Diseases of the Esophagus (2010) **23**, 106–111
DOI: 10.1111/j.1442-2050.2009.01007.x

DISEASES OF THE ESOPHAGUS

Original article

Effect of glutamine in patients with esophagus resection

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SUMMARY. **Glutamine is the most abundant amino-acid in the extra- and intracellular compartments of the human body, which accounts for over 50% of its free amino-acid content. Utilization of glutamine peptides is explicitly useful, resulting in a decrease in the number of postoperative infectious complications, period of hospitalization, and therapeutic costs. This article aims to study the effects of glutamine on systemic inflammatory response, morbidity, and mortality after esophagectomy. A prospective, randomized, double-blind, and controlled trial was used. Following sealed-envelope block randomization, the patients were divided into two groups. Members of the glutamine group (group G) received glutamine (Dipeptiven, Fresenius) as continuous infusion for 6 hours at 0.5 g/kg for 3 days prior to, and 7 days following surgery; while patients of the control group were given placebo. We examined 30 patients in group G, and 25 patients as controls. In both patient groups, the levels of total protein, albumin, pre-albumin, retinol binding protein, transferrin, transferring-saturation, C-reactive protein, procalcitonin, lymphocte, Interleukin-6, Interleukin-8, tumor necrosis factor alpha, and serum lactate were determined prior to surgery (t_0), directly after surgery (t_u), following surgery on day 1 (t_1), day 2 (t_2), and day 7 (t_7). For statistical analysis Mann–Whitney U test and chi-square test were used. There was no significant difference between the two groups regarding age, male/female ratio, and SAPS II scores. Intensive care unit morbidity and mortality was similar in both groups (group G: 24 survivors/6 nonsurvivors; Control: 17 survivors/8 nonsurvivors; $P = 0.607$). Daily Multiple Organ Dysfunction Score did not differ significantly between the two groups. The observed inflammatory markers followed the pattern we described without significant difference. Based on our study, the glutamine supplementation that we used had no influence on morbidity, mortality, or postoperative inflammatory response after esophagectomy.**

KEY WORDS: **esophagectomy, glutamine, microalbuminuria, procalcitonin, systemic inflammatory response.**

INTRODUCTION

Glutamine is the most abundant amino-acid in the extra- and intracellular compartments of the human body, which accounts for over 50% of its free amino-acid content.[1] For quite some time, glutamine was considered to be a nonessential amino-acid, as the body is capable of producing it from glutamic-acid.[2] Glutamine possesses unique significance amid amino-acids.[3] Among its numerous functions, it has a major role in ensuring nitrogen transport between the tissues, thus actually regulating protein synthesis of the entire body. It is the most important component of renal and hepatic ammonium production and nucleic acid biosynthesis occurring in every cell of the organism.[4] It is the most important nutrient of the intestinal mucosa and cells with quick turn over like lymphocytes, cells of the renal tubules, fibroblasts, endothelial cells, and macrophages.[5]

Under stress conditions like trauma, burn injury, sepsis or extensive surgical intervention, endogenous glutamine production cannot counterbalance the increased demand and severe deficiency may develop.[6,7] In the 1970s, Fürst *et al.* observed that following surgical intervention, muscular glutamine content decreases, accompanied by muscle breakdown and nitrogen waste.[5]

In 2004, Jiang *et al.* performed a meta-analysis with the goal of summarizing the effect of glutamine supplementation in surgical patients. According to their study, the utilization of glutamine peptides is explicitly useful, resulting in a decrease in the number

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of postoperative infectious complications, period of hospitalization, and therapeutic costs.[8]

Our aim was to study the effect of preventive exogenous glutamine supplementation on postoperative complications and the postoperative inflammatory response in patients with esophagus resection because of tumour.

Study characteristics

Prospective, randomized clinical study.

