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Effect of parenteral glutamine in patients with gastrointestinal cancer undergoing surgery

Efecto de la glutamina parenteral en pacientes con cáncer gastrointestinal sometidos a cirugía

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Abstract

Background and objective: malnutrition during cancer treatment is common in patients; therefore, nutritional intervention has an important role in cancer prognosis. Total parenteral nutrition is indicated for patients subjected to a major surgery with gastrointestinal complications. Nutritional support could be improved with glutamine (Gln). Therefore, in this work, the effect of parenteral glutamine in patients with gastrointestinal cancer undergoing surgery was studied.

Material and methods: patients were classified into two groups: non-supplemented and supplemented (Gln; 0.4 g/kg/day). Both groups received parenteral nutrition. One and seven days after surgery the nutritional status was evaluated. Hematic cytometry, protein metabolism and biochemical data were analyzed. A questionnaire was also applied to assess gastrointestinal function.

Results: after the intervention, the nutritional status in both groups improved. However, the nutritional condition improved significantly better ($p = 0.008$) in the supplemented group. According to the gastrointestinal function evaluation, the supplemented group changed from severe to mild dysfunction ($p = 0.0001$). The non-supplemented group progressed from moderate to severe dysfunction, but no changes in blood cell markers were observed. The supplemented group improved its concentration of lymphocytes ($p = 0.014$). The plasma albumin concentration did not change in groups, but prealbumin improved significantly ($p = 0.012$) in the group that was supplemented with Gln.

Conclusion: intravenous nutritional support supplemented with glutamine can improve gastrointestinal function, improving the absorption of nutrients, which leads to a better state of nutrition. It also has positive effects on plasma concentration of lymphocytes, monocytes and prealbumin.

Key words:

Glutamine. Parenteral nutrition. Gastrointestinal cancer. Surgery. Nutritional status.

Resumen

Introducción y objetivo: los pacientes con cáncer desarrollan desnutrición durante el tratamiento antineoplásico, es por ello que el soporte nutricio tiene un rol importante. La nutrición parenteral es el soporte indicado para pacientes que fueron sometidos a cirugía con complicaciones gastrointestinales; este soporte puede ser suplementado con glutamina. Evaluamos el efecto de la glutamina parenteral en pacientes con cáncer gastrointestinal sometidos a cirugía.

Material y métodos: se aleatorizaron los pacientes en dos grupos. Ambos grupos recibieron nutrición parenteral, en un grupo no suplementada y en otro grupo suplementada con glutamina (0,4 g/kg/día). Las medidas se tomaron el día uno y el día siete posteriores a la cirugía; en ambas mediciones se evaluó el estado nutricional, se tomó una muestra sanguínea para analizar parámetros bioquímicos y se aplicó un cuestionario de función gastrointestinal.

Resultados: después de la intervención, el estado nutricional mejoró en ambos grupos, sin embargo, en el grupo suplementado mejoró significativamente ($p = 0,008$). De acuerdo a la función gastrointestinal, el grupo suplementado progresó de disfunción severa a leve ($p = 0,0001$), mientras que el grupo no suplementado progresó de disfunción moderada a severa. En cuanto a los parámetros bioquímicos, no hubo cambios en el grupo no suplementado. En ambos grupos no hubo cambios en las concentraciones plasmáticas de albúmina. En el grupo suplementado mejoraron de manera significativa las concentraciones de linfocitos ($p = 0,014$) y prealbúmina ($p = 0,012$).

Conclusión: el apoyo nutricio endovenoso suplementado con glutamina puede mejorar la función gastrointestinal, mejorando la absorción de nutrimentos, lo que conlleva a un mejor estado de nutrición. Asimismo, tiene efectos positivos en las concentraciones plasmáticas de linfocitos y monocitos y prealbúmina.

Palabras clave:

Glutamina. Nutrición parenteral. Cáncer gastrointestinal. Cirugía. Estado nutricional.

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INTRODUCTION

According to the World Health Organization (WHO), cancer is one of the main causes of death in the world. Lung, liver, gastric, colorectal, breast and esophagus cancer have the highest mortality and incidence rates. In 2012, it was reported that around 8.2 million people died as a result of this disease (1).

