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• BRIEF REPORTS •

Effect of glutamine on change in early postoperative intestinal permeability and its relation to systemic inflammatory response

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Abstract

AIM: To study the effects of glutamine (Gln) on the change of intestinal permeability and its relationship to systemic inflammatory response in early abdominal postoperative patients.

METHODS: A prospective, randomized, double-blind and controlled trial was taken. Twenty patients undergoing abdominal surgery were randomized into Gln group (oral administration of glutamine, 30 g/d, for 7 d, *n*=10) and placebo group (oral administration of placebo, 30 g/d, for 7 d, *n*=10). Temperatures and heart rates of all patients were daily recorded. White blood cell counts(WBC) and biochemical variables were measured before operation and 4 and 7 d after drug administration. Serum concentrations of glutamine, endotoxin, diamine oxidase and malondialdehyde and urine lactulose/mannito (L/M) ratio were measured before and 7 d after drug administration.

RESULTS: The patients in the 2 groups were comparable prior to drug administration. Serum Gln concentration was significantly decreased in the placebo group and increased in the Gln group 7 d after drug administration. Urine L/M ratio was significantly increased in the placebo group and decreased in the Gln group. The serum concentration of endotoxin, diamine oxidase and malondialdehyde was significantly decreased in the Gln group compared with those in the placebo group. Temperatures, heart rates and WBC counts were significantly lower in the Gln group than those in the placebo group.

CONCLUSION: Gut is one of the sources of systemic inflammatory response in abdominal postoperative patients and glutamine can decrease intestinal permeability, maintain intestinal barrier and attenuate systemic inflammatory response in early postoperative patients.

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INTRODUCTION

Gut has been considered as one of the central organs responding to stresses in surgical patients[1]. In the last few years, animal experiments and clinical researches have proved that the intestinal permeability increases during stresses, such as severe trauma, operation. Glutamine as a semi-essential amino acid is a special nutrient to intestinal mucosal cells. It can reduce the permeability of gut, but becomes increasingly exhausted after severe trauma or operation. In this research we studied the effects of glutamine on the change of intestinal permeability and its relationship to systemic inflammatory response in abdominal postoperative patients.

MATERIALS AND METHODS

Patient grouping

A prospective, randomized, double-blind and controlled trial was taken. Twenty abdominal surgical patients aged 18-65 years and without any severe disease in liver, kidney, cardiovascular system and hematopoietic system, were randomized into Gln group (oral administration of glutamine, 30 g/d, for 7 d, *n*=10) and placebo group (oral administration of placebo, 30 g/d, for 7 d, *n*=10). Their sex, age, body mass and operation type were similar (Tables 1, 2).

Table 1 General data of two groups

	Placebo group	Glutamine group
Age (yr)	48.3±12.2	48.3±10.8
Male/Female	7/3	6/4
Weight (kg)	54.2±11.1	56.7±12.1

Drug dose and administration

Glutamine was dissolved in warm water (1 g in 10 mL) and orally taken or by gastric tube (10 g one time, and 3 times per day) after operation for 7 d. Placebo was administered as glutamine.

Measurement

Temperature and heart rate of all patients were daily recorded from the day before operation to the end of drug administration.

Peripheral blood was sampled on the morning of the day before operation, the day before drug administration, 4 and 7 after drug administration. Liver and kidney functions were measured.

Peripheral blood was sampled on the morning of the day before and 7 d after drug administration for the measurement of the concentration of the serum glutamine (Gln)[2], diamine oxidase (DAO)[3] and malondialdehyde (MDA)[4] .

Peripheral blood was sampled before and 7 d after drug administration for the measurement of the concentration of serum endotoxin with an endotoxin detection kit (Shanghai Yihua Clinical Technology Company).

On the morning before and the 7th dafter administration, 6 h' s urine was collected after 50 mL lactulose/mannito (L/M) solution (lactulose 10 g and mannito 5 g) was taken for the measurement of the levels of lactulose and mannito with method of enzyme[5,6] and calculation of the ratio of L/M.

Statistic method

Results were expressed as mean±SD and analyzed with Student *t*-test. $P<0.05$ was considered statistically significant.

