Nutrición Hospitalaria

Nutr Hosp. 2015;32(4):1676-1682
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original/*Cancer*

Effectiveness of immunonutrition on inflammatory markers in patients with cancer; randomized clinical trial

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Abstract

Background: **malnutrition is a common complication in patients with cancer and is associated with immunosuppression and alterations with inflammatory response.**

Objective: **the aim of our study was to evaluate the effect of enteral nutrition supplemented with two enteral formulas on inflammatory markers (CRP, IL-6 and FNTα) in cancer patients undergoing chemotherapy.**

Design and methods: **randomized control trial, conducted at the Hospital Juarez of Mexico in patients with cancer undergoing chemotherapy with IRN < 97.5 and SGA B/C. Patients were randomly allocated to two groups: group I (immunomodulatory), group II (high ω3). The intervention began on the first day of chemotherapy until day 10 after. We evaluated nutritional status and an inflammatory marker on days 0, +5, +10 QT. Statistical analysis was performed with T Student, x^2 and analysis of variance for repeated measurements. P < 0.05 was considered statistically significant.**

Results: **a total of 29 patients were analyzed, 27 (62.8%) females and 16 (37.2%) males. Mean age 43.91 + 11.3 years old. Malnutrition prevalence was 48.8% moderate and 51.2% severe. Prealbumin levels significantly increase in group II *vs* group I (p < 0.05). Both groups maintenance body weight, lean mass and fat mass. No decrease levels of CRP, IL-6 and FNTα.**

Conclusions: **enteral supplementation during chemotherapy inhibits nutritional deterioration and maintenance body weight and lean mass. No decreased levels of inflammatory markers.**

(*Nutr Hosp*. 2015;32:1676-1682)

DOI:10.3305/nh.2015.32.4.9507

Key words: *Nutrition. Immunonutrition. Inflammation. Cancer.*

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Recibido: 24-VI-2015.
Aceptado: 26-VII-2015.

EFECTIVIDAD DE LA INMUNONUTRICIÓN SOBRE LOS MARCADORES INFLAMATORIOS EN PACIENTES CON CÁNCER; ENSAYO CLÍNICO ALEATORIZADO

Resumen

Antecedentes: **la desnutrición es una complicación frecuente en los pacientes oncológicos y se relaciona con inmunosupresión y alteraciones en la respuesta inflamatoria.**

Objetivo: **evaluar los efectos de la suplementación de dos fórmulas enterales sobre los marcadores inflamatorios (PCR, IL-6 y el TNF-α) en pacientes con cáncer sometidos a quimioterapia.**

Diseño y métodos: **se hizo un ensayo clínico, aleatorizado, realizado en el Hospital Juárez de México en pacientes con cáncer sometidos a quimioterapia con IRN < 97,5 y EGS B o C. Los pacientes se dividieron en dos grupos: grupo I (imunomoduladora), grupo II (ácidos ω-3). La intervención se inició en el primer día de la quimioterapia hasta el décimo día posterior a esta. Se valoró el estado nutricional y se determinaron los marcadores inflamatorios en los días 0, +5 y +10 de QT. Se hizo análisis paramétrico. Se aplicó t de Student, X2 y análisis de varianza para mediciones repetidas. Se consideró p < 0.05 como estadísticamente significativo.**

Resultados: **se estudiaron 43 pacientes, 27(62,8%) mujeres y 16 (37,2%) hombres. La media de edad fue de 43,91 + 11,3 años. La prevalencia de desnutrición moderada fue de 48,8% y severa de 51,2%. El grupo II presentó un incremento en los niveles de prealbúmina con respecto a la basal *vs* el grupo I (p < 0,05). En ambos grupos se observó el mantenimiento del peso corporal, el porcentaje de masa magra y de masa grasa. No se observó disminución de los niveles séricos de PCR, IL-6 y TNFα (p = NS).**

Conclusiones: **la administración de suplementos enterales durante la quimioterapia inhibe el deterioro nutricional y mantiene el peso y la masa magra. No se observó disminución de los marcadores inflamatorios.**

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Palabras clave: *Nutrición. Inmunonutrición. Inflamación. Cáncer.*

Introduction

Cancer is one of the mail causes of death around the world, it has been credited with 13% of the deaths, and in Mexico it's only under metabolic cardiovascular and nutritional diseases. The World Health Organization estimates that 12 million people will die from this disease by 2030[1].

