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Impact of Perioperative Enteral Immunonutrition on Infectious Complications After Major Gastrointestinal Surgery

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Abstract

Objective: To study the impact of perioperative, enterally administered whey protein concentrate on infectious complications after major elective gastrointestinal surgery in a tertiary care hospital.
Materials and Methods: Prospective non-randomized study conducted from June 2008–April 2010, which included 50 consecutive patients who underwent major elective gastrointestinal surgery for benign and malignant diseases. The primary outcome measured was the rate of infectious complications, and the secondary outcome was length of postoperative stay.
Results: 50 patients were divided into two equal groups: Group 1 and Group 2 (n=25 each). One group received immune-enhanced enteral nutrition (IMEN) perioperatively, and the control group received standard enteral nutrition (SEN) during the same period. There were no significant differences between the two groups with regard to complications (P=0.26), either infective (P=0.76) or non-infective (P=0.65). There was no significant difference in the duration of postoperative stay (P=0.25) between the two groups. There was also no significant difference in the pre- and postoperative White Blood Cell (WBC) count, C-Reactive Protein (CRP), and albumin levels. However, a subgroup analysis carried out to identify malnourished patients in the immunonutrition group revealed significant reduction in the length of postoperative stay (P=0.03) but not the rate of infectious complications (P=0.20).
Conclusion: Perioperatively administered immunonutrition did not decrease the incidence of postoperative infectious complications and the duration of postoperative stay. Malnourished patients given immunonutrition in the perioperative period showed a significant reduction in the length of postoperative hospital stay but not the incidence of infective complications.

Key words: *Immunonutrition, enteral nutrition, perioperative nutrition, infectious complications, postoperative complications*

Introduction

Immunonutrition is defined as modulation of the activities of the immune system, as well as the consequences on the patient of immune activation, by nutrients or specific food items fed in amounts above those normally encountered in the diet [1]. Malnutrition is a well-known cause of increased morbidity and mortality in surgical patients, and severe malnutrition may cause ongoing energy deficits in the postoperative period, resulting in an increased risk of infectious complications [1,2]. Gastrointestinal patients, especially those with underlying malignancy, are at high risk of developing malnutrition. Operation and trauma always lead to postoperative malnutrition and immunity depression, which are the main causes of the increase of postoperative complications, including poor wound healing, infection, and prolonged hospital stay [1-3] Different specific nutrients used in the various studies have included amino acids (arginine and glutamine), omega(ω)-3 fatty acids, and RNA nucleotides [2]. Glutamine is essential for protein and nucleotide synthesis. Increased metabolic demands of inflammation or injury lead to glutamine consumption [3]. Glutamine supplementation administered enterally can reverse intestinal atrophy and prevent bacterial translocation [3]. Furthermore, glutamine has effects on immune function and may decrease the inflammatory response and infectious complications. Several trials have determined the efficacy and feasibility of adding glutamine to standard nutritional support [3,4]. Arginine is considered a semi-essential amino acid, acting as an immunomodulator and with favorable effects in catabolic conditions such as severe sepsis and postoperative stress [3,5]. Supplementation with arginine has been shown to have beneficial effects on the immune response by improving the response of peripheral blood cells to mitogen, enhancing natural killer cell activity, and increasing lymphokine-activated natural killer cell populations [5]. Omega–3 fatty acids replace arachidonic acid in cell membranes and modulate immune function. The use of these fatty acids has been reported to decrease the total number of gastrointestinal and infectious complications and improve postoperative liver and kidney function through modulation of tissue prostaglandin levels [3,5]. Important targets for immunomodulation are: enhancing the cell-mediated response; altering the balance of pro- and anti-inflammatory cytokines; prevention of excessive activation of nuclear factor κ-B; facilitation of optimal activity of activator protein-1; and moderation of tissue nutrient depletion [3,5]. Inclusion of antioxidants or substances which increase glutathione synthesis in immunonutrient mixes seems to be beneficial. Glutathione plays a pivotal role because it acts directly as an antioxidant and maintains other components of defense in a reduced state [5]. Whey protein is the collection of globular proteins isolated from whey, a by-product of cheese manufactured from cow's milk [5,6]. It is typically a mixture of beta-lactoglobulin (~65%), alpha-lactalbumin (~25%), and serum albumin (~8%), which are soluble in their native forms, independent of pH [5]. The protein fraction in whey (approximately 10% of the total dry solids within whey) comprises four major protein fractions and six minor protein fractions. The major protein fractions in whey are beta-lactoglobulin, alpha-lactalbumin, bovine serum albumin, and immunoglobulins. Glutathione stimulation is thought to be the primary immune-modulating mechanism [2,3,5,6].