METHODS

Following approval by the Regional Research Ethics Committee, we included all our patients with esophagus resection because of cancer between 2006 and 2008. All patients had advanced stage esophageal cancer. Patients with benign disease were not included in the study. Written informed consent was obtained from all patients prior to surgery. A transhiatal approach was used for esophagectomy. Following sealed envelope block randomisation, the patients were divided into two groups. Members of the glutamine group (group G) (n = 30) received 0.5 g/kg glutamine (Dipeptiven, Fresenius) in the form of continuous intravenous infusion for 6 hours at 3 days prior to, and 7 days following surgery; while patients of the control group (n = 25) were given placebo. The two groups were on the same nutritional regimen after surgery. Through a jejunal stoma implanted during surgery, patients first received re-hydrating saline solution at 10 mL/h following surgery; then 15 kcal/kg on day 1, 20 kcal/kg on day 2, 25 kcal/kg on day 3, and finally 30 kcal/kg from day 4 onwards in the form of enteral nutrients (Fresubin, Fresenius) until oral nutrition. The patients did not receive supplemental parenteral nutrition along with enteral nutrition. Study end point was patient discharge from the Intensive Care Unit (ICU) or day 7 following surgery. The patients were not followed after the 7th day.

Biochemical measurements

In both patient groups, the levels of total protein, albumin, pre-albumin, retinol binding protein (RBP), transferrin, transferrin-saturation, C-reactive protein (CRP), procalcitonin (PCT), lymphocte, Interleukin-6 (IL-6), Interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), and serum lactate were determined prior to surgery (t_0), directly after surgery (t_u), following surgery on day 1 (t_1), day 2 (t_2), and day 7 (t_7). Serum PCT levels were measured by immunoluminometric assay (LUMItest®, BRAHMS Diagnostica GmbH, Berlin, Germany), normal range: <0.5 ng/mL

Multiple Organ Dysfunction Score (MODS)

The clinical progression of patients was followed by the MODS score system.

Statistics

Statistical analyses were performed using χ^2 and Mann–Whitney U-tests. Differences were accepted significant if $P < 0.05$. Our data are provided in the forms of median value, interquartile range, and standard deviation as appropriate. The number of patients required was calculated by power analysis according to PCT results from our previous pilot studies on a similar population. Therefore, for type I a = 5% and type II (power) of 90%, we needed 50 patients.

RESULTS

Fifty-five patients were studied over 3 years; 30 received glutamine-supplementation and 25 were given placebo. Patient data are shown in Table 1.

There were no major differences in preoperative weight loss among the two groups. Following the surgical procedure, no significant difference was identified regarding infectious complications in the postoperative period.

Effect of glutamine on the biochemical parameters of nutritional status

Serum total protein

Changes in serum total protein levels showed similar kinetics in both patient groups. Compared with preoperative values, we found continuous decrease at three postoperative time points. On day 7, we observed an increase in both groups not reaching preoperative levels (Fig. 1).

Albumin

Albumin kinetics were similar to that of total protein at the first four measurement points, while on day 7

Table 1 Patient data

	Glutamine group n = 30	Control group n = 25	P
Age (year)	56 (48–64)	58 (44–75)	NS
Gender (male/female)	20/10	14/11	NS
Duration of surgery (min)	310 (150–360)	330 (180–420)	NS
Height (cm)	174 (160–176)	173 (165–180)	NS
Weight (kg)	63 (45–95)	68 (44–98)	NS
BMI	23,5 (17–33)	23 (18–33)	NS
Survivor/non-survivor:	25/5	19/6	NS
SAPS II	16 (7–42)	17 (7–35)	NS

Data are shown as median values (interquartile range). For statistical analyses, Mann–Whitney U and χ^2 tests were used. BMI, body mass index; NS, not significant.