Malnutrition is a common complication in cancer patients, and according to the series it may vary between 40 and 80% with a multifactorial cause, and it is related with the depression of the immune system, alterations in the inflammatory response[2,3,4], as well as a decrease in the fat reserves and muscle tissue, resulting in increased morbidity and mortality.

In cancer patients substances such as IL-1b, IL-1[a] and gamma interferon, differentiation factor D or leukemia inhibitory factor are released and cause immune system depression[6,7]. However, it is observed that some changes in the immune system may be modulated by specific nutritional substrates[8,9]. In recent years the standard enteral diet preparations have been modified with immunomodulatory agents, such as arginine, glutamine, ω3 fatty acids, nucleotides, and others. Trying not only to improve the nutritional status, but also to regulate the immune response, the inflammatory response, and modulate the nitrogen balance.

Eicosapentaenoic acidω3 inflammatory mechanisms may mediate different signaling pathways and second messengers. It has the ability to block the activity of cytokines, such as IL-1, IL-6 and TNFα, which are the main component for the development of cachexia associated to cancer, besides promoting production of PGE3 and series 5 of leukotrienes, which reduces the inflammatory response[8,10-15]. There are new alternatives emerging due to the possibility of nutritionally supplementing eicosapentaenoic acid ω3.

Proper nutrition intervention can prevent side effects of malnutrition, improve quality of life and increase the response and tolerance to treatment. However, so far there are no recommendations about the type of enteral formula and the role of the inflammatory response in cancer patients receiving chemotherapy.

The primary aim of our study was to evaluate the effectiveness of the supplementation of two enteral formulas, in the inflammatory immune response in cancer patients undergoing chemotherapy, with the secondary goal of maintaining weight and lean body mass.

Materials and methods

Design and Participants

We conducted a randomized clinical trial in Hospital Juárez de México, in patients of both sexes aged 18 years and under 65 years diagnosed with cancer (solid tumors) in treatment with chemotherapy, and who had a nutritional risk index of <97.5 and a Subjective Global B or C Assessment from August 2011 to July 2013. Patients with terminal cancer, liver failure (BT >3.5 mg/dL), renal failure (serum creatinine >2.5 mg/dL), dysfunctional digestive tract, surgery in the last 6 months, added immune or inflammatory pathology (Rheumatoid Arthritis, Inflammatory bowel disease, acquired immunodeficiency), as well as steroid users, were excluded.

Measurements, randomization and intervention.

Eligible participants were recruited and selected out of the outpatient oncology service, they were informed about the nature of the study, and the proposal of managing two groups, to then answer all their questions.

Patients were randomized in a simple 1:1 mapping from a computer-generated list using Medcal version 13, into two groups: a) patients receiving an energy intake of 30 kcal/kg/d plus enteral immunomodulating diet (group I, n=23) and b) patients receiving enteral isocaloric, isonitrogenous diet, in addition to an enteral diet supplemented with acid ω-3 (group II, n=20). Both groups received a daily intake of 500 ml during the first 10 days of chemotherapy.

At the start of the study and on day +5 and +10 of chemotherapy, blood tested parameters were: prealbumin (mg/dL), transferrin (mg/dL), total number of lymphocytes, IL-6 (pg/mL), TNF-α (pg/ml) and CRP (mg/dL). Anthropometry and body composition was measured at the beginning and end of the study, as serum albumin (g/dL).