Around 40 to 80% of cancer patients develop malnutrition during their treatment; this could increase up to 90% in advanced disease (2). Malnutrition in cancer patients may occur due to different reasons: a) basic mechanisms of malnutrition; b) cancer cachexia; c) metabolic and digestive disorders; d) physiological disorders of the patient (anorexia-cachexia syndrome); and e) side effects of cancer treatment. Specially, gastrointestinal cancer may induce mechanical and functional complications, which could alter eating patterns in patients. In these types of cancer, the patients usually present a deteriorated digestion and malabsorption (3), leading to malnutrition.

Since it was established that cancer patients present a deteriorated nutritional status, a nutritional intervention has an important role in the treatment. The aim of nutritional support is to guarantee nutritional requirements, reduce micronutrient deficiencies, maintain muscle mass, and improve food intake and quality of life. In surgical patients, nutritional support therapy has an important role in the prevention and treatment of malnutrition and catabolism. Total parenteral nutrition (TPN) is indicated in the postoperative in the following circumstances: a) undernourished patients; b) patients poorly tolerating enteral nutrition; c) postoperative complications impairing gastrointestinal function in patients who are unable to receive and absorb adequate amounts of oral or enteral feeding for at least seven days; and d) gastrointestinal surgery. This support could be improved when it is supplemented with immunomodulatory nutrients such as glutamine. This amino acid may be considered when the patients require parenteral nutrition (4-7).

Glutamine (Gln) is the most abundant free non-essential amino acid in the body. Its primary source is skeletal muscle, but during catabolic status, infection, surgery or trauma, it is considered as semi-essential due to a depletion of its concentrations (8,9). The main functions of this amino acid are: a) main substrate for enterocytes; b) precursor of glutathione, the main endogenous antioxidant; c) prevention of bacterial translocation; and d) reduction of morbidity in surgery, sepsis, infection and trauma (10,11). Gln deprivation is related to muscle loss and reduced protein synthesis; therefore, Gln is conditionally indispensable in cancer, because it is characterized as being a hypermetabolic and hypercatabolic situation (13,14).

The aim of the study was to analyze the effect of parenteral glutamine in patients with gastrointestinal cancer who were undergoing surgery on nutritional status and gastrointestinal function.

PATIENTS AND METHODS

STUDY DESIGN

A prospective, interventional and longitudinal study was conducted between January 2015 and November 2017 at the Oncology Hospital of the (Instituto de Seguridad Social del Estado de Mexico y Municipios (ISSEMyM) in Mexico. Patients who entered the study met the following inclusion criteria: men and women over 18 years of age with primary cancer diagnosis (esophagus, gastric, colon, rectum, pancreas or liver), subjected to surgery, hospitalized and with indication of TPN minimum of seven days. Patients with renal failure, hepatic failure or with cachexia were not included in the study. Written informed consent was obtained from all patients and the study was approved by the local Committee of the hospital.

Patients were allocated in two groups by simple randomization method (15). Group 1 received only TPN (non-supplemented) and group 2 received TPN enriched with Gln dipeptide. The dose of intravenous glutamine supplementation was 0.4 g/kg/day and it was administered in the form of N(2)-L-alanyl-L-glutamine. The Department of Nutrition of the hospital did the calculation of the nutritional requirements for intravenous nutrition. The energy requirement was calculated by the Harris-Benedict formula and the protein intake was 1.5-2.0 g/kg of patient weight (16).

The measurements were performed at two different times: day one and day seven with the nutritional intervention with TPN after the surgery. The nutritional status was evaluated with the Subjective Global Assessment (16,17), which considers anthropometric, biochemical, clinical and dietetic data. In addition, blood samples were taken to analyze protein metabolism and a questionnaire was applied to measure gastrointestinal function.

ANTHROPOMETRIC MEASUREMENTS

Weight and body composition were measured with an electric bioimpedance bascule (Tanita®, Bc533). The weight, muscle and bone mass was recorded in kilograms, while fat mass and water were expressed in percentage. Height was measured with a mobile Seca® stadiometer (Seca 213) and recorded in meters. Arm muscle circumference was taken with a metallic anthropometric tape and recorded in centimeters. The skin fold thickness was measured with Slim-guide® in millimeters.

BLOOD SAMPLE

Samples were obtained by venipuncture; glucose (mg/dl), urea (mg/dl), and creatinine (mg/dl) values were obtained by an enzymatic method. Prealbumin (mg/dl) was studied by immunonephelometry and albumin (g/dl) concentration was obtained by colorimetry. Lymphocytes (10^3/µl), monocytes (10^3/µl) and neutrophils (10^3/µl) were counted in an automated cell counter. All the analyses were performed using Roche® reactants.