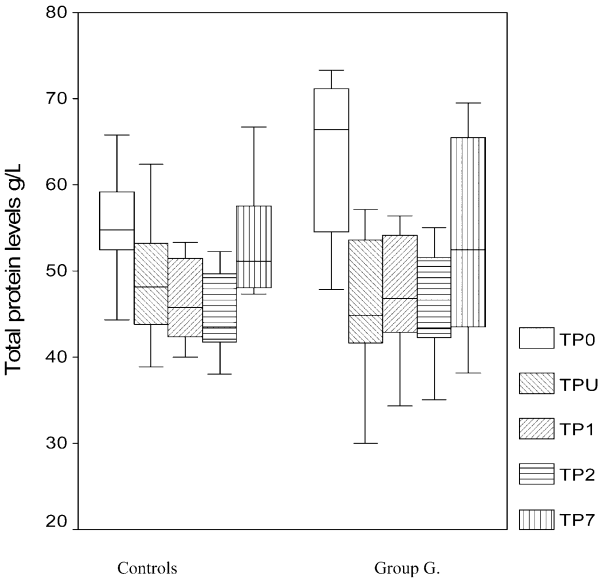

Fig. 1 Changes in serum total protein (TP) levels (g/L) in Glutamine group (group G) compared with controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

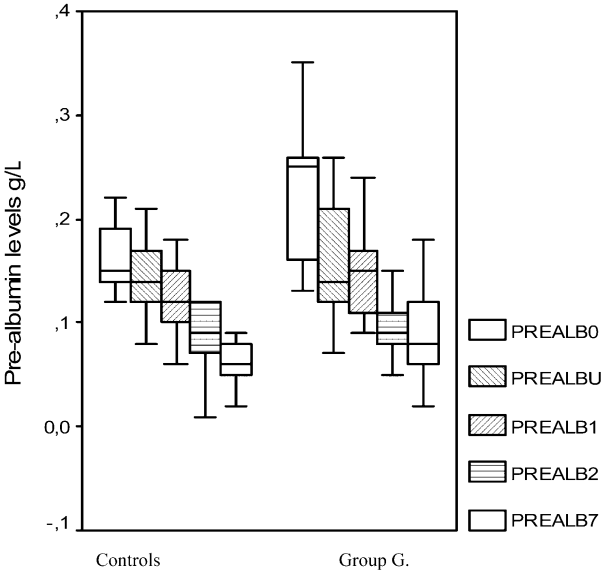

Fig. 3 Pre-albumin (PREALB) levels (g/L) before and after surgery in the two patient groups, glutamine (group G) and controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

further decrease was observed in group G, although this variation did not show a statistically verifiable difference (Fig. 2).

Pre-albumin

Severe malnutrition was not verified in either of the two patient groups prior to surgery; pre-albumin showed decreasing tendency in both groups following operation, but no difference was found between the two groups (Fig. 3).

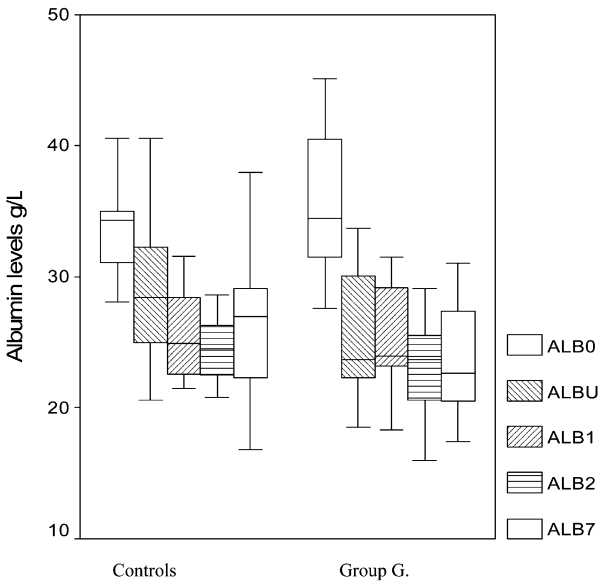

Fig. 2 Kinetics of serum albumin (ALB) levels (g/L) in patients with glutamine supplementation (group G) compared with controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

RBP

During our measurements, RBP levels showed changes similar to that of total protein levels in both groups: gradual decrease at all three measurement points and then elevated values on day 7. Statistically confirmed difference was not found between the two groups at any measurement point (Fig. 4).