Outcome Measures

The primary endpoint of the study was that participants presented a reduction in inflammatory markers CRP, IL-6 and TNF-α in patients diagnosed with cancer and being treated with chemotherapy, who had a Nutritional Risk Index <97.5 and Subjective Global Assessment B or C. We use the Subjective Global Assessment developed by Detsky in 1987 as a screening test, which is a clinical method of assessment of nutritional risk of a measurable patient through a medical history and physical examination, standardized and validated in several countries. Results are classified into three groups: a) well nourished, b) moderately malnourished and c) severely malnourished. The nutritional risk index formula was used as the objective evaluation method: NRI = [1.519 * serum albumin (g/L)] + [41.7 * (current weight/usual weight)]. Where: NRI 100 = well nourished NRI 97.5-100 = mild malnutrition, NRI 83.5-97.5 = moderate malnutrition and NRI <83.5 = severe malnutrition. Measurements of IL-6 and TNF-α were performed by flow cytometry using a 4 color FACS Calibur machine (Becton-Dickinson) with the human inflammatory cytokine kit. CRP de-

terminations were carried out with the CardioPhase hsCRP reagent using the BN system (Siemens Health Care Diagnostics) Marburg / Germany.

Anthropometric measurements included weight in kg, height in meters, as well as Quetelet index. The percentage of weight loss (as related to normal weight corresponding to 6 months before the study) and changes in Quetelet index were calculated. Body composition was determined using a portable electronic scale, with a maximum capacity of 330 lb (TANITA). The secondary endpoints were prealbumin, transferrin, albumin, lymphocyte count, and adverse secondary events to treatment.

In order to determine the secondary endpoints, which were prealbumin, transferrin, albumin, and lymphocyte count, blood samples were used using the Advia 1200 device (Siemens Healthcare Diagnostics, Deerfield, IL USA). Side effects associated with chemotherapy were neutropenia, vomiting, mucositis and neutropenic colitis. The adverse events associated with treatment that were evaluated, were the presence of abdominal distension, vomiting, diarrhea, or taste sensitivity.

Statistical analysis.

Sample Size: The sample size was calculated expecting a reduction of 31 mg mL for CRP,[16] two-tailed with a type I error of 5% and a power (1-β) of 0.80.

Data Analysis: Data are presented with measures of central and dispersion tendency for quantitative variables. A Student t test was carried out for independent groups. For nominal variables X2. The difference between repeated measurements in each group was performed using variance analysis (ANOVA) for more than two measurements. A value of $p<0.05$ was considered as statistically significant. Data were captured and analyzed in SPSS version 15 statistical software.

All participants signed the informed consent form. The study was approved by the Research Ethics Committee of the Hospital under institutional record HJM 1848/01.05.19.

Results

A total of 43 patients were eligible for the study. Fig. 1. The average age was 43.91 + 11.3 years, 62.8% (n = 27) women and 37.2% (n = 16) men. The demographic characteristics of the population studied are presented in table I.

The distribution of patients according to nutritional model was 23 patients in group I (immunomodulatory) and 20 patients in group II (ω-3 acids) table II.

The most common type of tumor was gynecologic in 48.9%, followed by gastrointestinal tract and testicular in 13.9% each, Non-Hodgkin lymphoma in 9.3%; head and neck tumors in 7%, and finally others: including medulloblastoma, cystadenoma, extragonal germinal 7%. The stages of the mayority were II and III. The characteristics of the type and stage of tumor per group are shown in table III.

The overall prevalence of moderate malnutrition was 48.8% and 51.2% for severe malnutrition by Subjective Global Assessment (SGA). Although Quetelet index (BMI) was reported at 25.8+ 5.1, the weight loss was recorded at 11.6 +7.6% of normal weight in the last six months, which may represent a loss of 1.9% per month. There were no significant intergroup differences in the biochemical measurement of nutritional parameters reporting an average albumin of

