group receiving polymeric nutritional supplements with immunonutritional additives. The MeSH terms used were: head and neck neoplasms, enteral nutrition, immune, arginine, immunonutrition, surgery. Papers were identified by computerised searches of PubMed.

Data extraction and outcomes

Data were collected on age, sex, weight, body mass index, energy intake, duration of supplementation, the type of surgery, The outcomes recorded included biochemical changes, immunological changes, wound infections, fistula formation, mortality, and length of postoperative hospital stay.

Results

Through data base searches, 2,017 references were identified. After applying limits of humans and clinical

Table I
Trial design

Study	*Inclusion criteria*	*Exclusion criteria*	*Stratification*	*Outcome*	*Duration of follow up*
Snyderman, 1999[28]	Curative surgery squamous cell carcinoma (stage II-IV) of oral cavity, pharynx or larynx	Malabsorption, immune disorder or immunosuppressive drugs, active infection, morbid obesity	Site of surgery (larynx vs other), stage (T1-3 vs T4, N0 vs N1-3) & preoperative weight loss (1-10lb, 11-20lb & > 20lb)	Weight, laboratory parameters, clinical complications (defined), tolerance to feeding, length of hospital stay	1 month post operation
Riso, 2000[27]	Surgery for carcinoma (stage I-IV) of oral cavity, pharynx or larynx	Impaired renal or hepatic function, autoimmune disease, IDDM, active infection	None	Clinical complications (not defined), tolerance to feeding, laboratory parameters	To hospital discharge
Van Bokgorst-De van der Schueren, 2000/2001[29,30]	Recent weight loss undergoing surgery for carcinoma of oral cavity, pharynx or larynx	Nourished, steroids, other trial drugs, renal or hepatic impairment, immune deficiency	Type of operation and radiotherapy	Weight, laboratory parameters, clinical complications (not defined), tolerance to feeding, length of hospital stay, quality of life, hand grip	16 months
De Luis, 2002[20]	Surgery for carcinoma of oral cavity or larynx	Impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements, recent weight loss	None	Weight, laboratory parameters, clinical complications (not defined), tolerance to feeding, length of hospital stay	3 months post hospital discharge
De Luis, 2003[24]	Recent weight loss undergoing surgery for carcinoma of oral cavity or larynx	Nourished, impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements	None	Weight, laboratory parameters	5 days post operation
De Luis, 2004[23]	Surgery for carcinoma of oral cavity or larynx	Impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements, recent weight loss	None	Weight, laboratory parameters, clinical complications (not defined), tolerance to feeding, length of hospital stay	To hospital discharge
De Luis, 2005[21]	Recent weight loss undergoing surgery for carcinoma of oral cavity or larynx	Nourished, impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements	None	Weight, laboratory parameters	6 days post operation
Felekis, 2005[26]	Surgery for head and neck cancer	Not stated	Not stated	Major and minor complications (not defined), Septic complications, mortality	Not stated
De Luis, 2005[22]	Surgery for carcinoma of oral cavity or larynx	Recent weight loss, impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements	Not stated	Weight, laboratory parameters, clinical complications (not defined), steroids, recent tolerance to feeding, length of hospital stay	12 weeks
De Luis, 2007[25]	Surgery for carcinoma of oral cavity or larynx	Recent weight loss, impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements	None	Weight, laboratory parameters, clinical complications (defined), tolerance to feeding, length of hospital stay	Not stated
De Luis, 2010[34]	Surgery for carcinoma of oral cavity or larynx	Recent weight loss, impaired renal or hepatic function, active infection, autoimmune disease, steroids, recent nutritional supplements	None	Weight, laboratory parameters, clinical complications (defined), tolerance to feeding, length of hospital stay	15 days
Casas, 2008[31]	Surgery for carcinoma of oral cavity and larynx	Impaired renal or hepatic function, active infection, utoinmune disease, steroids, recent nutritional supplements	None	Weight, laboratory parameters, clinical complications, tolerance to feeding, length of hospital stay	To hospital discharge
Buijs, 2010[32]	Surgery for head and neck cancer	Impaired renal or hepatic function, active infection, utoinmune disease, steroids	Type of surgery and previous radiotherapy	Long term survival, locoregional recurrence, distant metastases and second primary tumors	10 years
Felekis, 2010[33]	Surgery for head and neck cancer	Impaired renal or hepatic function, autoinmune disease	Not stated	Major and minor complications, tolerance, inmunological markers	Not stated

