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Original

Oral glutamine in addition to parenteral nutrition improves mortality and the healing of high-output intestinal fistulas

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Abstract

Objective: **Anastomotic leakage is one of the most important causes of morbidity and mortality in gastrointestinal surgery. We investigated the effect of oral glutamine on the healing of high-output intestinal fistula.** ***Setting:*** **A tertiary Universitary Hospital of the University of Mato Grosso, Cuiaba, Brazil.** ***Patients and methods:*** **28 patients (25 males and 3 females; median age = 45 [18-71] years old) admitted with high output post-operative small bowel fistulas (median volume in 24 h: 850 [600-2,200] mL) during a 4 years period were retrospectively studied.** ***Interventions:*** **In the first two years 19 (67.9%) patients received only TPN as the initial nutritional support. In the last two years however, due to a change in the protocol for the nutritional support in cases of intestinal fistula 9 patients (32.1%) received oral glutamine (0.3 g/kg/day; 150 mL/day) in addition to TPN. Endpoints of the study were mortality, resolution of the fistula, and length of hospital stay (LOS).** ***Results:*** **The overall mortality was 46.4% (13 patients). Fistula closure was observed in all other 15 patients (53.6%) that survived. In the subset of survived patients LOS was similar in those who received or not received glutamine. The multivariate regression analysis showed that resolution of the fistula was 13 times greater in patients that received oral glutamine (OR = 13.2 (95% CI = 1.1-160.5); p = 0.04) and 15 times greater in non-malnourished patients (OR = 15.4 [95% CI = 1.1-215.5]; p = 0.04).** ***Conclusions:*** **We conclude that oral glutamine accelerated the healing and diminished the mortality in this series of patients with post-operative high-output intestinal fistula receiving TPN.**

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Key words: *Fistula. Glutamine. Anastomotic dehiscence. Small bowel. Parenteral nutrition. Malnutrition.*

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GLUTAMINA ORAL EN ADICIÓN A NUTRICIÓN PARENTERAL MEJORA LA MORTALIDAD Y LA CICATRIZACIÓN DE FÍSTULAS INTESTINALES DE ALTO DÉBITO

Resumen

Objetivo: **La fístula anastomótica es una de las principales causas de morbilidad y mortalidad en cirugía general. Investigamos el efecto de la glutamina oral en la cicatrización de fístulas intestinales de alto débito.** ***Ámbito:*** **Una unidad terciaria de un Hospital Universitario de la Universidad Federal de Mato Grosso, Cuiabá, Brasil.** ***Pacientes y métodos:*** **28 pacientes (25 M y 3 F; edad mediana = 45 [18-71] años) admitidos con fístulas pos-operatorias del intestino delgado de alto débito (volumen mediano en 24 h: 850 [600-2.200] mL) durante un período de 4 años fueron retrospectivamente estudiados.** ***Intervenciones:*** **En los dos primeros años 19 pacientes (67,3%) recibieron únicamente TPN como suporte nutricional. En los últimos dos años sin embargo, debido a un cambio del protocolo para el suporte nutricional en casos de la fístula intestinal 9 pacientes (32,1%) recibieron glutamina oral (0,3 g/kg/día; 150 mL/día) además de TPN. Las variables de resultado del estudio fueron la mortalidad, la resolución de la fístula, y el tiempo de hospitalización (LOS).** ***Resultados:*** **La mortalidad fue de 46,4% (13 pacientes). La cicatrización de la fístula fue observada en 15 pacientes (53,6%) que sobrevivieron. Entre los pacientes que sobrevivieron la permanencia hospitalaria fue similar en aquellos que recibieron o no recibieron glutamina. El análisis multivariante mostró que la resolución de la fístula fue 13 veces mayor en los pacientes que recibieron glutamina oral (OR = 13,2 (95% CI = 1,1-160,5); p = 0,04) y 15 veces mayor entre los pacientes no desnutridos (OR = 15,4 [95% CI = 1,1-215,5]; p = 0,04).** ***Conclusiones:*** **La glutamina oral acelera la cicatrización y disminuyó la mortalidad en nuestros pacientes con fístula intestinal de alto débito que recibieron TPN.**

