Objective: To examine the effect of enteral administration of glutamine in patients with peritonitis or abdominal trauma. Methods: In a prospective, interventional, observer-blind, randomized clinical trial, 120 patients, aged 18-60 years, were randomized to receive either enteral glutamine 45 g/day for 5 days in addition to standard care (n=63; group A) or standard care alone (n=57; group B). Surgical intervention was done as needed. Results: The two groups were comparable for sex and severity of illness scores. Following treatment, serum malondialdehyde (MDA) levels in group A increased from 4.4 (8.0) to 7.2 (4.8) mmol/mL, whereas those in group B decreased from 3.9 (4.9) to 3.1 (5.0) mmol/mL; these changes were not statistically significant. Reduced glutathione levels increased from 0.03 (0.04) to 0.06 (0.12) mg/g Hb (p=0.032) after treatment in group A, and from 0.03 (0.03) to 0.05 (0.04) mg/g Hb (p=0.001) in group B. Infectious complications were equally frequent in the two groups (group A: 44; group B: 37; p=0.571). Survival rate and duration of hospital stay were also comparable in the two groups. Conclusion: Enteral glutamine supplementation offers no advantage in patients with peritonitis or abdominal trauma. [Indian J Gastroenterol 2007;26:70-73]

Critical illness patients, characterized by enhanced oxidative stress and depressed immune defense mechanisms, are at risk of sepsis, have prolonged hospital stay, and high mortality rates. 1-5 Addition of antioxidant therapy, also known as immunonutrition, to standard treatment in such patients may favorably impact their outcomes.

Glutamine, an essential component of glutathione, is one such antioxidant. It helps the kidneys in excreting urea and acid load. It also helps in preserving lean body mass by assisting in the synthesis of purines, pyrimidines and muscle proteins. It helps maintain intestinal barrier and cellular immunity by serving as a fuel for enterocytes and lymphocytes.

The increased glutamine demand during illness is normally met by mobilizing glutamine stores in the skeletal muscles and lungs. 6,7 However, increased consumption causes rapid decrease in glutamine stores, resulting in altered protein dynamics, depressed immune functions and poor prognosis. Thus, these patients may benefit from glutamine supplementation.

Most animal and clinical studies in the past have been done using parenteral glutamine supplementation. 1,3,5 The few trials with enteral glutamine supplementation have had conflicting results. 2,4,8,9

Methods

We conducted this prospective, observer-blind, randomized clinical trial over a one-year period after approval by the local research committee. Patients aged 18-60 years admitted to our unit with (a) bowel perforation peritonitis with Mannheim Peritonitis Score (MPI) ≤ 26, or (b) abdominal trauma with Injury Severity Score (ISS) between 20 and 50, were included. Patients with uncontrolled co-morbidity, drug allergies, and pregnancy were excluded. All patients provided written informed consent. Immediately after admission, a detailed history was taken, physical examination performed, and blood samples drawn for complete blood count, kidney and liver function tests, C-reactive protein, blood sugar, arterial blood gas analysis, prothrombin time and partial thromboplastin time. Chest X-ray and ECG were obtained. MPI and ISS were calculated using standard methods. 10,11 In addition, two aliquots of blood, 0.2 mL in EDTA for reduced glutathione and 0.5 mL of serum in plain vial for malondialdehyde (MDA) levels, were drawn. Sample for reduced glutathione was preserved at minus 4°C immediately. Serum MDA and plasma reduced glutathione levels were estimated as previously described. 12,13

All patients received intravenous fluids and electrolytes (equivalent to estimated deficit), oxygen (5 L/min) by mask, antibiotics (usually ceftriaxone 1 g IV 12 hourly and metronidazole 500 mg IV 8 hourly) and omeprazole 20-40 mg IV OD. Blood transfusion was administered if indi-
Glutamine in critically ill surgical patients

Kumar, Kumar, Sharma, Jain

Nasogastric intubation, bladder catheterization, and jugular venous cannulation were done in all patients. Ultrasonography and contrast-enhanced CT were done when indicated. Injection enoxaparin 20 mg (~0.25 mL) was administered at admission followed by 20 mg OD till ambulation, for prophylaxis against deep venous thrombosis. Surgical treatment was guided by the patient’s clinical condition. A feeding jejunostomy was performed in patients undergoing gastro-duodenal surgery.

Patients were randomized using a computer-generated randomization, stratified for nature of disease (peritonitis or trauma) into two groups. Both groups received isocaloric, isonitrogenous feeds freshly prepared at our hospital kitchen to deliver 25-50 Kcal/Kg body weight/day (as calculated by Harris-Benedict equation) and 1-2 g protein/Kg body weight/day started 24 hours after admission or operation, administered by mouth or through a nasogastric or jejunostomy tube. Patients in group A received 15 g of glutamine14 (dissolved in 100 mL of water, swallowed or given through feeding tube) three times a day for 5 days in addition to the above feeds. Glutamine supplementation began 24 hours after admission/operation. Reduced glutathione and MDA levels in sera were re-estimated in both groups of patients on the morning of next day after 5 days of dietary treatment.

Patients were clinically monitored every day. Serological, microbiological and radiological investigations were done as needed. Patients were discharged when they were afebrile, fully ambulatory, tolerating feeds, and needing no active nursing assistance.