Table II
Nutritional supplements and regimes

Study	*Nº groups*	*Groups*	*Control*	*Active*	*Isocaloric/ isonitrogenous*	*Target energy intake*	*Duration of supplementation (days)*		*Post-op day commenced*
							Preop.	*Postop.*	
Snyderman, 1999[28]	4	1. Active pre & post operative, 2. Active postoperative only, 3. Control pre & post operative, 4. Control postoperative only	Polymeric (Replete®, Resource®, Isosource®, Jevityr® Vivonex®, Osmolite®)	Polymeric + arginine (Impact®)	Not stated	Preoperation 500 kcal Postoperation 1,000 kcal	> 5 days	> 7 days	Not stated
Riso, 2000[27]	2	1. Active 2. Control postoperative enteral, both with parenteral nutrition for 3 days	Polymeric (Nutrison protein plus®)	Polymeric + arginine (Nutrison intensive®)	Yes	31 kcal/kg	None	> 10 partial	Within 24 h > 21 total laryngectomy
Van Bokhorst-De van der Schueren, 2000/2001[29,30]	3	1. No pre-op + postoperative, 2. Pre-op + post-operative, 3. Arginine supplemented pre-op + post-operative	Polymeric	Polymeric + arginine	Yes	150% of basal requirement	7-10 days	> 10 days	Within 24 h
De Luis, 2002[20]	2	Postoperative	Polymeric	Polymeric + arginine + fiber	Yes	Requirements	None	> 10 days	Within 24 h
De Luis, 2003[24]	2	Postoperative	Polymeric	Polymeric + arginine	Yes	Requirements	None	> 10 days	Within 24 h
De Luis, 2004[22]	2	Postoperative	Polymeric +fiber	Polymeric + arginine + fiber	Yes	Requirements	None	> 10 days	Within 24 h
De Luis, 2005[21]	2	Postoperative	Polymeric	Polymeric + arginine	Yes	Requirements	None	> 10 days	Within 24 h
Felekis, 2005[26]	2	Active pre & post operative *vs* no	Polymeric	Undefined enteral immunonutrition	Yes	Not stated	6 days	8 days	Not stated
De Luis, 2005[22]	2	Postoperative	Polymeric + arginine	Polymeric + ω3 fatty acids	Not stated	Requirements	None	12 weeks	At hospital discharged
De Luis, 2007[25]	2	Postoperative	Polymeric	Polymeric + arginine	Yes	Requirements	None	> 10 days	Within 24 h
De Luis, 2010[34]	2	Active postoperative	Polymeric + medium dose arginine	Polymeric + high dose arginine	Yes	Requirements	None	15 days	Within 24 h
Casas, 2008[31]	3	Postoperative	Polymeric	1. Polymeric + arginine 2. Polymeric + arginine, RNA and ω3 fatty acids	Yes	Requirements	None	> 10 days	Within 24 h
Buijs, 2010[32]	2	Pre and postoperative	Polymeric	1. Polymeric 2. Polymeric + arginine	Yes	Requirements	7-10 days	10 days	Within 24 h
Felekis, 2010[33]	2	1. Postoperative 2. Pre and postoperative	Polymeric (Nutrison®, Nutricia®)	Pre: Polymeric + arginine, RNA and ω3 fatty acids (Impact®) Post: Polymeric + arginine, RNA and ω3 fatty acids (Impact®)	Yes	Requirements	Group active for 5 days	8 days	Not stated

trial 232 were retrieved, after exclusion of duplicates and irrelevant references, 14 were retrieved. The remaining references described 14 trials that fulfilled the inclusion criteria and could provide data for review.

