Nutrition 31 (2015) 200–204

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Effects of oral glutamine during abdominal radiotherapy on chronic radiation enteritis: A randomized controlled trial

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ARTICLE INFO

Article history:
Received 22 November 2013
Accepted 11 August 2014

Keywords:
Radiotherapy
Chemotherapy
Chronic radiation enteritis
Glutamine

ABSTRACT

Objective: Glutamine has been proposed as a preventive treatment for toxicity related to cancer therapies. The aim of this study was to test the efficacy of glutamine in the prevention of radiation enteritis.

Methods: A randomized, double-blind, controlled trial was performed including 69 patients who were assigned to receive either glutamine (Gln, 30 g/d) or placebo while they were receiving abdominal radiotherapy. Patients were re-evaluated 1 y after completion of treatment. The presence of chronic enteritis was assessed using the Radiation Therapy Oncology Group scale. Nutritional status was evaluated using subjective global assessment, weight, and bioimpedance. Relative risk (RR) and its confidence interval (CI) were also calculated.

Results: The trial initially included 69 patients (34 Gln, 35 placebo), but 11 patients were lost during follow-up (4 Gln, 7 placebo; $P = 0.296$). Chronic enteritis was developed by 14 % of patients: Gln 16.7 % versus placebo 11.1% (RR = 1.33; 95 % CI, 0.35–5.03; $P = 0.540$). Most cases of enteritis were grade I (75 %), with no differences between groups. The stool frequency increased after radiotherapy in patients who received Gln (from 1 ± 1 to 2 ± 2 stools per day, $P = 0.012$), but remained unchanged with placebo (1 ± 1 stools per day, $P = 0.858$; difference between groups $P = 0.004$). There were no differences between the two groups in terms of weight, fat mass, or fat-free mass index, or between patients with enteritis and those without intestinal toxicity.

Conclusions: Chronic enteritis is a relatively infrequent phenomenon, and Gln administration during radiotherapy does not exert a protective effect.

Introduction

Radiation-induced tissue damage is a complex process in which oxidative stress, inflammation, cellular apoptosis, and genetic changes are involved. The acute toxicity caused by radiotherapy (RT) may be observed during exposure, lasts >1–2 mo, and is caused by the loss of functional, replicating cells. Chronic injury is the consequence of the loss of parenchymal cells and the alteration of microcirculation in the irradiated organ, changes that produce fibrosis and loss of function in organs, and which typically appear months to years after exposure [1]. Factors such as radiation dose and mode of administration, sensitivity of organs to radiation, the volume of irradiated tissue, concomitant treatments (e.g., chemotherapy), and some patient characteristics (e.g., age), influence the development of toxicity following RT [2]. More than 50 % of patients who receive pelvic RT may subsequently suffer gastrointestinal (GI) symptoms, such as diarrhea, that compromise quality of life. Radiation-induced diarrhea has many causes, including bacterial overgrowth, changes in bowel transit, malabsorption, psychological factors, and medications [3].

Glutamine (Gln) may protect the gut during RT by means of its particular functions. Glutamine contributes to intestinal

This research was supported by grants received from the Fundación de la Sociedad Española de Endocrinología y Nutrición (FSEEN), and the Consejería de Sanidad (Consejería, GRS 326/B/08) (Junta de Castilla y León, SACYL GRS 326/B/08). AVC, MDBP, and FCC designed the research. AVC and ACF conducted the research. ICR revised the manuscript. All authors revised and approved the final manuscript. The authors have no conflicts of interest to declare.

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0899-9007/
http://dx.doi.org/10.1016/j.nut.2014.08.003

trophism, is the precursor of glutathione (a key molecule in the antioxidant chain), modulates the inflammatory response, protects cells from various insults by producing heat-shock proteins, and also influences apoptosis [4,5]. Few studies have assessed the effects of Gln on radiation enteritis [6–9]. A previous trial showed an increase in the number of cases of acute diarrhea in patients receiving Gln during RT compared with placebo [10]. The hypothesis of this study was that the biological effects of Gln could prevent the development of either acute or chronic radiation enteritis. The aim of the present study was to assess the development of chronic radiation enteritis in the population recruited in this previous trial.

Methods and participants

The methodology followed in this trial was reported previously [10]. Briefly, a randomized controlled, double-blind study was designed to compare the effectiveness of Gln versus placebo in the prevention of radiation enteritis. The study was evaluated by the local Research Ethics Committee, which confirmed that it followed the Declaration of Helsinki, and was registered with Clinical Trials (ref. no. NCT00828399).

Participants

Inclusion criteria included being age >18 y and undergoing abdominal or pelvic RT due to a neoplasm in that location, independent of other cancer treatments (surgery, chemotherapy, or brachytherapy). Exclusion criteria included a life expectancy <1 y, short bowel syndrome, intestinal diseases (e.g., inflammatory bowel disease, celiac disease, or Whipple disease), moderate or severe chronic kidney disease, and the inability to receive either oral medication or to understand the information provided. All patients signed an informed consent document. The treatment group received supplementation with 30 g/d of oral Gln (Glutamina NM©, Nutrición Médica, Madrid) and the control group received a placebo (supplementation of 30 g/d of whole casein, Proteína NM©, Nutrición Médica, Madrid) beginning 3 d before starting RT until completion of the antitumoral treatment. Researchers did not modify the patients' dietary habits; rather, patients followed their usual diet including protein amount and sources.

