Nutrición Hospitalaria

Nutr Hosp. 2015;31(4):1689-1692
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original/*Cáncer*

Tissue effects of glutamine in rectal cancer patients treated with preoperative chemoradiotherapy

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Abstract

Background: **The aim was to evaluate the effects of glutamine on tumor regression and histological damage in patients with rectal patients following chemoradiotherapy previous to surgery.**

Material and methods: **Ten patients with rectal cancer surgically removed after chemoradiotherapy were included, a subgroup of a randomized trial that compared glutamine and placebo in the prevention of acute radiation enteritis. Samples of neoplasm and healthy tissue were evaluated by an expert pathologist searching for signs of tumor regression, muciphages, and signs of radiation-induced damage.**

Results: **There were no differences in the grade of tumor regression with either glutamine or placebo. All patients who received glutamine presented muciphages, compared with 28.6% of the placebo group (p = 0.038). Histological damage was similar in patients receiving glutamine or placebo, and between those with radiation enteritis or without toxicity.**

Conclusion: **Glutamine did not exert a protective effect over chemoradiotherapy in rectal cancer or healthy rectal tissue.**

(*Nutr Hosp*. 2015;31:1689-1692)

DOI:10.3305/nh.2015.31.4.8521

Key words: *Glutamine. Chemoradiotherapy. Enteritis. Muciphages.*

EFECTOS TISULARES DE LA GLUTAMINA EN PACIENTES CON CÁNCER DE RECTO TRATADOS CON QUIMIORRADIOTERAPIA PREOPERATORIA

Resumen

Introducción: **El objetivo fue evaluar los efectos de la administración de glutamina sobre la regresión tumoral y sobre el tejido sano en pacientes con cáncer rectal que recibieron quimiorradioterapia.**

Material y métodos: **Se incluyó 10 pacientes con cáncer rectal operado después de quimiorradioterapia, un subgrupo de un ensayo clínico que comparó glutamina con placebo en la prevención de enteritis aguda. Un patólogo experto analizó las muestras de tumor y tejido sano, buscando datos de regresión tumoral, mucífagos y daño por radiación.**

Resultados: **No hubo diferencias entre placebo y glutamina en el grado de regresión tumoral. Todos los pacientes con glutamina presentaron mucífagos, frente al 28,6% con placebo (p = 0,038). El daño sobre tejido sano fue similar en los pacientes con glutamina y placebo, y entre aquellos con y sin enteritis.**

Conclusión: **La glutamina no ejerce un efecto protector frente a la quimiorradioterapia sobre el tumor o el tejido rectal sano.**

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Introduction

Glutamine is an amino acid with antioxidant and trophic properties that has been widely used as an immunonutrient with the purpose of modifying the progression of several diseases. Regarding the toxicity caused by radiotherapy, a previous trial from our group showed an increase in the number of cases of acute and chronic diarrhea in patients receiving glutamine during radiotherapy, compared with placebo[1,2]. The aim of the current study was to assess the effects of glutamine on tissue damage and tumor regression in rectal cancer patients treated with chemoradiotherapy.

Subjects and methods

The methodology followed in this trial has been previously reported[1]. Briefly, a randomized, controlled,

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Recibido: 11-XII-2014.
Aceptado: 15-I-2015.

double-blind study was designed to compare the effectiveness of glutamine versus placebo in the prevention of radiation enteritis. The treatment group received 30 g/day of oral glutamine and the placebo group received 30 g/day of whole casein, from 3 days before starting radiotherapy until the completion of antitumor treatment. The study was evaluated by the local Research Ethics Committee, which confirmed that the study followed the Declaration of Helsinki, and it was registered in Clinical Trials (www.clinicaltrials.gov) with the number NCT00828399. Written informed consent was obtained from every patient.

The current analysis included a subgroup of patients with rectal cancer in which surgery was indicated after the completion of chemoradiotherapy. The sample obtained in the operating room was processed according the standard procedure of the center, and analyzed by a pathologist experienced in colorectal tumors. A classification of rectal cancer regression after chemoradiotherapy has been developed by Ryan *et al*, after previous work by Mandard *et al*[3,4]. The grades of regression described by Ryan include: grade 1, complete or almost complete regression (no viable or isolated tumor cells); grade 2, partial response (residual tumor smaller than fibrosis); grade 3, no response (significant fibrosis exceeded by tumor or residual tumor without extensive fibrosis). In our center, a modified version of Ryan's grades is routinely used: grade 0 (complete response), grade 1 (moderate response), grade 2 (minimum response), and grade 3 (no response to treatment). The following histological changes associated with radiotherapy were searched in normal rectal tissue: lymphoplasmacytic or eosinophilic infiltration of the lamina propria, eosinophilic abscesses in crypts, edema or fibrosis of the lamina propria, fibrosis of the submucosa, thickening of the arteries of submucosa, alteration of architecture, and the presence of muciphages[5,6,7].

The normal distribution of quantitative variables was examined by the Shapiro-Wilk test. Those matching a normal distribution were summarized as the mean and standard deviation (SD) and compared with paired Student's t-test. Categorical variables were summarized as percentages and compared with the c^2 test.