Characteristics of trials, patients and interventions

Fourteen randomised controlled trials published between 1999 and 2010 were identified with a total of 836 patients all undergoing surgery for head and neck cancer (tables I and 2)[20-34]. Twelve trials compared polymeric feeds with immunonutrition[20-21,23-33] and two trials compared two types of immunonutrition started at hospital discharge[22,34].

Patient characteristics

Table III illustrates baseline patient characteristics. All studies used isocaloric and isonitrogenous feed regimens.

Wound infection and fistula formation

The effects of immunonutrition on wound infections and fistula formation are detailed in table IV. Occurrence of wound infection was reported in five trials. The risk of wound infection ranged from 0% (0/45) to 4.8% (4/82) in immunonutrition fed groups and from 0% (0/45) to 12.5% (3/24) in control groups. The effects of immunonutrition in malnourished patients could only be ascertained from the study by RISO et al.[27], where 13 patients were considered malnourished. These patients had reduced wound infections when given immunonutrition ($p < 0.05$).

Occurrence of fistula formation was reported in nine trials and ranged from 0% (0/23) to 5% (4/82) in immunonutrition fed groups and from 0% (0/38) to 18.9% (7/37) in control groups.

Hospital stay

Mean postoperative hospital stays were long (table IV) with broad standard deviations. De Luis et al.[23] reported a significant ($p < 0.05$) reduction in postoperative stay, 25.8 days versus 35 days in intervention and control groups, respectively. RISO et al.[27] reported a reduced hospital stay in the intervention group ($p < 0.05$).

Immunological parameters

The trials examined reported on a broad range of biochemical and immunological parameters including interleukin-6, tumour necrosis factor-a, C-reactive protein, T-cell subsets and total lymphocyte counts. Riso et al.[27] demonstrated an increase in total lymphocytes, CD4 and CD4/CD8 ratio on postoperative day 4 ($p < 0.05$).

Malnourished patients ($n = 13$) in the study by Riso et al.[27] showed reduced preoperative immune status in some variables (CD4, CD4/CD8, IgA, IgG), with some parameters (CD4, CD4/CD8) increasing postoperativly compared with baseline but not between the two groups.

Casas-Rodera et al.[31] showed no significant intergroup differences in the trend of the two plasma proteins, lymphocytes and weight. In the three groups that were compared 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. The control group showed the highest levels of TNFα at the fourteenth postoperative day.

Long-term survival and locoregional recurrence

Buijs et al.[32] showed that the median overall long-term survival was 34.8 months in the arginine-supplemented group and 20.7 months in the control group ($P = 0.019$). Disease-specific survival was 94.4 months in the arginine-supplemented group and 20.8 months in the control group ($P = 0.022$). Locoregional recurrence occurred in 4 of the 17 patients in the arginine group and in 9 of the 15 patients in the control group.

Discussion

The authors examined 14 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, including a trial that studies the benefits of a high dose of arginine as a postoperative nutrition of head and neck cancer patients[34].

A reduction in the length of postoperative hospital stay was seen in some trials, but the reason for this reduction is not clear. Lenght of hospital stay was reduced in six studies. Overall reduction in these studies conrresponded to about a 3.5 day, which is clinically and economically important. In two studies, fistula formation was more common in those patients receiving immunonutrition, yet length of hospital stay was reduced[27-28].

Regarding the local complications, occurrence of fistula formation was reported in nine trials; in 5 trials[20,23,25,33,34] decrease in fistula rate was detected and no effect was detected in 4 trials[21,27,28,31]. Luis et al.