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Palabras clave: *Fístula. Glutamina. Dehiscencia anastomótica. Intestino delgado. Nutrición parenteral. Desnutrición.*

Introduction

Anastomotic leakage is one of the most important causes of morbidity and mortality in gastrointestinal surgery. The amount of leakage in 24 h categorizes the fistula in high- (above 500 mL/day) and low-output (less than 500 mL/day). High-output fistula is usually associated with poorer prognosis and greater length of hospital stay (LOS) when compared with low-output fistula[1]. Nutritional support with either enteral (EN) or total parenteral nutrition (TPN) is the most important weapon in the management of these cases. Enteral feeding may have considerable advantages over parenteral feeding in critically ill surgical patients such as those with fistula[2]. In particular, EN when compared with TPN improves intestinal barrier function, maintains immune competence, and reduces the rate of infectious complications[3]. However, patients presenting with high-output fistula are most prone to receive TPN than EN.

Glutamine, a conditionally essential amino acid, is the most important fuel for the enterocytes and immune cells[4]. Either enteral or intravenous route has been used to deliver glutamine in critical patients aiming at reducing infectious morbidity with controversial results[5]. Glutamine supplies nitrogen for purine and pirimidine synthesis that is essential for cells in mitosis[6]. Consequently, the use of glutamine seems to decrease the occurrence of bacterial translocation and inflammatory response, reducing the possibility of events such as systemic inflammatory response syndrome, sepsis, and MODS[5]. Moreover, diets enriched with immune nutrients seem to reduce the days of mechanical ventilation and hospitalization[7].

To date, no paper of our knowledge has investigated the effect of oral glutamine in promoting healing after anastomotic dehiscence. Experimentally, peri-operative oral glutamine supplementation seems to both increase anastomotic resistance and improve collagen maturation at the anastomotic site[8]. Theoretically thus, glutamine could improve fistula closure by enhancing both healing process and gut trophism. In the Julio Muller Universitary Hospital of the Federal University of Mato Grosso the protocol of nutritional support for intestinal fistula changed recently. In this new protocol, oral glutamine was given for patients candidates for TPN due to high-output intestinal fistulas. This study aimed at investigating whether the introduction of oral glutamine in the new protocol have modified the results of the treatment of postoperative high-output intestinal fistula.

Materials and methods

Over a 4-year period the charts of 45 patients with small bowel fistulas (17 with low output and 28 with high output) seen at the Department of Surgery of Julio Muller Universitary Hospital (HUJM) were reviewed.

Table I
Clinical features of the 28 patients with post-operative high-output fistula

Variable	*N*	*%*
Clinical condition		
Peptic ulcer	6	21.4
Trauma	5	17.9
Crohn	3	10.7
Gastric cancer	3	10.7
Small bowel obstruction	3	10.7
Right colon cancer	2	7.2
Miscellaneous	6	21.4
Site		
Duodenum	3	10.7
Jejunum	20	71.4
Ileum	5	17.9
Serum albumin		
< 3.0 g/dL	13	46.4
> 3.0 g/dL	15	54.6
Nutritional status		
Malnutrition	13	46.3
Normal	15	54.6
Hospital of origin		
HUJM	18	64.3
Other	10	35.7
Age		
< 50y	18	64.3
> 50y	10	35.7
Oral glutamine		
Yes	9	32.1
No	19	67.9
Gender		
Male	25	89.3
Female	3	10.7

Inclusion criteria of the study were postoperative anastomotic dehiscence and high output fistula. Twenty-eight patients (25; 89.3% males and 3; 11.7% females; median age = 45 [18-71] years old) with high output post-operative small bowel fistula (median volume in 24 h: 850 mL, ranging from 600 to 2,200 mL) were eligible for the study. Nine patients (32.1%) were operated on in other hospitals and were transferred to this tertiary unit to receive specialized treatment for intestinal fistula whereas 19 (67.9%) were originally patients from this hospital. In all cases the leakage was due to anastomotic breakdown. Clinical characteristics of the patients can be observed in table I.