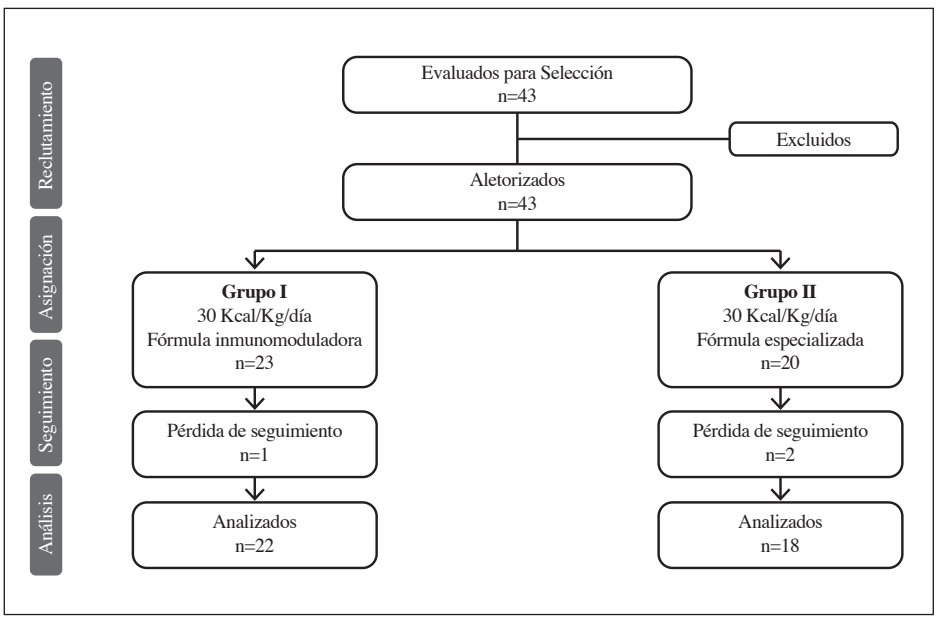

Fig. 1.—Analysis by intent-to-treat

Table I
Demographic characteristics and distribution of the population studied. (means + SD)

Característica	*Grupo I n=23*	*Grupo I n=20*	*p*
Edad (años)	44.3±11.12	43.45±11.80	0.808
Peso (Kg)	63.32±12.96	67.35±12.02	0.299
Talla (Cm)	158.48±9.40	160.10±8.46	0.558
IMC	25.27±5.12	26.43±5.11	0.461
Género (F/M)	16/7	11/9	0.336

No statistical differences

Table II
Distribution of patient per nutritional model

	Paciente	*Modelo*	*Característica*
Grupo I	n=23	Inmunomoduladora	Producto enteral adicionado con arginina, glutamina, ω-3, RNA (Inmunex®)
Grupo II	n=20	Especializada	Ac grasos ω-3 (Prosure®)

3.9+0.45 g/dL, prealbumin of 19.4 +7.5 mg/dL, transferrin 236+ 71.29 mg/dL, and total lymphocytes of 1016+ 672 uL .

The systemic inflammatory markers CRP, IL-6 and TNFα were homogeneously elevated in both groups, with a mean of 15.88 + 24.31mg/dL for CRP, 21.86+ 41.43 pg/mL, and 5.48 + 2.33 pg/mL for IL -6 and TNFα respectively. During the follow-up of both groups, a constant elevation of CRP and TNFα from baseline to chemotherapy day +10 was observed. CRP increased to 15.88 + 24.31mg/dL at 38.26+ 147.75mg/dL, with an intragroup I $p<0.05$, for TNFα of 5.48+2.33pg/mL at 7.01+6.89pg/mL. table IV While for IL-6 there was a decrease observed in both groups 21.86+41.43pg/mL at 17.18+16.27pg/mL, with higher results in group II (ω-3 acids), although not statistically significant figure 2.

Regarding the prealbumin levels there was a more significant increase observed in group II (ω-3 acids) vs group I (immunomodulatory) were statistically significant ($p <0.05$) table V. Transferrin levels increased in the second measurement vs baseline in group I (immunomodulatory), but the difference was not statistically significant.

In the analysis of body composition, both groups showed constant body weight, fat mass percentage, and lean mass, but no statistically significant difference between groups was observed.

There was a negative correlation between the proportion of lean mass to CRP serum levels; while high

Table III
Type and stage of cancer observed by group

Tipo de Cáncer	*Grupo I n=23*	*Grupo I n=20*
Ginecológicos	56.5% (13)	40% (8)
Ovario		
CaCu		
Endometrio		
Mama		
Testicular	4.4% (1)	25% (5)
LNH	4.4% (1)	15% (3)
Gastrointestinal	17.3% (4)	10% (2)
Esófago		
Gástrico		
Duodeno		
Colon y recto		
Cabeza y cuello	8.7% (2)	5% (1)
Otros	8.7% (2)	5% (1)
Estadios		
I	13% (3)	5% (1)
II	34.8% (8)	20% (4)
III	47.8% (11)	60% (12)
IV	4.4% (1)	15% (3)