The present study was conducted to study the impact of perioperative, enterally administered whey protein concentrate on infectious complications after major elective gastrointestinal surgery in a major tertiary care hospital. The primary outcome measured was the rate of infectious complications. Length of postoperative stay was the secondary outcome measured.

Materials and Methods

This is a prospective non-randomized study which included 50 consecutive patients who underwent major elective gastrointestinal surgery for benign and malignant diseases. The study period is from June 2008–April 2010. Ethical committee approval was obtained for the study.

Inclusion criteria

1. Age group is 15–75 years
2. Absence of major systemic illness like liver or renal failure
3. Elective abdominal surgery

Exclusion criteria

1. Patients undergoing small bowel resection and anastomosis
2. Patients with liver disease
3. Intolerance to milk protein
4. Presence of postoperative intestinal obstruction
5. Pregnancy
6. Patients who had undergone neoadjuvant therapy

Twenty-five patients were given perioperative immunonutrition (Group 1). The patients were given 20 g of immunomodulator (Kabipro, Fresenius-Kabi, Pune, India) (Table 1) three times a day for at least 5 days preoperatively and 5 days postoperatively either orally or through tube feeds. The control groups consisting of twenty-five patients were given a conventional diet during the same period (Group 2). All patients received antibiotic prophylaxis with cephazolin of 1 g half an hour before the procedure; the dose was repeated if the duration exceeded 4 hrs. Preoperative variables which were measured included body mass index, serum albumin, total leucocyte count, differential leucocyte count, and C-reactive protein (CRP). Postoperatively, serum albumin (total and differential counts) was measured on days 1, 3 and 7. C-reactive protein was measured on day 7.

Table 1. Composition of kabipro (Fresinius kabi, Pune, India).

Nutrition information	Units	Per 100g powder
Energy	Kcal	364
Protein	G	42
Fat	G	3
Carbohydrates	G	41
Sucrose	G	0.0
Dietary fiber	G	5.0
Vitamins		
A	Mcg	1000
D	Mcg	15
E	Mg	20
K	Mcg	120
C	Mg	100
B1	Mg	2
B2	Mg	2.6
B6	Mg	2.4
B12	Mcg	4
Niacinamide	Mg	24
Folic acid	Mcg	400
Pantothenic acid	Mg	7
Biotin	Mcg	75
Choline	Mg	210
Minerals		
Sodium	Mg	230
Potassium	Mg	900
Chloride	Mg	710
Calcium	Mg	500
Phosphorus	Mg	390
Magnesium	Mg	125
Iron	Mg	24
Zinc	Mg	4.0
Copper	Mg	2.0
Manganese	Mg	5.0
Iodine	mcg	200

Infective complications such as surgical site infections, urinary tract infections, thrombophlebitis, central line infections, and respiratory tract infections were recorded. Secondary outcomes measured included duration of postoperative stay and overall morbidity. Patients who had wound infections as evidenced by positive cultures were put on therapeutic antibiotics.

Statistical Analysis

Descriptive results are reported as the number of patients, mean +/– SD, and median and range in case of there being data that is not normally distributed. An Independent-Samples t-test and two-Independent-Samples test (for data not normally distributed) were used to compare variables among the groups. A Fisher exact test was used to compare discrete variables. All p-values are two-sided, and significance was set at $p < 0.05$. The SPSS package version 13 for Windows (IBM, Armonk, New York, USA) was used for the statistical analysis.

