International Surgery Journal
*Raghavendra et al. Int Surg J. 2019 Mar;6(3):903-908*
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20190822

**Original Research Article**

# Effects of perioperative enteral glutamine on surgical outcome in gastrointestinal cancer patients

**Raghavendra[1]*, Raghupathi S.[2]**

[1]Department of Surgery, KMC Mangalore, Karnataka, India
[2]Department of Surgery, Sri Devraj URS Medical College, Kolar, Karnataka, India

**Received:** 13 January 2019
**Accepted:** 13 February 2019

***Correspondence:**
Dr. Raghavendra,
E-mail: drraghudn@gmail.com



## ABSTRACT

**Background:** Previous trials have shown that perioperative glutamine could protect patients from infectious complications after gastrointestinal cancer operations.
**Methods:** 54 patients with a planned elective operation for gastrointestinal cancer were divided into two groups: GROUP A**:** patients given glutamine enriched enteral nutrition perioperatively (n=27), GROUP B: patients given enteral feed without glutamine (n=27). Patients were assessed in terms of post-operative complications like infective complications, anastomotic leak, need for reintervention, length of hospital stay and mortality.
**Results:** In group A seven patients and in group B six patients had surgical site infection post operatively (p=0.750). In group A five patients and in group B three patients had lung and urinary tract infection post operatively (p=0.444). In group A three patients and in group B five patients had intra-abdominal abscess/collection post operatively (p=0.444). In group A one patient and in group B three patients had anastomotic leak post operatively (p=0.299). In group A three patients and in group B three patients had reintervention in form of ultrasound guided aspiration and ultrasound guided pigtail aspiration for intra-abdominal collection (p=1.000). In group A and in group B mean length of hospital stay was 26 days and 23 days respectively (p=0.346). In group A and in group B mean length of post-operative hospital stay was 13 and 12 days respectively (p=0.642). There was no mortality in our study. No significant difference between the groups was found in complication rates, length of hospital stay.
**Conclusions:** Routine perioperative glutamine to the patients undergoing major gastrointestinal surgery is not beneficial.

**Keywords:** Gastrointestinal cancer, Glutamine, Immunonutrition, Perioperative

## INTRODUCTION

Major abdominal operations lead to post traumatic dysregulation of immune system, which is characterized by suppression of immune functions.[1,2] Nutritional intervention matters the most, as the worsening of nutritional status has been acknowledged as a crucial factor influencing surgical outcomes.[3] There is increasing evidence that optimized nutritional support in the perioperative period may decrease the number of adverse events after major gastrointestinal surgery.[1,2] During the last decade, perioperative nutrition has been transformed from a tool to provide calorie and nitrogen support to a therapeutic device aimed at boosting the immune system and enhancing resistance to complications.

Nutrition provision is recognized to be an important aspect in the perioperative management of elective gastrointestinal (GI) surgery patients, and the timely provision of nutrition has been associated with improved postoperative outcomes.[3] The benefits of nutrition provision in surgical patients are traditionally thought to

arise from the provision of macronutrients such as calories for energy and protein for wound healing, as well as to reduce the impact of catabolism in the postoperative period.[4] However, it has been theorized that due to the complex inflammatory, immune and oxidative stress that is experienced post-operatively, providing specific nutrients in supra physiological doses may provide vital substrates that serve to modulate these immune and metabolic responses and thus improve clinical outcomes.[4] In view of this, during the early 1990s, new nutrition support formulas emerged, commonly referred to as immunonutritients, immune-enhancing diets.[4]

Infectious and other types of complications following gastrointestinal cancer, head and neck cancer, and cardiac surgery are frequent and add significantly to patient morbidity as well as to hospital length of stay and costs.[5] Published estimates of complication rates after surgery for patients with gastrointestinal cancer, head and neck cancer, and cardiac disease suggest that these rates range between 15% and 54%.[6] Infectious complications include wound infections, abdominal abscess, pneumonia, urinary tract infections, and sepsis.