Table 2 Detailed clinical data of patients in two groups

Group	Case(*n*)	Sex	Age(yr)	Diagnosis	Operation type
Gln group	1	Male	55	Cardiac orifice cancer	Total gastrectomy
	2	Male	30	Acute suppurative cholangitis	Cholecystectomy choledochostomy
	3	Female	40	Rectal cancer	Anterior resection of rectum
	4	Male	47	Sigmoid cancer	Sigmoidectomy
	5	Male	62	Cardiac orifice cancer	Proximal subtotal gastrectomy
	6	Female	28	Rectal cancer	Anterior resection of rectum
	7	Female	52	Cholecystolithiasis	Cholecystectomy
	8	Male	49	Gastric cancer	Subtotal gastrectomy
	9	Male	60	Gastric cancer	Subtotal gastrectomy
	10	Male	60	Cardiac orifice cancer	Proximal subtotal gastrectomy
Placebo group	1	Male	50	Pancreas pseudocyst	Cyst-jejunal Roux-en-y anastomosis
	2	Female	56	Ascending colon cancer	Right semi-colectomy
	3	Female	60	Rectal cancer	Anterior resection of rectum
	4	Female	54	Sigmoid cancer	Sigmoidectomy
	5	Male	48	Cardiac orifice cancer	Proximal subtotal gastrectomy
	6	Male	43	Ascending colon cancer	Right semi-colectomy
	7	Male	64	Gastric cancer	Proximal subtotal gastrectomy
	8	Female	29	Gastric cancer	Proximal subtotal gastrectomy
	9	Male	43	Sigmoid cancer	Sigmoidectomy
	10	Male	36	Acute biliary pancreatitis	Selective cholecystectomy

RESULTS

General condition

During the research, there were no complication and death in both Gln group and placebo group.

Temperature

The highest, average and lowest temperatures increased after operation. The highest and average temperatures from d 3 to 6 and the lowest temperatures from d 2 to 6 in the Gln group were significantly lower than those in the placebo group.

Heart rate

The highest, average and lowest heart rates increased after operation in patients of both groups. The highest and average heart rates on d 2, 3 and 5 and the lowest heart rates from d 2 to 5 were significantly lower in the Gln group than in the placebo group.

WBC count

WBC counts increased from the first day after operation in both groups with the maximum being above 12.0×10^9/L. WBC counts decreased to normal level 4 d later in the Gln group, but 7 d later in the placebo group.

Serum concentration of Gln

In the placebo group, the serum concentration of Gln decreased from 432.17±142.68 μmol/L to 250.78±77.10 μmol/L (P<0.05), whereas in the Gln group the serum concentration of Gln increased from 361.17±161.25 μmol/L to 583.22±171.52 μmol/L (P <0.05). The serum concentration of Gln in the Gln group was significantly higher than that in the placebo group (P<0.01) (Table 3).

Table 3 Serum levels of Gln in two groups (μmol/L)

Group	Before drug administration	7 d after drug administration
Placebo group	432.17±142.68	250.78±77.10[b]
Gln group	361.17±161.25	583.22±171.52[ad]

[a]P<0.05, [b]P<0.01, *vs* before drug administration; [d]P<0.01, *vs* placebo group.

Serum DAO concentration

Serum DAO concentrations were not significantly different in the 2 groups before drug administration. Seven days after drug administration, serum DAO concentrations increased in the placebo group and decreased in the Gln group (P<0.01). The difference in serum DAO concentrations was very significant (P<0.01) between the two groups (Table 4).

Table 4 Serum DAO levels in two groups (U/mL)

Group	Before drug administration	7 d after drug administration
Placebo group	2.06±0.48	3.18±1.13
Gln group	2.26±0.63	1.25±0.65[bd]

[b]P<0.01 *vs* before administration; [d]P<0.01 *vs* placebo group.

Serum MDA concentration

Serum MDA concentrations were not significantly different in the 2 groups before drug administration. Seven days after drug administration, they increased in the placebo group and decreased in the Gln group (P<0.01). The serum MDA concentrations were significantly different between the two groups (P<0.01) after drug administration (Table 5).

Table 5 Serum MDA levels in two groups (nmol/mL)

Groups	Before drug administration	7 d after drug administration
Placebo group	3.94±0.56	4.85±0.63[b]
Gln group	4.46±0.67	3.53±0.59[bd]

[b]P<0.01 *vs* before drug administration; [d]P<0.01 *vs* placebo group.