Observation and Results

The majority of patients in Group 1 (Table 2) were well nourished (with a mean BMI of 20.84). There were 16 males and 9 female patients (with a mean age of 46.52 years). Twenty-three of them underwent surgery for malignancy and two for benign conditions. The mean albumin was 3.44, and the baseline CRP was 14.7. The length of postoperative stay ranged from 7–33 days (with a mean of 16.44 days). The mean BMI of patients in Group 2 was 18.9. There were 10 male and 15 female patients (with a mean age of 43.7 years). Twenty-three underwent surgery for malignancy and two for benign pathologies. The mean albumin was 3.31, and the baseline CRP was 21.03. The length of postoperative stay ranged from 9–27 days (with a mean of 14.28 days). The details of surgery performed on patients of both groups are summarized in table 3. Table 4 details the postoperative complications in each group. Eight of

Table 2. Baseline patient characteristics.

Variables	Group 1 (IMEN)	Group 2 (SEN)
Age in yrs.	46.52 (15.38)	43.7 (16.57)
Gender M:F	16:9	10:15
BMI	20.84 (04.21)	18.9 (3.8)
Etiology - benign:malignant	2:23	2:23
Albumin gm/dL	3.44 (0.33)	3.31 (0.56)
Total leucocyte count	7132 (2500)	9148 (3003)
CRP	14.7 (21.6)	21.03 (40.73)
Length of postoperative stay (days)	16.44 (7.9)	14.28 (4.77)

p-values: not significant between the two groups. Values are expressed as mean (SD), **CRP:** C-reactive protein, **BMI:** body mass index, **IMEN:** immunonutrition, **SEN:** standard enteral nutrition.

Table 3. Details of surgery.

Details of Surgery	Group 1 (IMEN) (n = 25)	Group 2 (SEN) (n = 25)
Transhiatal Esophagectomy	2	2
Subtotal Gastrectomy	3	3
Total Gastrectomy	3	3
Right Hepatectomy	2	2
Frey's Procedure (Pancreaticojejunostomy with head coring)	2	2
Whipple's Procedure (Pancreaticoduodenectomy)	8	8
Colorectal Surgeries	5	5

IMEN: immunonutrition, **SEN:** standard enteral nutrition. No statistical difference between the two groups.

25 patients (32%) in Group 1 had infective complications. Surgical site infections accounted for five of the eight (63%). In Group 2, seven patients (28%) had infective complications; of these, surgical site infections and respiratory tract infections accounted for two each. There was no significant difference between the groups (P=0.76). Three patients in Group 1 and two in Group 2 had surgery-related non-infective complications such as biliary and pancreatic fistula and were not significant (p=0.65). The incidences of overall complications were 13 and 9 in Group 1 and Group 2 respectively, which were also insignificant (p=0.26).

General complications were very few, with only one patient from Group 1 having postoperative delirium, which was managed medically. One patient had abdominal distension on the second postoperative day after commencement of IMEN and was managed conservatively till the ileus settled down. There was no mortality in either group. There was no significant difference in secondary outcomes measured, including the duration of postoperative stay (p=0.25) (Table 5). Leucocytes (WBC) and CRP levels were used to evaluate the inflammatory response. Of the variables analyzed on blood chemistry, values of serum albumin decreased in both groups on postoperative day (POD) 1 and gradually increased by POD 7. There was no significance between the groups. The counts showed a rise on POD 1 and 3 in both groups. By POD 7 both the groups showed a drop in the total leucocyte counts (Table 6). The polymorph count also did not differ significantly on POD 1, 3, and 7. The postoperative CRP levels were 53.33 in Group 1 and 38.24 in Group 2, with no statistical significance (p=0.164).