Table I
Comparison of the grade of tumor regression after preoperative chemoradiotherapy

Grade of regression	*Glutamine n (%)*	*Placebo n (%)*	*p*
Grade 0 Complete regression	0 (0.0)	1 (14.3)	0.788
Grade 1 Moderate regression	1 (33.3)	2 (28.6)	
Grade 2 Minimal regression	2 (66.7)	4 (57.1)	
Grade 3 No regression	0 (0.0)	0 (0.0)	

Results

The samples of 10 patients could be examined after surgery, three of them had received glutamine and seven placebo. The mean age was 72.3 (1.9) years, 70.0% were males, the median dose of radiotherapy received was 45.0 Gy (interquartile range = 5.4), and 30.0% developed acute radiation enteritis. There were no significant differences between the intervention groups in these characteristics. Tumor regression was similar in both groups, and in all patients some degree of response to treatment was observed (Table I). No significant differences were found between those who developed acute enteritis and those without toxicity: grade 0 (0.0% vs.16.7%), grade 1 (25.0% vs. 33.3%), and grade 2 (75.0% vs. 50.0%) (p = 0.615).

Histological changes in the normal rectum are summarized in tables II and III. Some changes were not observed in the studied samples, like eosinophilic infiltration or edema of the lamina propria.

Table II
Comparison of histological changes in the rectum after preoperative chemoradiotherapy according to treatment

Grade of regression	*Glutamine n (%)*	*Placebo n (%)*	*p*
Lymphoplasmacytic infiltration of lamina propria	3 (100.0)	7 (100.0)	1.000
Eosinophilic infiltration of lamina propria	3 (100.0)	7 (100.0)	1.000
Eosinophilic abscesses in crypts	0 (0.0)	3 (42.9)	0.175
Edema of submucosa	0 (0.0)	5 (71.4)	0.038
Fibrosis of submucosa	2 (66.7)	3 (42.9)	0.490
Fibrosis of intima media of the arteries of submucosa	2 (66.7)	2 (28.6)	0.260
Alteration of architecture	0 (0.0)	1 (14.3)	0.490

Table III
Comparison of histological changes in the rectum after preoperative chemoradiotherapy according to the development of acute radiation enteritis

Grade of regression	*Acute enteritis n (%)*	*No enteritis n (%)*	*p*
Lymphoplasmacytic infiltration of lamina propria	3 (100.0)	7 (100.0)	1.000
Eosinophilic infiltration of lamina propria	3 (100.0)	7 (100.0)	1.000
Eosinophilic abscesses in crypts	1 (33.3)	2 (28.6)	0.880
Edema of submucosa	1 (33.3)	4 (57.1)	0.429
Fibrosis of submucosa	1 (33.3)	4 (57.1)	0.429
Fibrosis of intima media of the arteries of submucosa	1 (33.3)	3 (42.9)	0.778
Alteration of architectures	1 (33.3)	0 (0.0)	0.107

All the patients who received glutamine presented muciphages, but only 28.6% of the placebo group did ($p = 0.038$). These cells were found in 57.1% of patients with acute radiation enteritis and in 33.3% of those without intestinal toxicity ($p = 0.490$).

Discussion

There are scarce opportunities to evaluate the effects of immunonutrients on human tissues due to the ethical issues related to the invasive procedures needed to obtain the samples. This study, in which rectal tumor and some normal tissue were surgically removed after chemoradiotherapy following the current guidelines, offers the opportunity to describe the histological effects of glutamine. Although limited by the few patients included in this study, some observations could be highlighted.

First, there were no differences in the efficacy of chemoradiotherapy in the two groups. This result may add some evidence against the potential trophic or protective role of glutamine on neoplastic cells, an adverse effect described in animals but with inconsistent data in humans[8]. In addition, a similar evolution of tumoral markers had been observed in the patients recruited in this trial who received glutamine and those who received placebo, and the frequency of the different grades of regression was similar to that described by Ryan[1,3]. Some *in vitro* studies have found that the administration of glutamine does not inhibit the cytotoxic effects of chemoradiotherapy, and could even enhance them[9].

Second, the presence of muciphages was significantly more frequent in patients who received glutamine. These cells are mucosal macrophages containing mucin, which is obtained from the phagocytosis of damaged crypts[4,10]. Although they can be found in almost 50% of rectal biopsies of healthy people, muciphages have been related to intestinal diseases and the repair of mucosal damage[11,12,13]. This finding may corroborate the link between the administration of oral glutamine and the development of acute radiation enteritis that has been previously presented[1].

Third, pathological findings in the normal rectum after the administration of chemoradiotherapy were unspecific and may be poorly related to the symptoms of enteritis. The only significant difference between glutamine and placebo was the presence of edema in the submucosa, and there were no differences between patients who developed intestinal toxicity and those with diarrhea.

In conclusion, and with all the caution that the limited number of patients imposes, these results may support that glutamine does not exert a protective effect on the normal rectum or rectal carcinoma.

Acknowledgements

AVC, MDBP, and FC designed the research. AVC and ACF conducted the research. MHM performed the pathology. ICR revised the manuscript. All authors revised and approved the final manuscript.

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