Table 6 Levels of serum endotoxin in two groups (EU/mL)

Group	Before drug administration	7 d after drug administration
Placebo group	0.21±0.07	0.25±0.08
Gln group	0.23±0.05	0.18±0.06[ab]

[a]P<0.05 *vs* before drug administration; [b]P<0.01 *vs* placebo group.

Serum endotoxin concentration

Levels of serum endotoxin in the 2 groups were not significantly different before drug administration. After 7 d, the serum endotoxin concentrations increased in the placebo group significantly and decreased in the Gln group (P<0.05) with a very significant difference between the two groups (P<0.01, Table 6).

Ratio of urine L/M

The ratio of L/M was not significantly different in the 2 groups initially, which was 134.00±18.48 in the placebo group and 146.102±20.21 in the Gln group. After 7 d, the ratio of L/M significantly increased in the placebo group ($P<0.01$), and significantly decreased in the Gln group ($P<0.05$). Then, the ratio of L/M was significantly lower in the Gln group than in the placebo group ($P<0.01$, Table 7).

Table 7 Changes of urine L/M ratio in two groups

Group	Before drug administration	7 d after drug administration
Placebo group	134.00±18.48	194.83±45.31[b]
Gln group	146.10±20.21	117.47±25.68[ad]

[a]$P<0.05$, [b]$P<0.01$, *vs* before drug administration; [d]$P<0.01$ *vs* placebo group.

DISCUSSION

Normally, besides digestion and absorption, the gut functions as a mucosal barrier to bacteria, endotoxin and some other toxins. Whether the mucosal barrier works well or not is closely related to intestinal permeability. To measure it, some material with large molecular weight was used as a probe. Lactulose/mannito was most often used[7]. During the period of severe trauma or operation, the intestinal mucosal barrier was damaged, and therefore the intestinal permeability increased from which bacteria and endotoxin can easily transfer through the intestinal mucosa and invade tissue and blood, which is called bacterial translocation. Then the bacteria and endotoxin in blood would inversely affect the intestinal mucosal barrier and get it further damaged, thus forming a vicious circle. The more critical condition was that systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction sysdrome (MODS) could even occur[8]. Therefore, how to maintain the function of intestinal mucosal barrier in severe trauma or postoperative patients and how to decrease the permeability and bacterial translocation to avoid the occurrence of SIRS and MODS have become a very important problem.

Brooks *et al*.[9] took L/M as a molecular probe to measure the intestinal permeability in 25 cases of gastrointestinal tumor. The ratio of L/M was greatly increased in the placebo group. Li *et al*.[10] measured 24 hours' urine ^{99m}T-DTPA taken orally in 8 cases of postoperative patients 7 d after operation. The excretory rate of ^{99m}T-DTPA was 13.71±4.85%, which almost doubly increased to that before operation (6.64±3.95%). In this research, serum Gln concentration decreased by 41.97%, and increased by 61.48% in the Gln group after administration of Gln for 7 d, when compared with the level before administration. It was significantly higher in the Gln group than in the placebo group. The ratio of L/M was not significantly different in the two groups initially. After 7 d, the ratio of L/M significantly increased in the control group and significantly decreased in the Gln group. The ratio of L/M was significantly lower in the Gln group than in the placebo group. This result showed that supplement of ectogenetic Gln could significantly decrease the intestinal permeability. Jiang *et al*.[11,12] also proved this in surgical patients. Supplement of alanyl-glutamine could increase serum Gln level and decrease urine L/M ratio.

Li *et al*.[13-16] studied that measurement of serum DAO was helpful to determine the degree of intestinal mucous damage. In their research after administration of Gln, serum DAO level significantly increased in the placebo group and significantly decreased in the Gln group compared with the level before drug administration. The change in serum endotoxin level was similar in the 2 groups. This change of serum endotoxin level was related to the fact that high serum Gln level could enhance the function of intestinal mucosal barrier. Low serum endotoxin level was helpful to reduce SIRS in patients. Some reseaches showed that endotoxin in early trauma could lead to the increase of production and release of cytokines such as TNF-α,IL-6, IL-8, which could take part in the generation of SIRS[17].

Haga *et al*.[18] studied the postoperative conditions of 292 gastrointestinal patients. The result was that 245 patients had SIRS early after operation, which was 83.9%. The possibility of postoperative complication and MODS in these patients was much higher than that in those without SIRS. The results in our study indicate that SIRS can be reduced in early postoperative patients.

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