Immunonutrition refers to provision of specific nutrients on immune system. Immunonutrition for surgical and critically ill patients, involving nutritional support with arginine, glutamine, ω-3 fatty acids and nucleotides (RNA) either alone or in combination, has been gaining increasing attention.[7] Numerous clinical studies on the effects of perioperative immunonutrition following surgery or trauma have shown beneficial effects, reducing postoperative morbidity after major abdominal surgery.[8]

Glutamine serves as an important energy source for the gut mucosa. Various immunologic cells and other rapidly dividing cells require glutamine for their metabolic processes.[9] Glutamine is a respiratory substrate for enterocytes and lymphocytes and also provides a source for nucleotide synthesis in lymphocytes undergoing blastiogenesis.[10,11] Glutamine may also modulate the inflammatory response in the gut by reducing concentrations of pro-inflammatory cytokines IL-6 and IL-8, thereby protecting the intestinal mucosa.[12] Under conditions of stress consumption of glutamine outstrips production, resulting in a decrease in glutamine concentration and an associated immune dysfunction.[10,13] Moreover, a reduction in glutamine concentration has been linked with morphological changes in intestinal architecture that predispose to bacterial translocation which has been implicated in the development of the systemic inflammatory response syndrome.[10,14]

Several clinical studies on the effects of peri-operative immunonutrition following surgery or trauma have been conducted in the west but in India very few studies have been conducted. Our study aimed to examine the immunomodulatory effect of glutamine in GI surgery for GI cancer by measuring clinical outcome of the patient post-operatively.

## METHODS

This is a prospective trial. This study was conducted in Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India over a period of one and a half years from July 2013 to December 2014. The study was approved by the Ethical Committee of the institute. A total 54 patients undergoing elective gastrointestinal surgery for gastrointestinal cancer by the participating consultant surgeons in the Department of General Surgery, PGIMER, Chandigarh, India were included in the study. Consenting men and women between 18 and 70 years of age with respectable gastrointestinal tumor based on CECT abdomen/MRI/ERCP/EUS, fit to be operated upon based on functional status were included in the study. Patients with history of ongoing infection, gastrointestinal obstruction, hepatic or renal dysfunction, clinically unfit for surgery with widespread metastasis/unresectable tumours based on CECT abdomen/MRI/MRCP/ERCP/EUS and patients refusing to enroll were excluded. Patients were prospectively divided into the two groups so as each group includes 27 patients.

Group A: Oral supplementation of glutamine at the dose of 30gm/day for 5 days before and 5 days after surgery if patient was orally allowed as powder mixed with water. If there was any contraindication for oral supplementation post operatively then glutamine powder was supplemented through feeding jejunostomy or nasogastric tube.

Group B: Oral or enteral feeding as in group A, but without glutamine.

Standard operative technique was followed in all patients as per departmental protocol. The surgery performed and extension of resection depended on preoperative radiologic investigations and on table assessment. Patients were given betadine scrub bath at the time of induction of anaesthesia. All patients were given antibiotic intravenously; and antibiotic continued/changed post operatively depending on the clinical condition of patient.

### *Assessment of outcome*

All patients were assessed pre and postoperatively till the discharge from hospital. Outcome measures were in terms of post operation complications like post-operative infective complications including surgical site infection, blood culture positive sepsis, pulmonary, urinary infection, intra-abdominal abscess, anastomotic leak, need for reintervention, length of hospital stay, mortality.

### *Statistical analysis*

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL,

version 18.0 for Windows). Mean and medians was calculated for all quantitative variables and for measures of dispersion standard deviation or standard error was calculated. Normality of data was checked by measures of Kolmogorov Smirnov tests of normality. For normally distributed data means of 2 groups were compared using student t-test. For skewed data Mann-Whitney test was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared by using Chi square or Fisher's exact test whichever is applicable. All statistical analysis tests were two tailed and P value <0.05 was taken as significant.

## RESULTS

A total of 57 patients who underwent gastrointestinal surgery for gastrointestinal cancer between July 2013 to December 2014 were included in the study. Fifty four patients met the inclusion criteria and consented to participate in the study were included in this study. Three patients were excluded from the study as they were found to have widespread metastatic disease. All patients underwent clinical evaluation and necessary investigations preoperatively. They all underwent surgery as briefed before. Patients were evaluated post operatively till their discharge from the hospital.