Malnutrition assessed by global subjective evaluation was present in 13 (46.4%) cases (10 with severe [grade C] and three with mild malnutrition [grade B]). Serum albumin was assayed on admission day one. Thirteen patients (46.4%) showed serum albumin

Table II
Distribution of the patients according to the use of oral glutamine

Variable	Group N (%)		P
	Glutamine	Without glutamine	
Males	7/9 (77.8)	18/19 (94.7)	0.23
> 50 years old	5/9 (55.6)	6/19 (31.6)	0.67
Malnutrition	3/9 (33.3)	10/19 (52.6)	0.43
Serum albumin < 3.0 g/dL	3/9 (33.3)	10/19 (52.6)	0.43
Jejunum	8/9 (88.9)	16/19 (84.2)	1.00
HUJM*	6/9 (66.7)	12/19 (63.2)	1.00

* = Patients operated on at the Julio Muller Universitary Hospital.

below 3.0 g/dL. All patients received TPN either in the first 48 h from the diagnosis of the anastomotic leakage or immediately after admission if referred from other hospital. The daily requirements offered were 30 kcal and 1.5 g of protein per kilogram of body weight.

Patients were divided in two groups according to two different protocols. During the last two years of the study nine patients (32.1%) received approximately 0,3 g/kg/day of oral glutamine (Glutamin, Support, Brazil) three times a day (50 mL per dose containing water and glutamine powder; 150 mL/day) in addition to TPN (glutamine group). In the first two years, oral glutamine therapy was not yet included in our protocol and thus patients received only TPN (n = 19; 67.9%) as the sole nutritional support. No patients received glutamine either parenterally or enterally. The distribution of the patients who received or not received oral glutamine according to the clinical characteristics can be seen in table II.

Patients were followed-up daily until they were discharged or died. Endpoints of the study were mortality, resolution of the fistula, and LOS. Prognostic factors (independent variables) studied were gender, age (analyzed as a categorical variable, including patients less or above 50 years-old), use of oral glutamine, nutritional status (malnourished or not), albumin level (below or above 3.0 g/dL), and referral of the patient (HUJM or other hospital).

Statistical analysis

Chi-square or Fisher's exact test were used for univariate analysis of categorical variables for both fistula closure and mortality. Student T test or Mann-Whitney test was used to compare LOS and days of parenteral nutrition in the two groups. Multivariate logistic regression analysis was carried out taking fistula closure (yes or no) and mortality (yes or no) as dependent variables. All independent variables were examined together using the enter method for multivariate regression. A 5% level ($p <= 0.05$) was considered as significant. Data were presented as either mean ± SD or median (range) as appropriated.

Results

The overall mortality was 46.4% (13 patients). Fistula closure was observed in all other 15 patients (53.6%) that survived. Thus, for the rest of the analysis both considered endpoints (mortality and fistula closure) were studied together. Spontaneous closure was achieved in eight (53.3%) patients whereas seven (46.7%) required an operation to complete resolution of the leakage. Patients receiving oral glutamine did not present an increased output during evolution.

Length of hospital stay

The mean LOS was 42 (18-98) days. LOS was greater in patients that received glutamine (53 days; ranging from 33 to 93 days) than in others (33 days; ranging from 7 to 55 days; $p = 0.01$). However in the subset of patients that survived LOS was similar in patients that received (51 days; ranging from 35 to 92 days) or not received (39 days; ranging from 27 to 58 days; $p = 0.13$) oral glutamine. The length of days on TPN was 24 (7-55 days) and was similar in either patients treated (29 days; ranging from 7 to 55 days) or not treated with glutamine (21days; ranging from 8 to 40 days; $p = 0.17$). Age, fistula closure, albumin, hospital of origin, and nutritional status did not correlate with either LOS or days in TPN.

Fistula closure and mortality

There was a similar distribution between patients with only TPN and oral glutamine in addition to TPN with respect to sex, age, site of the fistula, nutritional status, albumin level and hospital of origin (table II). The univariate associations for the potential prognostic factors in fistula closure/mortality can be seen in table III. Malnutrition, low albumin, and use of oral glutamine were significantly related to fistula closure and mortality. The multivariate logistic regression analysis showed that resolution of the fistula was 13 times greater in patients that received oral glutamine (OR = 13.2 [95% CI = 1.1-160.5]; $p = 0.04$) and 15 times greater in non-malnourished patients (OR = 15.4 [95% CI = 1.1-215.5]; $p = 0.04$). Other independent variables examined showed no correlation with fistula closure in the multivariate model of logistic regression analysis.