Table III
Baseline patient characteristics

			Age		*Sex (M:F)*		*Weight*		*BMI*	
Study	*Control*	*Active*	*Control*	*Active*	*Control*	*Active*	*Control*	*Active*	*Control*	*Active*
Snyderman, 1999[28]	47	82	61	63	2:1	3:1	67	71	Not recorded	Not recorded
Riso, 2000[27]	21	23	63	61	18:3	21:2	66.2	64.1	23.2	22.1
Van Bokhorst-De van der Schueren, 2000/2001[29,30]	16 + 15	17	55 + 60	59	11:6 + 7:8	12:5	62.8 + 55.3	61.6	Not recorded	Not recorded
De Luis, 2002[20]	24	23	59	63	3:21	2:21	67.5	68.2	24.1	26.2
De Luis, 2003[24]	18	18	59	63	1:27	1:17	69.2	69.1	24.1	26.2
De Luis, 2004[23]	45	45	60.6	60.2	3:42	3:42	69.3	69.8	25.1	25.2
De Luis, 2005[21]	15	14	63.0	60.7	3:12	2:12	Not recorded	Not recorded	24.1	24.6
Felekis, 2005[26]	17	20	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
De Luis, 2005[22]	38	35	60.2	62.5	36:2	32:3	65.5	68.2	23.8	24.6
De Luis, 2007[25]	37	35	61.5	61.5	3:34	4:31	68.5	68.4	25.1	24.0
De Luis, 2010[34]	57	58	62.6	62.5	45:12	45:13	71.4	70.7	25.8	25.6
Casas, 2008[31]	15	29	54.2	54.8	15:0	27:2	66.4	65.9	Not recorded	Not recorded
Buijs, 2010[32]	15	17	60	59	7:8	12:5	Not recorded	Not recorded	Not recorded	Not recorded
Felekis, 2010[33]	20	20	63.2	61.0	18:2	18:2	Not recorded	Not recorded	Not recorded	Not recorded

Table IV
Outcomes

	Wound infections		*Fistula formation*		*Lenght of postoperative hospital stay*		*Post-op death*		*Long-term survival*		*Disease specific survival*		*Locoregional recurrence*	
Study	*Control*	*Intervention*	*Control*	*Intervention*	*Control*	*Intervention*	*Control*	*Intervention*	*Control*	*Intervention*	*Control*	*Intervention*	*Control*	*Intervention*
Snyderman, 1999[28]	2	4	1	4	17.4	15.3	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Riso, 2000[27]	3	2	1	1	28.0	25.0	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Van Bokhorst-De van der Schueren, 2000/2001[29,30]	Not stated	Not stated	Not stated	Not stated	41 + 46	31	0 + 1	2	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2002[20]	3	1	5	0	31.2	22.8	2	3	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2003[24]	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2004[23]	0	0	5	2	35.0	25.8	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2005[21]	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Felekis, 2005[26]	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	1	1	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2005[22]	0	0	0	0	Not stated	Not stated	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2007[25]	0	0	7	1	28.2	27.9	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis, 2010[34]	2	2	6	2	25.7	27.2	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Casas, 2008[31]	2	2	2	4	18.2	20.4	0	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Buijs, 2010[32]	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	20.7 months	34.8 months	20.8 month	94.4 month	9(15)	4(17)
Felekis, 2010[33]	Not stated	Not stated	2	1	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