Both the groups were matched for age and sex. Of the fifty four patients twenty eight were males and twenty six were females. Mean age of patients in Group A was 52 yr and mean age of patients in Group B was 49 yr (Table 1).

**Table 1: Demographic profile of the patients.**

| Parameter | Group A n = 27 | Group B n = 27 | p value |
|---|---|---|---|
| Age (years) | 52±12 | 49±12 | 0.461 |
| **Sex** | | | |
| Male | 17 | 11 | |
| Female | 10 | 16 | |

**Table 2: Diagnosis of patients.**

| Diagnosis | Group A | Group B | Total |
|---|---|---|---|
| Colorectal carcinoma | | | |
| Carcinoma right colon | 3 | 0 | 12 |
| Anorectal carcinoma | 4 | 2 | |
| Carcinoma sigmoid colon | 2 | 1 | |
| **Carcinoma gall bladder** | | | |
| Incidental | 3 | 2 | 08 |
| **Carcinoma esophagus** | | | |
| Middle 1/3rd | 1 | 3 | 10 |
| Lower 1/3rd | 3 | 3 | |
| Cholangiocarcinoma | 4 | 2 | 6 |
| Carcinoma head of pancreas | 3 | 0 | 3 |
| Carcinoma stomach | 1 | 2 | 3 |
| Hepatocellular carcinoma | 1 | 0 | 1 |
| Neuroendocrine tumors | 1 | 2 | 3 |
| Cystic neoplasm of pancreas | 1 | 1 | 2 |
| **Gastrointestinal stromal tumors** | | | |
| Stomach | 0 | 2 | 3 |
| Ileum | 0 | 1 | |
| Periampullary carcinoma | 0 | 3 | 3 |
| Total | 27 | 27 | 54 |

The diagnosis of the patients were as enlisted in (Table 2). The most common indication for surgery in both the group was hepatobiliary cancer (carcinoma gallbladder, cholangiocarcinoma, hepatocellular carcinoma, carcinoma head of pancreas, periampullary carcinoma). The most common surgery in both the group was Whipple's procedure. Other indications for surgery were colorectal cancer, carcinoma oesophagus, carcinoma stomach and gastro-intestinal stromal tumours (Table 2).

The various surgeries patients underwent are enlisted in (Figure 1). Whipple's procedure was the common surgery performed.

The postoperative morbidity was seen in 25/54 (46.3%) patients of whom 13/54 (24.07%) patient were in the Group A and 12/54 (22.22%) were in the Group B (Table 3). There was no mortality in our study. The outcomes variables of both the groups are shown in Table 3.