QUESTIONNAIRE FOR GASTROINTESTINAL FUNCTION

The gastrointestinal function questionnaire includes four categories: a) stool frequency; b) stool consistency; c) stool emergency;

and d) abdominal discomfort. Each category consisted of four items with a Likert scale where 4 points represent normal function; 5 to 8 points represent mild dysfunction; 9 to 12 points, moderate dysfunction; and 13 to 16 points, severe dysfunction (Appendix 1).

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS version 22 (SPSS Inc., Chicago, Illinois). Baseline quantitative characteristics of the patients were represented by mean ± standard deviations. Categorical variables were displayed as frequencies and percentages. The Chi-square test was used to analyze the association between categorical variables and the t-test was used to compare groups between day 1 and day 7 after surgery.

RESULTS

Between January 2015 and September 2017, 70 subjects were recruited. Group 1 (non-supplemented with Gln) included 40 patients and group 2 (supplemented with Gln) included 30 patients. Table I shows baseline characteristics for the patients studied. There was no significant difference between both groups with regard to gender, oncologic diagnosis and anthropometric measurements. Before intervention, a physical examination was performed to measure clinical manifestations. The majority of patients presented micronutrient deficiency (70%), muscle wasting (62.5%) and dehydration (40%).

According to the anthropometric measurements (Table I), the average tricipital skinfold was below the standard and the average arm circumference was within normal values in both groups. Body composition, mean visceral fat, bone mass, muscle mass and water percentage were normal in all patients. The weight loss percentage indicated that the majority of patients presented a severe risk of malnutrition in both groups.

At the beginning of the treatment both groups presented more cases of severe and moderate malnutrition. After seven days with nutritional intervention, both groups improved their nutritional status (Table II).

In group 1 (non-supplemented, day 7), the majority of the patients (44%) presented moderate malnutrition, but the cases with severe malnutrition decreased. In group 2 (supplemented with Gln), the majority of patients presented moderate (44%) and mild malnutrition (44%), and only 12% presented severe malnutrition. Therefore, the nutritional status was significantly better in the group supplemented with Gln ($p = 0.008$).

The treatment response of gastrointestinal function is shown in table III. At day one the majority of patients (44%) in group 1 presented mild dysfunction, and just one case presented normal function. In group 2, the majority of patients (48%) had moderate dysfunction compared to severe (36%) or mild (16%) dysfunction; no one presented normal function.

After the intervention (day 7), severe dysfunction cases increased to 36% in group 1, while mild dysfunction cases decreased to 32%. In group 2 the majority of patients (80%) improved their gastrointestinal function. This improvement was observed in the cases of moderate and severe dysfunction that improved to mild dysfunction, reducing almost all cases of severe dysfunction. Therefore, there was a significant difference ($p = 0.0001$) between baseline and day seven.

Treatment response on protein metabolism is shown in table IV. At the beginning of the treatment with TPN, both groups presented moderate hypoalbuminemia according to the average albumin value. At day seven there were no significant changes. According to the concentration of prealbumin, both groups increased its value, but only in the group supplemented with Gln the change was significantly different ($p = 0.012$). It is important to mention that in both groups prealbumin concentrations increased, but the average concentration was below normal clinical levels.

Table V shows the treatment response on blood cell markers. In the non-supplemented group, at day seven, no significant changes were found in the concentration of lymphocytes and monocytes. However, the neutrophil concentration decreased but there was no significant change. In the supplemented group with Gln, the average concentration of lymphocytes and monocytes increased at day seven, but only significant differences were found in the lymphocytes ($p = 0.014$). There was no significant change in the average value of neutrophils at day seven in this group.

Both groups presented hyperglycemia at day one and seven. In addition, there were no significant changes in the average concentration of glucose at day seven. According to the average value of urea and BUN, both groups presented levels above normal on day one and day seven, without significant changes. Creatinine in the non-supplemented group significantly decreased ($p = 0.019$).