The outcome parameters studied included MDA and reduced glutamine levels, infectious morbidity,2,15 length of hospital stay, and mortality (death directly attributable to peritonitis or trauma within 30 days of illness).

We had planned to exclude those patients from analysis who received <3 days of randomized treatment; none had to be excluded for this reason.

Statistical tests used included χ² test for infectious morbidity and mortality, Mann-Whitney U test for length of hospital stay, and paired t test for serum MDA and reduced glutathione. Significance was taken at p≤0.05.

Results

Between April 2004 and March 2005, 158 patients were admitted with peritonitis and trauma to our surgical unit. Of these, 38 patients (23 with peritonitis, 15 with trauma) did not meet the inclusion criteria, and 120 patients (93 peritonitis, 27 trauma) were enrolled in the study. In patients with peritonitis, sites of bowel perforation were: ileum 48, gastroduodenal ulcers 29, jejunum 7, appendix 5 and large bowel 4. Of patients with trauma, most (24/27) had penetrating injuries (stabbing 20, gunshot 4); internal injuries in these patients included: stomach 10, small bowel 6, large bowel perforation 4, omentum and mesenteric 2, renal 2, splenic 2 and pancreatic 1. Three patients had blunt abdominal trauma, with jejunal perforation, liver laceration and lung laceration in one patient each.

Of the 120 patients, 63 (age 30 [SD 10] years, 49 male) were randomized to group A, and 57 (34 [12] years; 41 male) to group B. Group A included 48 patients with peritonitis (MPI = 21.6 [4.4]) and 15 with abdominal trauma (ISS = 23.7 [4.5]); these numbers in group B were 45 (MPI = 21.2 [4.8]) and 12 (ISS = 26.5 [9.0]), respectively. The two groups were comparable in severity of illness scores and gender ratio. Group A patients were younger than group B patients (p=0.036).

All patients tolerated glutamine well. Serum MDA levels changed from 4.4 (8.0) to 7.2 (4.8) nmol/mL (p=ns) after 5 days of treatment in group A, and from 3.9 (4.9) to 3.1 (5.0) nmol/mL (p=ns) in group B. Levels of reduced glutathione increased significantly after 5 days of treatment in both the groups. In group A, these increased from 0.03 (0.04) to 0.06 (0.12) mg/g Hb (p=0.032), and in group B from 0.03 (0.03) to 0.05 (0.04) mg/g Hb (p=0.001).

The number of patients with infectious complications was similar in the two groups (group A: 44, group B: 37; p =0.571), as was the number of infectious complications (group A: 50 [wound infections 36, intra-abdominal infections 11, pneumonia 2, septicemia 1], group B: 45 [32, 12, 1, 0, respectively]). The number of survivors in group A (55; without complications 19, with complications 36) and group B (52 [20, 32, respectively]) was similar (p=0.721). The median (range) hospital stay in group A was 11.0 (2-29) and in group B was 9.0 (2-82) days. Length of hospital stay was comparable in the two groups (p=0.291) using Mann-Whitney U test.
Critical ill patients are at increased risk of infectious complications, namely, sepsis, pneumonia, bacteremia and wound infection. In our study, 67% of patients had an infectious complication, with wound infection being the commonest (84%) followed by intra-abdominal abscess formation (28%). In Western countries, pneumonia has a major share in postoperative morbidity. This may be related to the severity of illness: patients needing ICU care show high incidence of chest complications. Our patients, though critically ill, did not usually require ICU care.

The high incidence of infectious complications is due to increased gut permeability, abnormal lymphocyte and macrophage function, colonic apoptosis, and diminished secretory IgA function. Glutamine supplementation has been shown to reverse all these ill effects in animal and in-vitro studies. But its clinical utility remains uncertain. In our study, glutamine supplementation did not decrease the risk of infectious complications.

Uncontrolled sepsis is associated with profound oxidative stress, measurable by products of lipid peroxidation in plasma. Glutamine therapy may be expected to lead to decrease in levels of serum MDA and increase in those of reduced glutathione levels. However, in our study, serum MDA levels did not change in either group. An increase in levels of reduced glutathione following glutamine supplementation was expected after glutamine administration; however, since these levels increased in the control group too, the increase in group A too may not be due to glutamine replacement. This is further strengthened by our findings that infectious morbidity was also not influenced by glutamine therapy.

Only a few studies have evaluated the effect of glutamine supplementation on duration of hospital stay, and the results have been contradictory. Our study also did not show any effect on hospital stay, possibly because the risk of infectious complications did not show any decrease.

The high mortality in critically ill patients is due to depressed immune defense mechanisms. This may be partly due to rapid glutamine depletion and increased glutamine requirement. In initial studies, glutamine supplementation led to decreased mortality. However, subsequent studies have failed to show any beneficial effect of glutamine on either short- or long-term mortality. Our results are consistent with these recent reports.

In conclusion, our study failed to show any clinical or biochemical benefit of glutathione supplementation by the enteral route in critically ill patients with peritonitis or abdominal trauma.

References
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Correspondence to: Dr. Sunil Kumar, B-901, Pawittra Apartments, Vasundhara Enclave, Delhi 110 096. E-mail: drskg.15@rediffmail.com

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