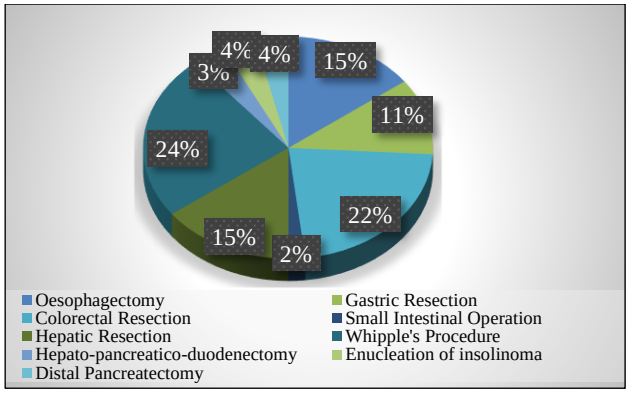


**Figure 1: Distribution of operative procedures.**

In group A 7/27(25.9%) and in group B 6/27(22.2%) patients had surgical site infection. There was no statistically significant difference among Group A and Group B in relation to post-operative sepsis and surgical site infection (p=0.750). In group A 5/27(18.5%) and in group B 3/27(11.1%) patients had lung and urinary tract infection. There was no statistically significant difference among Group A and Group B in relation to post-operative lung and urinary tract infection (p=0.444). In group A 3/27(11.1%) and in group B 5/27(18.5%) patients had intra-abdominal abscess/collection. There was no statistically significant difference among Group A and Group B in relation to post-operative intra-abdominal abscess/collection (p=0.444). In group A 1/27(3.7%) and in group B 1/27(3.7%) patient had intestinal obstruction post operatively. There was no statistically significant difference among Group A and Group B in relation to post-operative intestinal obstruction (p=1.000). In group A 3/27(11.1%) and in group B 3/27(11.1%) patients needed TPN post operatively for maintaining nutrition. There was no statistically significant difference among Group A and Group B in relation to post-operative need for TPN (p=1.000). In group A 1/27(3.7%) and in group B 3/27(11.1%) patients had anastomotic leak. There was no statistically significant difference among Group A and Group B in relation to anastomotic leak (p=0.299). In group A 3/27(11.1%) and in group B 3/27(11.1%) patients had reintervention in form of ultrasound guided aspiration and ultrasound guided pigtail aspiration for intra-abdominal collection. There was no statistically significant difference among Group A and Group B in relation to post-operative reintervention (p=1.000). In group A and in group B mean length of hospital stay was 26 days and 23 days respectively. Shortest hospital stay in this group was for 10 days and the longest hospital stay was for 61 days but the postoperative stay was just 20 days. This patient waited preoperatively for her bilirubin level to come down and to control cholangitis. So, we calculated the length of post-operative hospital stay to overcome the problem of pre-operative lengthy hospital stay for various reasons. In group A and in group B mean length of post-operative hospital stay was 13 and 12 days respectively. There was no statistically significant difference among Group A and Group B in relation to length of hospital stay and post-operative hospital stay, where p value was 0.346 and 0.642 respectively.

**Table 3: The post-operative outcomes.**

| Parameters | Group A, N = 27 | Group B, N = 27 | p value |
|---|---|---|---|
| Post-operative sepsis/wound infection | 7 | 6 | 0.750 |
| Post operative lung infection/urinary tract infection | 5 | 3 | 0.444 |
| Post-operative intra abdominal abscess/collection | 3 | 5 | 0.444 |
| Post-operative intestinal obstruction | 1 | 1 | 1.000 |
| Post-operative need for TPN | 3 | 3 | 1.000 |
| Anastamotic leak | 1 | 3 | 0.299 |
| Reintervention | 3 | 3 | 1.000 |
| Length of hospital stay | 26±11 | 23±10 | 0.346 |
| Length of post-operative hospital stay | 13±7 | 12±4 | 0.642 |

## DISCUSSION

Nutritional support in perioperative period became initially popular through the observation that malnutrition is associated with a poor surgical outcome. Malignancies and surgical stress can influence negatively patient's immune system and other defense mechanisms. Infections are common problem after major abdominal surgical procedures, contributing to increased morbidity, mortality and healthcare costs.[4,6] The causes of postoperative complications following gastrointestinal cancer surgery are multifactorial and dependent to an extent on the primary surgical disease, the type and magnitude of operation. It has been well established and documented that malnutrition is an independent negative factor associated with post-surgical complications, mortality, and prolonged hospital stay and therefore, higher healthcare costs.[5,6] In addition, malnutrition is often associated with pathologic situations such as cancer, chronic inflammation or organ dysfunction that increase the risks of surgery.[3,15] The objectives of perioperative nutritional support are: to minimize the

negative protein balance, which avoids malnutrition; to maintain immunological function, thus improving postoperative recovery; to reduce intestinal function recovery time; and, to shorten hospital stay.[16]