DISCUSSION

The results suggested that supplementation with Gln for seven days could improve nutritional status in patients with gastrointestinal neoplasia. It was found that the concentrations of prealbumin increased significantly in the supplemented group. However, the serum levels of albumin did not change in both groups. Since prealbumin is a marker of nutritional status with a half-life in plasma of two days, it is more sensitive to changes in protein-energy status than albumin (18). The group that received TPN enriched with Gln for seven days improved serum levels of prealbumin in postoperative gastrointestinal cancer patients as shown by Lu et al. (19).

Gastrointestinal tract provides a barrier against bacteria or toxins. However, cancer patients, as well as individuals who undergo surgery, have an increase in intestinal permeability related to bacterial translocation. This fact causes complications like sepsis, malnutrition or organ failure (20). It is known that Gln has an important role in the intestinal mucosa integrity because it is the main substrate for the intestinal mucosa cells. In cancer patients this integrity could be decreased (21,22). Our results showed that supplementation with Gln significantly improved gastrointestinal function of the majority of the patients. However, the non-supplemented group progressed to severe dysfunction after seven days. This could happen due to the fact that patients subjected to surgery have higher intestinal permeability, leading to bacte-

Table I. Patient baseline characteristics

	Group 1 (TPN) n = 40, n (%)	Group 2 (TPN + glutamine) n = 30, n (%)	p value
Sex			
Women	16 (40%)	18 (60%)	0.128
Men	24 (60%)	12 (40%)	
Oncologic diagnosis			0.247
Gastric	11 (28%)	6 (20%)	
Esophagus	3 (8%)	1 (4%)	
Colon	18 (44%)	9 (28%)	
Rectum	0	5 (16%)	
Pancreas	3 (8%)	8 (24%)	
Liver	5 (12%)	2 (8%)	
	Group 1 (TPN) x ± SD (n = 40)	**Group 2 (TPN + glutamine) x ± SD (n = 30)**	**p value**
Age	59.44 ± 12.52	57.8 ± 11.99	0.587
BMI* (kg/m^2)	25.17 ± 5.69	23.91 ± 4.29	0.333
Triceps skinfold (mm)	16.04 ± 7.72	13.95 ± 6.35	0.269
Arm circumference (cm)	27.88 ± 3.98	27.41 ± 3.81	0.590
Visceral fat (kg)	9.14 ± 4.01	8.19 ± 4.03	0.432
Water (%)	51.09 ± 7.67	54.42 ± 6.72	0.154
Muscle mass (kg)	43.13 ± 9.79	45.81 ± 7.73	0.324
Bone mass (kg)	2.32 ± 0.33	2.52 ± 0.33	0.063
Weight loss (%)	10.51 ± 9.66	8.87 ± 7.52	0.551

*BMI: body mass index. Comparisons were performed with the Chi-square test. *Statistically significant difference between groups, p < 0.05.*

Table II. Nutritional status after surgery

	Group 1 (TPN) Basal values n = 40, n (%)	Group 1 (TPN) Final values n = 40, n (%)	p value
Mild malnutrition	7 (16%)	11 (28%)	
Moderate malnutrition	14 (36%)	18 (44%)	0.527
Severe malnutrition	19 (48%)	11 (28%)	
	Group 2 (TPN + glutamine) Basal values n = 30, n (%)	**Group 2 (TPN + glutamine) Final values n = 30, n (%)**	**p value**
Mild malnutrition	8 (28%)	13 (44%)	
Moderate malnutrition	15 (48%)	13 (44%)	0.008*
Severe malnutrition	17 (24%)	4 (12%)	

*TPN: total parental nutrition. Comparisons were performed with the Chi-square test. *Statistically significant difference between groups, p < 0.05.*

rial translocation. Group 2 patients presented complications due to bacterial infection. A Gln-enriched enteral diet for seven days in critical ill patients could prevent gastrointestinal infections, but no significant differences were found between the supplemented and non-supplemented group. A study carried out by Conejero et al. showed similar results (23). It is worth mentioning that the gastrointestinal function study could be limited due to the distribution of diagnoses (type of cancer) and the number of patients per group.