Chronic radiation enteritis assessment

In this phase of the study, patients were re-evaluated 1 y post-RT. At that time, they were asked about the number and characteristics of stools, and intestinal toxicity was classified according to the criteria of the Radiation Therapy Oncology Group (RTOG): grade 0 (no diarrhea), grade I (5 stools per day, abdominal cramping, scarce bleeding), grade II (>5 stools per day, rectal mucus, intermittent bleeding), grade III (intestinal obstruction or bleeding that requires surgery), and grade IV (necrosis, perforation, or fistula).

Nutritional assessment

Nutritional status was evaluated using the Subjective Global Assessment (SGA). Anthropometry included the measurement of height and body weight, body mass index (BMI), dynamometry (Smedlay's Dynamo Meter©, Tokyo, Japan), and the determination of fat-free mass (FFM) and fat mass by bioelectrical impedance (Tanita Body Composition Analyzer TBF-300©). The fat-free mass index (FFMI) was calculated by dividing an individual's FFM by the square of their height (kg/m^2).

Statistical analysis

The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test. Those variables with a normal distribution were summarized as the mean and SD and compared using the paired Student's *t* test. Quantitative variables without a normal distribution were summarized by the median (Md) and interquartile range (IQR), and compared using Mann-Whitney's *U*-test. Categorical variables were summarized as percentages and compared using the χ^2 test. Relative risk (RR) and its 95 % confidence interval (CI) were also calculated.

Results

Sixty-nine patients were originally recruited for the trial, however, only 57 could be reassessed 1 y after the end of RT (Fig. 1). The participants had received a daily dose of Gln of 0.4 (0.1) g/kg (minimum 0.3 g/kg, maximum 0.6 g/kg). No differences were found between the characteristics of the initial group of patients and those that completed the follow-up (Table 1).

Stool characteristics

Patients in both groups reported a stool frequency of once per day (Md, IQR = 1) before RT. After 1 y, the patients who had received Gln reported two stools per day (Md, IQR = 1). Those who were randomized to the placebo group reported one stool per day (Md, IQR = 1). The increase in stool frequency in the Gln group was significant ($P = 0.01$), as was the difference between the two groups at 1 y ($P = 0.004$). In the Gln group 56.7 % experienced changes in intestinal movements with respect to before RT versus 40.7 % in the placebo group ($P = 0.230$). There were no differences in the frequency of patients with liquid or soft stools between the Gln and placebo groups: 26.7 % (8 of 30) versus 11.1% (3 of 27), respectively, $P = 0.137$. However, more patients in the former group reported changes in stool consistency: 33.3 % (10 of 30) versus 7.4 % (2 of 27), $P = 0.020$.

Chronic radiation enteritis

Chronic enteritis was present in 14 % (n = 8) of the patients. Most cases were grade I intestinal toxicity (75 %, n = 6), with one patient each suffering from grade II (12.5 %) or grade IV (12.5 %) toxicity according to the RTOG criteria. In the Gln group 16.7 % presented diarrhea (n = 5) versus 11.1% (n = 3) in the placebo group ($P = 0.540$). The severity of chronic enteritis was similar between groups, with most cases being grade I (Gln 60 % versus placebo 100 %, $P = 0.600$). The RR for the development of chronic enteritis in patients who received Gln during RT was 1.33 (CI 95 %, 0.35–5.03). When subgroups of the different types of tumor were analyzed, there were no differences according to the treatment received (Fig. 2). The RR of chronic enteritis was 1.57 for urologic tumours (CI 95 %, 0.16–5.16), 17 for gynecologic tumors (CI 95 %, 0.06–4.70), and 0.58 for rectal cancer (CI 95 %, 0.07–4.95).

Nutritional status

During the administration of RT, most patients maintained weight and FFM, and few patients developed malnutrition (three with Gln, two with placebo), as a result of a stable energy and protein intake [10]. One year later, according to the SGA, one patient in the placebo group was malnourished; none of the patients in the Gln group were malnourished ($P = 0.288$). There were no differences between patients in terms of anthropometry (Table 2).

None of the patients with chronic enteritis was diagnosed as malnourished by SGA versus only one of those without intestinal toxicity ($P = 0.648$). Patients with chronic enteritis presented similar nutritional parameters as patients without toxicity (Table 2).

Discussion

To our knowledge, this is the first randomized, double-blind, controlled trial to evaluate the effects of the administration of oral Gln during RT on chronic radiation enteritis. During RT, more cases of acute diarrhea were found among patients who had received Gln than in those patients who received placebo [10]. One year later, patients who were randomly allocated to receive 30 g/d of Gln during RT presented significant changes in stool frequency