Subgroup analysis was done to identify patients with malnourishment based on body mass index (BMI) score and serum albumin values. The groups were divided based on a BMI value of 19 as a cutoff point (Table 7). Patients with BMI <19 accounted for 44% of the total number of patients in the immunonutrition group, and patients were also analyzed based

Table 4. Postoperative complications.

S. No	Complications	Group 1 (IMEN)	Group 2 (SEN)	P
A.	**Infective complications**	8	7	0.76
1	Respiratory tract infections	1	2	
2	Urinary tract infections	1	1	
3	Surgical site infection	5	2	
4	Intraabdominal abscess	0	0	
5	Bacteremia	0	1	
6	Infections of CVP catheter	1	1	
7	Sepsis	0	0	
B.	**Surgical complications**	3	2	0.65
1	Salivary fistula	1	0	
2	Pancreatic fistula	2	1	
3	Biliary fistula	0	1	
C.	**General complications**			
1	Delirium	1	0	
D.	**Enteral complications**			
1	Prolonged ileus	1	0	
	Overall morbidity	13	9	0.26
	Mortality	0	0	

IMEN: immune-enhanced enteral nutrition, **SEN:** standard enteral nutrition.

Table 5. Comparison of primary and secondary outcome variables.

Variables	Group 1 (IMEN) (n = 25)	Group 2 (SEN) (n = 25)	Odds Ratio (CI)	P
Rate of infectious complications (Primary Outcome)	8	7	1.21 (0.37–3.95)	0.75
Overall morbidity (Secondary Outcome)	13	9	1.92 (0.63–5.88)	0.25
Mortality (Secondary Outcome)	0	0		
Hospital stay (Secondary Outcome)	16.44	14.28		0.25

IMEN: immunonutrition, **SEN:** standard enteral nutrition.

on the etiology. No difference in primary or secondary outcomes was noted between patients with malignant or benign etiology.

In Group 1, patients with a BMI of less than 19 had a mean hospital stay of 12.63 days compared to 20 days in those with a BMI of more than 19 (p=.03). In Group 2, such a difference was not seen. Similarly, in Group 1 the mean albumin levels were significantly lower in those with a BMI of less than 19 (p=.01). Other variables such as the preoperative and postoperative CRP values and infective complications were not significant.

When the patients were grouped on the basis of serum albumin with a cutoff of 3.5, the patients in Group 1 with albumin less than 3.5 had significantly low BMI compared to those with albumin of more than 3.5 (p=.002). Other parameters such as CRP, length of postoperative stay and the infectious complications did not significantly differ between the groups (Table 8).

Discussion

Whey protein typically comes in three major forms: concentrate, isolate, and hydrolysate.

a. Concentrates contain a low level of fat and choles-

Table 6. Changes in blood parameters.

	Parameter	Group 1 (IMEN)	Group 2 (SEN)	P-value
A	**Albumin g/dL(sd)**			
	Preop.	3.44 (0.33)	3.31 (0.55)	0.32
	POD 1	2.53 (0.40)	2.59 (0.41)	0.61
	POD 3	2.49 (0.33)	2.65 (0.48)	0.17
	POD 7	2.69 (0.32)	2.88 (0.45)	0.09
B	**Total leukocyte count cells/mm3 (sd)**			
	Preop.	7132 (2500)	9148 (3003)	0.58
	POD 1	14,340 (8399)	16,644 (10363)	0.39
	POD 3	10,108 (4773)	9592 (3909)	0.68
	POD 7	11,032 (4486)	9800 (3115)	0.27
C	**Polymorphs % (sd)**			
	Preop.	64.16 (9.98)	63.7 (11.3)	0.90
	POD 1	82.88 (6.75)	86.2 (5.19)	0.06
	POD 3	78.72 (6.46)	76.16 (7.81)	0.21
	POD 7	73.80 (8.07)	70.6 (12.84)	0.30
D	**CRP**			
	Preop.	21.03 (40.73)	14.70 (28.69)	0.53
	Postop.	52.33 (42.40)	38.24 (26.19)	0.16

IMEN: immunonutrition, **SEN:** standard enteral nutrition, **CRP:** C-reactive protein, **POD:** postoperative day, **Sd:** standard deviation.