Transferrin

Concerning transferrin levels, we observed a gradual decrease compared with levels prior to surgery, then on day 7, transferrin level was higher in controls than in group G, but statistically this was not significant. (Controls: t_0: 1.89 [g/L] ± 0.28 versus group G: 1.89 ± 0.37 [g/L] $P = 0.83$; t_u: 1.53 ± 0.36 [g/L] versus 1.26 ± 0.41[g/L] $P = 0.19$; t_1: 1.31 ± 0.78 [g/L] versus 1.39 ± 0.43 [g/L] $P = 0.78$; t_2: 1.3 ± 0.43 versus 1.1 ± 0.35 [g/L] $P = 0.14$; t_7: 1.4 ± 0.3 [g/L] versus 1.02 ± 0.56 [g/L] $P = 0.29$.)

Transferrin saturation

Transferrin saturation increased following surgery in both patient groups with higher values found in Controls, and then a gradual decrease was observed with a repeated increase on day 7. There was no difference between the two groups at any measurement point (Controls: t_0: 27.3 ± 9.66 [%] versus group G: 18.55 ± 7.53 [%] $P = 0.23$; t_u: 36.7 ± 12.42 [%]

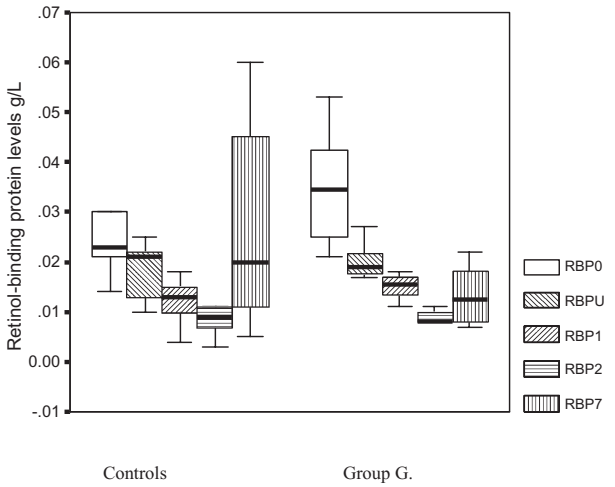

Fig. 4 Comparison of changes in retinol-binding protein (RBP) levels (g/L) in glutamine supplementation patients (group G) and controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

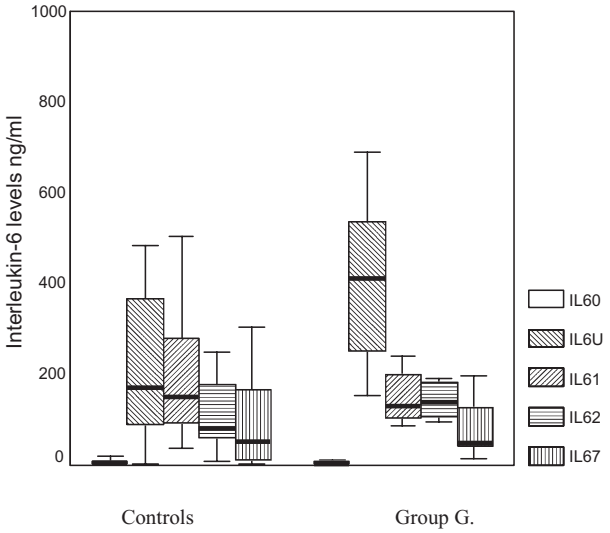

Fig. 5 Changes Interleukin-6 (IL-6) levels (ng/mL) between Glutamine group (group G) and controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

versus 20.2 ± 12.7 [%] $P = 0.52$; t_1: 9.65 ± 3.82 [%] versus 7.7 ± 3.77 [%] $P = 0.4$; t_2: 6.35 ± 3.9 [%] versus 8.05 ± 2.39 (%) $P = 0.92$; t_7: 10.35 ± 13.66 [%] versus 10.75±4.44 [%] $P = 0.89$.)