Table IV
Follow-up of the inflammatory response by groups (mean+SD)

	Basal		*+5*		*+10*	
	Grupo I	*Grupo II*	*Grupo I*	*Grupo II*	*Grupo I*	*Grupo II*
PCR (mg/dL)	16.23±25.11	18.81±26.62	39.58±126.1*	14.01±20.56	51.99±193.37	18.26±28.40
IL-6 (pg/mL)	12.29±6.47	29.00±58.63	21.82±39.53	17.72±13.61	18.22±18.34	15.75±13.36
TNF-α (pg/mL)	4.95±0.80	6.29±3.59	7.93±9.94	7.52±8.90	7.01±8.20	6.93±4.80

* $p < 0.05$ vs baseline

Table V
Measurement of nutritional biochemical parameters during follow-up (mean ± SD)

	Basal		*+5*		*+10*	
	Grupo I	*Grupo II*	*Grupo I*	*Grupo II*	*Grupo I*	*Grupo II*
Prealbúmina (mg/dL)	20.16±7.49	18.59±7.74*	23.626±8.52	20.45±7.92	20.45±7.11	25.30±8.17*
Transferrina (mg/dL)	249.39±69.9	220.75±71.52	266.23±99.97	212.29±80.72	236.59±57.98	215.18±60.23

* $p < 0.05$

levels of IL-6 were associated with greater weight loss ($p < 0.05$).

The side effects associated with chemotherapy present in the patients within the study were: neutropenia 25.6%, vomiting 11.6%, as well as moderate mucositis in 4.7%. The adverse events associated with the type of enteral formula, were reported only in group I (immunomodulatory), with 13% of the patients reporting an unpleasant taste.

Discussion

This randomized treatment study with an immunomodulator formula vs a specialized ω-3 acid-high formula in cancer patients receiving chemotherapy, revealed that there is no significant reduction in markers of systemic inflammation for either group.

The study population was homogeneous and was mostly formed by young adults and female patients, with gynecological and gastrointestinal types of cancer as the most common. A greater weight loss has been recorded for this type of tumors; therefore, even when the population studied had overweight, the recorded weight loss was greater than 10% of the usual weight in the last six months, classifying them with severe malnutrition, as reported by other authors[16,17].

Despite the weight loss, nutritional biochemical markers were within normal parameters. However, it should be considered that serum albumin is a reliable indicator of morbidity and mortality rather than nutritional status, because its values are influenced by malnutrition, hydration status, trans-capillary escape, as well as the inflammatory response.

Since the stage of the disease is a factor in weight loss, the applicability of this study included patients within stage II and III, where a more aggressive biological behavior of the tumor starts promoting an increased protein consumption and replacement. These stages also show increased metabolic demands of the production and release of biological mediators, such as pro-inflammatory cytokines and other tumor-derived products that contribute to the development of cachexia[18th].

Although several studies suggest that an immunomodulatory diet improves the immune and inflammatory function in cancer patients[14,19,20-23] and that supplementation with polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic ω3 acid can reduce the inflammatory response and modulate lymphocytes proliferation[13,16,17,18,20,24], during this study there was an increase in inflammatory markers, CRP and TNFα predominantly and a decrease in serum levels of IL-6 only in the group receiving the specialized formula high in ω3, but with no statistical significance.

In contrast to other studies, these comparisons should be carefully considered, because most authors describe a reduction of inflammatory markers during interventions within the perioperative stage for can-

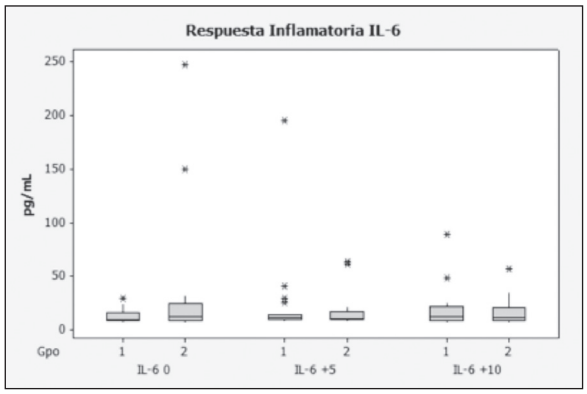

Fig. 2.—Changes in the measurement of IL-6 (pg/mL) during follow-up in both groups.

cer patients[25,26] and not during chemotherapy as in our study.