Discussion

The overall results confirm the poor prognosis in patients with high-output intestinal fistulas. The fin-

Table III
Univariate analysis of prognostic factors associated with fistula closure/mortality

Variable	*Fistula closure/mortality N (%)*		*OR (95% CI)*	*P*
	Yes	*No*		
Gender				
Male	12 (48)	13 (52)	0.5 (0.3-0.7)	0.60
Female	0 (0)	3 (100)		
Age				
< 50y	10 (55.6)	8 (44.4)	0.9 (0.4-2.0)	1.00
> 50y	5 (50)	5 (50)		
Serum albumin				
> 3.0 g/dL	4 (31.2)	11 (68.8)	2.9 (1.2-7.0)	0.02
< 3.0 g/dL	10 (76.9)	3 (23.1)		
Nutritional status				
Malnutrition	3 (23.1)	10 (76.9)	3.8 (1.3-11.0)	< 0.01
Normal	12 (80)	3 (20)		
Oral glutamine				
Yes	8 (89.9)	1 (11.1)	2.4 (1.3-4.5)	0.01
No	7 (36.8)	12 (63.2)		
Hospital of origin				
HUJM*	10 (55.6)	8 (44.4)	0.9 (0.4-2.0)	1.00
Other	5 (50)	5 (50)		

* = HUJM, Julio Muller Universitary Hospital.

dings also are in agreement with previous reports that have highlighted the vital influence of malnutrition to establish the prognosis[9, 10]. However, the most interesting finding of this study was the association of oral glutamine in addition to TPN with fistula resolution and thus, with better prognosis. In fact, patients that received oral glutamine during the course of TPN had approximately 13 times more chance of survival and having their anastomotic dehiscence healed.

However, it was interesting to notice that patients who received approximately 150 mL of glutamine by oral route have not increased fistula output. Although this was a retrospective study, these findings are important and evoke further controlled randomized trail to examine whether oral glutamine may accelerate or not the healing of high-output postoperative intestinal fistula and thus, diminish the mortality rate.

Luminal factors have been associated with gut mucosal trophism in many previous reports[11, 12]. Glutamine is the most important metabolic substrate to the enterocytes, and directly stimulates gut mucosal trophism. There is evidence from the literature that glutamine may increase the anastomotic healing process[13]. Taking all this in account it could be possible that the presence intraluminal glutamine near the fistula site may induce regional mucosal trophism that may result in faster fistula closure. Moreover, glutamine may improve gut and systemic immune response[4] and thus, diminish infectious complications that are common in these patients and really accounts for higher morbidity and mortality[13].

The maintenance of enteral nutrition in cases of high output fistulas may be contra-indicated. However, specific nutrients for the mucosa such as glutamine may enhance the gastrointestinal blood flow and thus cause some benefits[14]. In this context, it may be expected some improvement in gut immune response and healing[3, 15], and decrease in bacterial translocation[13]. In accordance, fibers which are considered as prebiotics may accelerate the healing of colorectal fistula[16]. Although patients on glutamine received additional nitrogen than others it is unlike that this minimal surplus was the key point of the observed benefit.

The greater LOS in patients receiving oral glutamine can be explained by the less mortality and longer length of days in treatment that occurred in this group. In fact, no differences were seen in the subset of survived patients who had received or not oral glutamine.

As far as our knowledge allows us to state, this is the first study that associated the use of oral glutamine in addition to TPN with postoperative intestinal fistula closure. However, there are a number of limitations of this current study. The data are retrospective and compared two groups of patients in two different periods, and even though not statistically significant, the rate of malnutrition in the group that received oral glutamine

was lower. However, the two groups were statistically comparable, and the use of oral glutamine survived the multivariate analysis, and together with malnutrition was significantly associated with fistula closure. Thus, the overall results permit the conclusion that in this series of cases of patients with high-output postoperative small bowel fistula receiving TPN oral glutamine associated to TPN accelerated the healing and diminished mortality. This conclusion may be limited to the studied population and thus further prospective randomized trials are necessary.

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