Table III. Gastrointestinal function after surgery

	Group 1 (TPN) Basal values n = 40, n (%)	**Group 1 (TPN) Final values n = 40, n (%)**	**p value**
Normal	1 (4%)	3 (8%)	
Mild dysfunction	18 (44%)	13 (32%)	0.204
Moderate dysfunction	11 (28%)	10 (24%)	
Severe dysfunction	10 (24%)	14 (36%)	
	Group 2 (TPN + glutamine) Basal values n = 30, n (%)	**Group 2 (TPN + glutamine) Final values n = 30, n (%)**	**p value**
Normal	0 (0%)	2 (8%)	
Mild dysfunction	5 (16%)	25 (80%)	*0.0001**
Moderate dysfunction	15 (48%)	2 (8%)	
Severe dysfunction	10 (36%)	1 (4%)	

*TPN: total parental nutrition. Comparisons were performed with the Chi-square test. *Statistically significant difference between groups, $p < 0.05$.*

Table IV. Protein metabolism after surgery

	Group 1 (TPN) Basal values (day 1) x ± SD (n = 40)	**Group 1 (TPN) Final values (day 7) x ± SD (n = 40)**	**p value**
Prealbumin (mg/dl)	9.8 ± 3.44	10.62 ± 5.3	0.582
Albumin (g/dl)	2.51 ± 0.62	2.36 ± 0.48	0.445
	Group 2 (TPN + glutamine) Basal values (day 1) x ± SD (n = 30)	**Group 2 (TPN + glutamine) Final values (day 7) x ± SD (n = 30)**	**p value**
Prealbumin (mg/dl)	9.44 ± 2.90	13.53 ± 8.26	0.012*
Albumin (g/dl)	2.44 ± 0.52	2.39 ± 0.49	0.971

*TPN: total parental nutrition. Results are expressed as mean ± standard deviation (x ± SD). Comparisons were performed with the t-test. *Statistically significant difference between groups, $p < 0.05$.*

Table V. Nutritional cell markers after surgery

	Group 1 (TPN) Basal values (day 1) x ± SD (n = 40)	**Group 1 (TPN) Final values (day 7) x ± SD (n = 40)**	**p value**
Lymphocytes (10^3/µl)	0.99 ± 0.53	0.94 ± 0.61	0.635
Monocytes (10^3/µl)	0.69 ± 0.29	0.88 ± 0.56	0.074
Neutrophils (10^3/µl)	9.44 ± 5.79	7.76 ± 4.35	0.225
	Group 2 (TPN + glutamine) Basal values (day 1) x ± SD (n = 30)	**Group 2 (TPN + glutamine) Final values (day 7) x ± SD (n = 30)**	**p value**
Lymphocytes (10^3/µl)	0.86 ± 0.56	1.16 ± 0.95	*0.014**
Monocytes (10^3/µl)	0.69 ± 0.43	1.13 ± 1.33	0.087
Neutrophils (10^3/µl)	9.48 ± 5.67	9.40 ± 9.40	0.972

*TPN: total parental nutrition. Results are expressed as mean ± standard deviation (x ± SD). Comparisons were performed with the t-test. *Statistically significant difference between groups, $p < 0.05$.*

Table VI. Biochemical data after surgery

	Group 1 (TPN) Basal values (day 1) x ± SD (n = 40)	**Group 1 (TPN) Final values (day 7) x ± SD (n = 40)**	**p value**
Glucose (mg/dl)	141.68 ± 50.88	140.60 ± 94.71	0.963
Urea (mg/dl)	50.49 ± 26.52	58.80 ± 57.26	0.405
Creatinine (mg/dl)	1.05 ± 0.74	0.69 ± 0.46	*0.019**
BUN (mg/dl)	23.57 ± 12.38	27.20 ± 27.19	0.351
	Group 2 (TPN + glutamine) Basal values (day 1) x ± SD (n = 30)	**Group 2 (TPN + glutamine) Final values (day 7) x ± SD (n = 30)**	**p value**
Glucose (mg/dl)	124.24 ± 43.66	130.92 ± 46.75	0.526
Urea (mg/dl)	40.76 ± 37.25	43.36 ± 21.60	0.687
Creatinine (mg/dl)	0.55 ± 0.25	0.56 ± 0.54	0.873
BUN (mg/dl)	15.87 ± 7.41	20.20 ± 10.12	0.124

*TPN: total parental nutrition. Results are expressed as mean ± standard deviation (x ± SD). Comparisons were performed with the t-test. *Statistically significant difference between groups, $p < 0.05$.*

Jun et al. demonstrated that parenteral glutamine supplementation in combination with enteral nutrition for seven days improves intestinal mucosa immunity. Also, it may contribute to the prevention and treatment of sepsis (24). Other studies support that Gln administration regulates the gut barrier function (23,24).