Effect of glutamine on the postoperative inflammatory response

TNF-α

TNF-α levels gradually increased from the first day after surgery until postoperative day 7, when maximal values were reached at twice the normal value; there was no difference at any measurement point. (Controls: t_0: 4.15 ± 3.23 [ng/mL] versus group G: 6.44 ± 1.54 [ng/mL] $P = 0.29$; t_u: 4.22 ± 2.11 [ng/mL] versus 4.82 ± 20.38 $P = 0.39$; t_1: 9.55 ± 11.08 [ng/mL] versus 8.34 ± 6.07 [ng/mL] $P = 0.99$; t_2: 9.00 ± 6.26 (ng/mL) versus 8.36 ± 5.43 [ng/mL] $P = 0.89$; t_7: 9.04 ± 6.26 [ng/mL] versus 8.33 ± 5.43 [ng/mL] $P = 0.97$).

IL-6

The level of IL-6 increased several fold following surgery; of note, its level was higher in group G than in Controls. At subsequent measurement points, IL-6 levels gradually decreased in both patient groups and there was no statistical difference between the groups (Fig. 5).

IL-8

IL-8 reached its maximal value on the first post-operative day, but there was no difference between the two patient groups at any measurement point (Fig. 6).

CRP and PCT

For both well-known inflammatory markers, we found the same kinetics that is described in medical literature, and there was no statistically confirmable difference between the two patient groups at any measurement point (Figs 7,8).

DISCUSSION

Extensive surgical interventions lead to glutamine depletion, the result of which severe postoperative

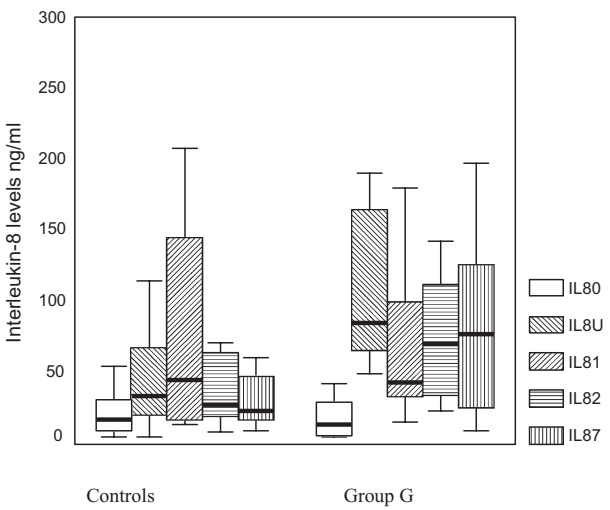

Fig. 6 Changes in Interleukin-8 (IL-8) levels (ng/mL) between Glutamine group (group G) and controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

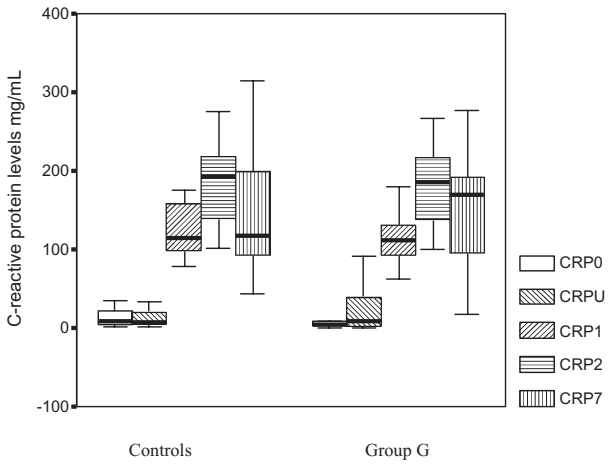

Fig. 7 Comparison of inflammatory changes in C-reactive protein (CRP) levels (mg/mL) in glutamine patients (group G) compared with controls. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