Considering that chemotherapy kills cancer cells by necrosis, followed by the release of inflammatory mediators, including nucleic acids, Hsp70, HMGB-1, calcium-bound proteins S100 and cytokines IL-1α; this could explain why we observe a trend in the increase of inflammatory markers during the different measurements[27].

Moreover, inflammation has been associated with many other cancer-independent conditions, such as cardiovascular disease, obesity, depression, hypertension, smoking, and even depression. In cancer patients it is assumed on the one hand, that inflammation promoted by the tumor and antitumor immunity coexist at different points[28]. Moreover, some results may show an increase in one pro-inflammatory marker and a decrease in another. These are clear contradictions in the effects and measurement of inflammation. In these cases we have used an inflammatory index where -1 is assigned to proinflammatory effects (means an increase in IL-1β, IL-6, TNFα or CRP or a decrease in IL-4 or IL-10): +1 if there was an anti-inflammatory effect (meaning a reduction in IL-1β, IL-6, TNFα or CRP or increase in IL-4 or IL-10); and 0 if there are no changes in inflammatory markers[29]. In our study we carried out a measurement of IL-10 as an anti-inflammatory marker and calculated the inflammatory index values obtained at baseline to 2.7, at day +5 of chemotherapy to 2.3, and finally on day +10 at 2.2, which results in a strong anti-inflammatory response in both groups.

As for the impact on biochemical nutritional markers we observed an increase in both transferrin and prealbumin at follow-up day +5 and then a decrease at day +10, a situation associated with the presence of side effects of chemotherapy. Side effects associated with chemotherapy in our population were neutropenia and effects on the gastrointestinal tract such as nausea, vomiting, and mucositis. The direct involvement of the gastrointestinal tract in the tumor process leads to alterations in the digestion and absorption of nutrients, with the consequent exacerbation of malnutrition and cachexia[23].

However, although our study population already had on admission varying degrees of malnutrition, a situation exacerbated by the effects of chemotherapy and which was reflected in the decline in prealbumin and transferrin at the end of follow-up; our analysis showed that supplementation with both formulas maintains body weight and lean body mass of the patient, both of them being prognostic factors previously described.

Inflammatory markers, particularly CRP and IL-6 have been correlated with weight loss and lean mass. Actually, in some studies CRP and albumin were identified as predictors of weight loss. We report a negative correlation between serum CRP levels and the percentage of lean mass, as well as a positive correlation between serum IL-6 levels and the percentage of weight loss[30].

The various enteral formulas on the market are generally well tolerated. During the study only one case of higher taste and odor sensitivity was reported in Group I with the immunomodulatory formula. This can be explained by the hydrolysis of its components and high osmolarity of the formula, a situation that is exacerbated by gastrointestinal changes that cancer patients undergo during chemotherapy.

Although nutritional support in cancer patients reverses the state of malnutrition and cachexia, while preventing complications and decrease in mortality rate, there are still many unanswered questions regarding what nutrients could be more effective against the inflammatory response in patients with cancer, as well as which could be the best biomarker of inflammation given the heterogeneity of genetic and epigenetic alterations, to the inflammatory response specific in some tissues and various signaling pathways that trigger inflammation. A possible limitation of our study was that only 43 participants were included, and we could increase this number in a power of 0.90 in the calculation of sample size. Another limitation was the limited time of the intervention compared to the duration of chemotherapy. We suggest a study with more participants and longer intervention and follow-up periods to compare the impact of immunonutrition vs ω-3 fatty acids.

Conclusions

The administration of enteral supplements during chemotherapy inhibits nutritional deterioration and maintains weight and lean mass. No decrease in serum levels of CRP, IL-6 and TNFα was observed. More studies are needed to determine the type of enteral formula that could be more useful in these patients, and which play a major role in the inflammatory response.

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