Cancer patients are usually immunosuppressed and present nutriment deficiencies. Additionally, they have more possibilities to develop septic complications than other patients. Gln is a precursor of purines and pyrimidines and also a primary substrate for lymphocytes (25). In our study, the concentrations of lymphocytes and monocytes improved significantly in the group supplemented with glutamine after seven days of intervention. However, neutrophil concentrations did not change. Chang et al. (26) have shown that Gln supplementation improves significantly lymphocyte proliferation stimulated by phytohemaglutinin.

Gln supplementation increased immune cells such as granulocytes and lymphocytes in malnourished abdominal surgery patients (preoperative and postoperative stage for five days). This was also shown by Asprer et al. (27). Besides, Manhart et al. demonstrated that glutamine supplementation in mice for ten days improves the gut immune system, preventing lymphocyte atrophy of Peyer's patches (28).

The main substrate for neutrophils is glucose. Vlessis et al. (29) suggested that neutrophils are able to use glutamine when the glucose is restricted. Despite the role of Gln in neutrophil is less defined, it is know that it increases the function of lymphocytes, macrophages and neutrophils exogenously during metabolic stress. However, more studies that could explain neutrophil behavior with glutamine are necessary. In fact, neutrophil concentration did not increase in this study.

TPN could usually cause metabolic alterations like hyperglycemia. Rosmarin et al. (30) demonstrated that TPN dextrose infusion rate was positively correlated with blood glucose concentrations. In fact, infusion rates over 4-5 mg/kg/min increase the risk of hyperglycemia. However, it is common that cancer patients are diagnosed with hyperglycemia due to a side effect of the treatment or an increase in use rate and liver production of glucose. In our study, only eight patients presented hyperglycemia, three of them had diabetes, three were related to a metabolic alteration due to TPN and two were subjected to Whipple surgery.

Gln is synthesized primarily in the muscle, being their main source (31). In hypermetabolic conditions like cancer, surgery, trauma or sepsis, the glutamine concentrations are depleted. This could explain why serum creatinine levels decreased in the control group due to muscle wasting, glutamine depletion and the absence of exogenous glutamine.

Cancer patients subjected to surgery and hospitalized are more likely to develop complications such as malnutrition. This circumstances could diminish quality of life and reduce treatment response. These data, in our opinion, support that glutamine supplementation in gastrointestinal cancer patients undergoing surgery is beneficial. These results substantially confirm the findings of other studies, which suggest that Gln have a positive effect on nutritional status, gastrointestinal function, protein metabolism and cell markers.

CONCLUSIONS

In this work, we found that glutamine could improve gastrointestinal function, diminishing diarrhea, urgency, abdominal pain and distention. When the gastrointestinal function gets better, nutrimental absorption increases, so nutritional status improves. In addition, glutamine has a positive effect in prealbumin, lymphocytes and monocytes concentrations which is reflected in a better nutritional status.

UNIVERSIDAD AUTÓNOMA DEL ESTADO DE MÉXICO

CENTRO ONCOLÓGICO ESTATAL ISSEMYM

ESCALA DE EVALUACIÓN DE FUNCIONALIDAD GASTROINTESTINAL

Paciente: _____ Fecha: _____

SÍNTOMAS/EVALUACIÓN DE LA GRAVEDAD

Categoría	Síntoma	Categoría 1	Categoría 2	Categoría 3	Categoría 4
1	Frecuencia de evacuaciones por día	0-2 evacuaciones por día (0)	3 evacuaciones por día (1)	4 evacuaciones por día (2)	5 o más evacuaciones por día (3)
2	Consistencia de las evacuaciones por día	Todas las evacuaciones son sólidas (0)	Evacuaciones sólidas y blandas (1)	Evacuaciones blandas (2)	Evacuaciones líquidas (3)
3	Urgencia de las evacuaciones por día	Nada urgente (0)	Algo urgente (1)	Urgente (2)	Muy urgente (3)
4	Molestia abdominal	Ninguna molestia (0)	Molestia leve a moderada (1)	Molestia algo severa (2)	Molestia muy severa (3)

Total: _____

0-2 (Función normal)

3-5 (Disfunción leve)

6-9 (Disfunción moderada)

10-12 (Disfunción severa)

Appendix 1.

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