complications may develop, including infections, wound-healing aberrations, impaired immune response, and increased intestinal permeability – this latter possibly resulting in multi-organ failure because of bacterial translocation. The aim/basic hypothesis of the current clinical study was whether L-alanil-L-glutamine supplementation can influence the development of postoperative complications and the postoperative inflammatory response[9] in patients with esophagus resection as a result of esophageal cancer. Studies performed to date reported the beneficial effects of glutamine supplementation in surgical patients; however this has only been trialled together with complete parenteral nutrition.[10] In our study, we have utilized enteral nutrition performed through a jejunal stoma supplemented by intravenous glutamine administration. We have not found any difference of postoperative morbidity or mortality in our study. Organ-functions were assessed by the MODS score-system, but no difference was found between the two patient groups.

For patients in critical condition, glutamine is the most important donor of nitrogen supply in the splanchnic region and the immune system. Performing a meta-analysis on 373 patients with extensive abdominal surgical intervention, Ya-Min Zheng found that glutamine administration decreased hospitalization period and thus hospitalization costs.[11] In our present study, no statistically confirmable difference was found between the two groups for either general hospitalization period or treatment period at the ICU.

Among pro-inflammatory cytokines, IL-6, IL-8, and TNF-α were examined as the most renowned bio-markers of surgical stress,[12] their release determined by the period and extensiveness of the surgical intervention; yet no difference was found between the two groups. Based on our study, glutamine supplementation has no effect on the IL6 and TNF-α production of blood mononuclear cells.[13] IL-6 plays a central role in initiating the synthesis of acute phase proteins in hepatocytes, but the CRP and PCT[14,15] levels that we examined have not shown any statistically verifiable difference.

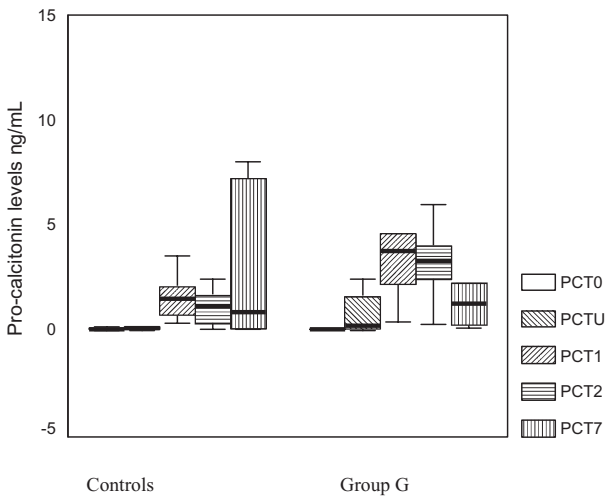

Fig. 8 Comparison of inflammatory changes in procalcitonin (PCT) levels (ng/mL) in glutamine patients (group G) compared withontrols. Data are represented in 'box-plot' format. Minimum-maximum, median, and interquartile range values are shown on the figure. Differences between the two groups were verified by the Mann–Whitney U-test at all observation points.

CONCLUSION

We studied the efficiency of preventive intravenous glutamine supplementation provided along with enteral nutrition in patients with esophagus resection because of cancer. Based on our study, the glutamine supplementation that we used had no influence on morbidity, mortality, or postoperative inflammatory response in the patients. The reason for this is unclear; it is conceivable that glutamine administration supplemented by enteral nutrition loses efficiency or probably the body consumes it as a source of energy. It is possible that the time or dose of glutamine supplementation should be increased in contrast to literature recommendations, perhaps to be used in the form of a continuous 24-hour infusion; however, further studies are required to prove this.

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