Recently, the main focus of clinical nutrition has moved from the issue of simply cover the energy and nitrogen requirements (nutritional support) to the new concept of supplementing selected nutritional substrates because of their specific pharmacological effects (nutritional therapy).[17] Attempts to augment the immune response have been made by enteral hyper alimentation, known as immunonutrition.[17] These feeds typically contain arginine, glutamine, omega-3 fatty acids, nucleotides or a combination of all these nutrients.[17] The main purpose of immunonutrition is to modulate postoperative metabolic response by giving perioperatively nutritional formulas supplemented with specific nutrients such as arginine, glutamine, omega-3 fatty acids, nucleotides and others.[17] Our study used oral glutamine which is one of the substances used in immunonutrition and checked its immunomodulating effect in GI surgery by measuring surgical outcome. In our study 54 patients were selected out of whom 27 patients were included in the group A and 27 patients were included in the group B. Perioperative oral/enteral glutamine was given for five days prior to surgery and for five days after surgery in the Group A. In Group B oral/enteral nutrition was given without glutamine. The postoperative morbidity was seen in 25(46.3%) patients of whom 13(24.07%) patients were in the Group A and 12(22.22%) were in the Group B. In group A 7/27(25.9%) and in group B 6/27(22.2%) patients had surgical site infection. There was no statistically significant difference among Group A and Group B in relation to post-operative sepsis and surgical site infection (p=0.750). In group A 5/27(18.5%) and in group B 3/27(11.1%) patients had lung and urinary tract infection. There was no statistically significant difference among Group A and Group B in relation to post-operative lung and urinary tract infection (p=0.444). In group A 3/27(11.1%) and in group B 5/27(18.5%) patients had intra-abdominal abscess/collection. There was no statistically significant difference among Group A and Group B in relation to post-operative intra-abdominal abscess/collection (p=0.444). In group A 1/27(3.7%) and in group B 1/27(3.7%) patient had intestinal obstruction post operatively. There was no statistically significant difference among Group A and Group B in relation to post-operative intestinal obstruction (p=1.000). In group A 3/27(11.1%) and in group B 3/27(11.1%) patients needed TPN post operatively for maintaining nutrition. There was no statistically significant difference among Group A and Group B in relation to post-operative need for TPN (p=1.000). In group A 1/27(3.7%) and in group B 3/27(11.1%) patients had anastomotic leak. There was no statistically significant difference among Group A and Group B in relation to anastomotic leak (p=0.299). In group A 3/27(11.1%) and in group B 3/27(11.1%) patients had reintervention in form of ultrasound guided aspiration and ultrasound guided pigtail aspiration for intra-abdominal collection. There was no statistically significant difference among Group A and Group B in relation to post-operative reintervention (p=1.000). In group A and in group B mean length of hospital stay was 26 days and 23 days respectively. Shortest hospital stay in this group was for 10 days and the longest hospital stay was for 61 days but the postoperative stay was just 20 days. This patient waited preoperatively for her bilirubin level to come down and to control cholangitis. So, we calculated the length of post-operative hospital stay to overcome the problem of pre-operative lengthy hospital stay for various reasons. In group A and in group B mean length of post-operative hospital stay was 13 and 12 days respectively. There was no statistically significant difference among Group A and Group B in relation to length of hospital stay and post-operative hospital stay, where p value was 0.346 and 0.642 respectively. There was no mortality in our study.

Glutamine is the most abundant free amino acid in the body and plays a vital role in amino acid transport and nitrogen balance.[18] It is a fuel for rapidly dividing cells such as enterocytes, lymphocytes so as to protect mucosa barricade and enhance immune function.[18] Glutamine has been demonstrated to be a conditional essential amino acid, which plays a central role in the response to stress. Glutamine also supports acid-base homeostasis, maintains the function and morphology of the gastrointestinal epithelium, and preserves the antioxidant stores in tissues.[18-20] Glutamine has been shown to enhance the immune response and augment host defences.

From the previous studies on perioperative immunonutrition supplementation it is seen that results are inconsistent, results have varied in different studies and in different populations.[18-21] Many trials of immunonutrients indicate several beneficial clinical effects in surgical patients. However, doubts remain about the efficacy of these immunonutrients due to contradictory findings among other trials. The theoretical grounding for glutamine supplementation is strong, particularly in relation to early enteral feeding post-surgery [18-21]. Glutamine has been shown to enhance the immune response and augment host defences and maintains the function and morphology of the gastrointestinal epithelium.[18-21]

Our study was one of the first studies to be conducted in India over effects of immunonutrition on such a large number of GI cancer patients. Our study tried to elucidate the role of glutamine, an aminoacid which is an essential component of immunonutrition on postoperative morbidity and mortality in GI cancer patients. It was seen that there was no statistically significant difference in glutamine group and control group in terms of postoperative infective complications like sepsis, surgical site infection, pulmonary infection, urinary tract infection, anastomotic leak, intestinal obstruction, need for TPN, intra-abdominal abscess/collection, need for

reintervention and length of hospital stay. There was no mortality in our study. From the previous studies it is seen that perioperative immunonutrition supplementation is beneficial in malnourished patients undergoing surgeries.[21] About 70% of the patients were well nourished in our study. So, this might be a reason for no significant difference between glutamine group and control group. It may be beneficial if we could identify that subgroup of patients with significant malnutrition and put them on an immune-enhanced diet for a minimum period of 5-10 days preoperatively if surgery can safely be postponed.[21]