Table 7. Comparison of groups with BMI <19 and >19.

	BMI<19		P-value	BMI>19		P-value
	Group 1 (IMEN) n=11	Group 2 (SEN) n=8		Group 1 (IMEN) n=11	Group 2 (SEN) n=8	
Length of stay (days)	12.63	20	.03	14.4	12.61	.89
CRP						
Preop.	14.20	26.39	0.81	21.04	6.54	.68
Postop.	50.02	54.14	0.84	35.97	40.34	.14
Albumin	3.25	3.59	.01	3.35	3.27	.74
Infectious complications	6	2	0.20	3	4	.58

IMEN: immunonutrition, **SEN:** standard enteral nutrition, **CRP:** C-reactive protein.

terol but, in general, have higher levels of bioactive compounds, and carbohydrates in the form of lactose — they are 29%–89% protein by weight [2,5,7].

b. Isolates are processed to remove the fat, and lactose, but are usually lower in bioactive compounds as well — they are 90%+ protein by weight. Both of these types are mild to slightly milky in taste [2,5,7].

c. Hydrolysates are predigested, partially hydrolyzed whey proteins that, as a consequence, are more easily absorbed, but their cost is generally higher. Highly hydrolyzed whey may be less allergenic than other forms of whey. They are very bitter in taste [2,5,7].

Whey has a high concentration of branched-chain amino acids (BCAAs) — leucine, isoleucine, and valine. Branched-chain amino acids, particularly leu-

Table 8. Comparison of groups with albumin <3.5 and >3.5.

	Cases		P-value	Control		P-value
	<3.5	>3.5		<3.5	>3.5	
Length of stay (days)	15.85	17.18	0.68	14.92	13.58	0.49
CRP						
Preop.	19.12	12.64	0.79	12.64	16.93	0.71
Postop.	53.73	50.54	0.85	41.36	34.86	0.54
BMI	18.72	23.53	.002	19.08	18.60	0.79
Infectious complications	6	2	0.67	5	2	0.24

cine, are important factors in tissue growth and repair [2,5,7]. Whey has potent antioxidant activity, likely by contributing cysteine-rich proteins that aid in the synthesis of glutathione (GSH), a potent intracellular antioxidant [5]. Glutathione is composed of glycine, glutamate, and cysteine. Cysteine contains a thiol (sulfhydryl) group that serves as an active reducing agent in preventing oxidation and tissue damage. Whey protein is an economical source of high-quality proteins [2,5,7].

Whey protein concentrates have been researched extensively in the prevention and treatment of cancer. In a review of whey protein concentrates in the treatment of cancer, Bounous [5] discusses the antitumor and anticarcinogenic potential. Whey protein is an effective and safe donor of cysteine for glutathione replenishment during its depletion in immune deficiency states. Cysteine is the limiting amino acid in the synthesis of glutathione. The amino acid precursors to glutathione available in whey might: (1) increase glutathione concentration in relevant tissues, (2) stimulate immunity, and (3) detoxify potential carcinogens [2,8,9].

Whey protein concentrates because of the lactoferrin have antimicrobial actions. Plasma levels of lactoferrin have been found to be elevated due to release from neutrophils during infection, inflammation, tumor development, and iron overload. Several studies have revealed that lactoferrin plays a direct role in the body's defense against pathogens, including findings that individuals more susceptible to infection have lower levels of neutrophil lactoferrin [5,10].

In current gastrointestinal surgical practice, perioperative nutritional support is a widely accepted standard of care [11]. In postoperative patients, in addition to providing caloric support at a time of intense catabolic activity, nutritional supplementation may reduce gut translocation and infective complications [6,11,12].