Table V
Immunological and biochemical end-points

Study	*Biochemical end points*	*Immunological endpoints*	*Total lymphocytes*		*IL-6 (pg/ml) post-op*		*TNF-alpha (pg/ml)*		*Postoperative day*
			Control	*Active*	*Control*	*Active*	*Control*	*Active*	
Snyderman, 1999[28]	Albumin, transferrin, haemoglobin,	Total Lymphocytes	1.29	1.51	–	–	–	–	7
Riso, 2000[27]	Albumin, pre-albumin, transferrin.	Total Lymphocytes, T-cell subsets, immunoglobulins.	1.0, 1.3, 1.5	1.2, 1.9, 2.2	–	–	–	–	1, 4, 8
Van Bokhorst-De van der Schueren, 2000/2001[29,30]	Albumin	Total white blood cells, total lymphocytes, T-cell subsets, IL-6 and TNFa after stimulation with lipopolysacharride, HLA-DR expression	NS	NS	NS	NS	NS	NS	1, 4, 7
De Luis, 2002[20]	Albumin, pre-albumin, transferrin.	Total Lymphocytes	1.55, 2.27	1.66, 2.10	–	–	–	–	7, 14
De Luis, 2003[24]	Albumin, pre-albumin, transferrin.	CRP, Lymphocytes, TNF alpha, Il-6.	1.56	1.63	9.9	35.6	5.8	5.1	5
De Luis, 2004[23]	Albumin, pre-albumin, transferrin.	Total Lymphocytes	1.55	1.88	–	–	–	–	14
De Luis, 2005[21]	Albumin, pre-albumin, transferrin.	Total lymphocytes CRP, TNF alpha, Il-6.	1.45	1.36	9.9	6.7	6.11	5.6	6
Felekis, 2005[26]	Not measured	None	–	–	–	–	–	–	–
De Luis, 2005[22]	Albumin, pre-albumin, transferrin.	Total Lymphocytes	2.09	2.27	–	–	–	–	30
De Luis, 2007[25]	Albumin, pre-albumin, transferrin.	Total Lymphocytes	1.55	1.68	–	–	–	–	12
De Luis, 2010[34]	Albumin, pre-albumin, transferrin.	Total Lymphocytes	1.56	1.82	–	–	–	–	10
Casas, 2008[31]	Albumin, transferrin.	Total lymphocytes CRP, TNF alpha, Il-6.	1.5	1.93, 1.91	17.57	30.66, 20.26	38.39	39.26, 46.29	7
Buijs, 2010[32]	Albumin, transferrin.	Total lymphocytes, CRP, TNF alpha, Il-6.	1.59	1.86, 1.97	23.6	14.01, 25.17	87.11	35.57, 36.79	14
Felekis, 2010[33]	Not measured	None	–	–	–	–	–	–	–
Snyderman, 1999[28]	Albumin, pre-albumin, fibrinogen	CRP, TNF alpha, Il-6.	–	–	4.1	7	2.7	2.9	8

Albumin (g/dl), pre-albumin (mg/dl), transferrin (mg/dl), lymphocytes (x 106 ml/mm^3), Interleukin (pg/ml), TNF (pg/ml).
TNF = Tumor necrosis factor; CRP = C-reactive protein; IL = Interleukin.
NS is Not stated.
*De Luis Control is ω3 fatty acid supplemented and active is arginine supplemented group.

showed statistical differences with less complications in arginine-enhanced group[20,23,25], and also showed a significant decrease of fistula complications in patients treated with the high arginine dose enhanced formula, if compared with a médium dose of arginine[34]. In this study, length of stay was similar in both groups, the presence of arginine in both groups could explain this fact. Perhaps, these differences in the literature could be explain by the diffent doses of arginine used.

Snyderman et al.[28] 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.

Riso et al.[27] confirmed that an enteral diet supplemented with arginine in the early postoperative period improved postoperative immunological status and speed up recovery from the imunodepression following surgical trauma. On malnourished patients of this study, administration of an enriched formula reduced major postoperative complications and length of postoperative stay significantly.

Felekis et al.[33], showed that the rate of complications was significantly reduced in the total number of patients receiving immunonutrition and in the particular subgroup of well-nourished patients receiving an immunoenhanced diet.

Buijs et al.[32] showed that a nutritional intervention with arginine –enriched nutrition before and after surgery may improve survival.

Casas-Rodera et al.[31] compare two immunoenhanced enteral nutritions with a control diet, and they 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 et al.[28] 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[35].

Based on these results, those planning future studies face challenges. There is little evidence from the randomised controlled trials reviewed here to guide the choice of intervention, patient groups or the value of preoperative supplementation. Clinically important end-points such as fistula formation, wound infection and pneumonia should be addressed. Any reduction in length of hospital stay needs to be explained. 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.

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