The drawback of our own study is the small number of patients included which could have resulted in type 2 errors in the statistical analysis. The small sample size was because of time bound study period; moreover, we did not study the other immune modulatory factors like IL-6, TNF-α and other nutritional status markers like prealbumin. Other limitations were different operating surgeons and the heterogeneity of the diseases involved in study, all the carcinomas of GI tract were involved not confining to a particular part. To conclude there was no significant difference between patients of group A (glutamine group) and group B in terms of post-operative morbidity, infective complications and length of hospital stay. Routine perioperative glutamine to the patients undergoing major gastrointestinal surgery is not beneficial.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Meakins JL. Host defense mechanisms in surgical patients: effect of surgery and trauma. Acta Chir Scand. 1989;550:43-51.
2. Chang Hr, Bistrian B: The role of cytokines in the catabolic consequences of infection and injury. JPEN. 1998;22:156-66.
3. Studley HO. Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA. 1936;106:458-60.
4. Jones NE, Heyland DK. Pharmaconutrition: a new emerging paradigm. Curr Opin Gastroenterol. 2008;24:215-22.
5. Braga M, Gianotti L: Preoperative immunonutrition: cost-benefit analysis. JPEN. 2005;29:S57-S61.
6. Waitzberg DL, Saito H, Plank LD, et al: Postsurgical infections are reduced with specialized nutrition support. World J Surg. 2006;30:1592-1604.
7. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001;286:944-53.
8. Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A, Eickhoff U, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg. 1999;134:1309-16.
9. Ward N. Nutrition support to patients undergoing gastrointestinal surgery. Nutr J. 2003;2:18-28.
10. Grant JP. On enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995;221:325-6.
11. Grimble GK, Westwood OM. Nucleotides as immune-modulators in clinical nutrition. Curr Opin Clin Nutr Metab Care. 2001;4:57-64.
12. Coëffier M, Marion R, Leplingard A, Lerebours E, Ducrotté P, Déchelotte P. Glutamine decreases interleukin-8 and interleukin-6 but not nitric oxide and prostaglandins E2 production by human gut in vitro. Cytokine. 2002;18:92-7.
13. Huckleberry Y. Nutritional support and the surgical patient. Am J Health Syst Pharm. 2004;61:671-82.
14. Lobo DN, Williams RN, Welch NT, Aloysius MM, Nunes QM, Padmanabhan J, et al. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled double-blind study. Clin Nutr. 2006;25:716-26.
15. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the result of a meta-analysis. Ann Surg. 1992;216:172-83.
16. Gianotti L, Braga M. Revising concepts of artificial nutrition in contemporary surgery: from energy and nitrogen to immuno-metabolic support. Nutr Hosp. 2011;26:56-67.
17. Richter B, Schmandra TC, Golling M, Bechstein WO. Nutritional support after open liver resection: a systematic review. Dig Surg. 2006;23:139-45.
18. Welbourne TC, Joshi S. Inter-organ glutamine metabolism during acidosis. J Parenter Enteral Nutr. 1990;14:77-85.
19. Hwang TL, O'Dwyer ST, Smith RJ. Preservation of small bowel mucosa using GLN-enriched parenteral nutrition. Surg Forum. 1986;37:56-8.
20. Burke DJ, Alverdy JC, Aoys E, Moss GS. Glutamine supplemented total parenteral nutrition improves gut immune function. Arch Surg. 1989;124:1396-9.
21. Perumal SK, Rammohan A, Sateesh J, Jeswanth S. Impact of perioperative enteral immunonutrition on infectious complications after major gastrointestinal surgery. Arch Clin Exp Surg. 2014;3:16-25.

**Cite this article as:** Raghavendra, Raghupathi S. Effects of perioperative enteral glutamine on surgical outcome in gastrointestinal cancer patients. Int Surg J 2019;6:903-8.