The consensus view from several randomized trials, meta-analyses and consensus statements favors perioperative nutritional support [6,11-13]. Commencement of nutritional support prior to surgery may provide additional benefit over postoperative supplementation alone [7,14]. It has been demonstrated that perioperative nutritional support improves postoperative outcome but only in selected groups of patients [14-16]. The latter population includes mostly severely malnourished individuals and those subject to major surgical procedures, such as esophagectomy, pancreatectomy and gastrectomy [17,18]. There are very few clinical trials focused on immunonutrition in well-nourished patients, and their results are contradictory [4,19]. Braga et al. [7] demonstrated that the benefits of perioperative enteral immunonutrition, in terms of reduced postoperative infections and shortened hospital stay, were similar in well-nourished and malnourished (weight loss >10%) patients. A subsequent randomized clinical trial carried out by the same group of researchers in 305 patients with gastrointestinal (GI) cancer and preoperative weight loss >10% provided additional data to support the idea that enteral immunonutrition (either preoperative or perioperative) can reduce postoperative infection rates [4,7,20]. The incidence of postoperative infections in the control group of 30.4% was significantly reduced to 13.7% and 15.8% in the preoperative and perioperative groups, respectively. Contrary to the above two studies, Heslin et al. demonstrated that postoperative enteral immunonutrition used in patients subject to upper GI surgery for cancer did not influence rates of postoperative complications (categorized as major and minor), and the length of hospital stay compared with intravenous crystalloid therapy. Similar results were reported by Lobo et al. in a group of 108 patients given either an immunomodulating or standard enteral diet after upper GI surgery [21,22]. There have been a number of studies addressing several aspects of immunonutrition [23-27]. But the studies were markedly influenced by the variability in definitions of malnutrition, incidence of malnutrition and other comorbidities, routes and duration of nutrition support, the amount and composition of diets, and the incidence of nutrition-related complication.

There are several gray areas in the field of immunonutrition, for example, the role of immunonutrition in critical care is in question, with many trials reporting negative results. [23-27]. To address one of the critical questions — the role of immunonutrition in well-nourished and malnourished individuals — we initiated this perioperative trial. This study fails to show a significant reduction in infectious complications in the immunonutrition group compared to the standard enteral nutrition group (p=0.76); moreover, there has been no significant reduction in the length of postoperative stay (p=0.25). The postoperative CRP levels do not show a decrease compared to the standard enteral nutrition group. There are no significant changes in the total leucocyte count, the polymorph count, or the albumin count in the postoperative period. But a subgroup analysis done to identify malnourished patients in the immunonutrition group revealed significant reduction in the length of postoperative stay (p=.03) but not the rate of infectious complications (p=0.20). The incidence of overall morbidity was also not significant between the groups. Patients with BMI <19 accounted for 44% of the total number of patients in the immunonutrition group, and patients were also analyzed based on the etiology. No difference in primary or secondary outcomes was noted between patients with malignant or benign etiology. Immunomodulators are beneficial when patients receive the critical minimum amount of them. This is a crucial issue, since many of the studies failed to identify and reach this minimal but 'beneficial' amount. One possible explanation for not detecting significance in our study could be due to the fact that the immunonutrients did not account for 60% of the total calorific requirement as recommended in the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [4,27-30].

The limitations of our study are that even though it is prospectively a non-randomized study, a larger study population would have increased the power of the study and the inclusion of accurate markers of inflammation such as Neoptrin, IL-6, and TNF-α would have further strengthened the study. Extrapolating the results of subgroup analysis, it may be beneficial if we could identify that subsect 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. Immunonutrition has good clinical potential. However, well-designed randomized control trials (RCTs) are now needed to answer the questions posed above.

Perioperatively administered immunonutrition did not decrease the incidence of postoperative infectious complications and the duration of postoperative stay. Malnourished patients given immunonutrition in the perioperative period showed a significant reduction in the length of postoperative hospital stay but not the incidence of infective complications.

Conflict of interest statement

The authors have no conflicts of interest or financial ties to disclose.

References

1. Grimble RF. Nutritional modulation of immune function. Proc Nutr Soc 2001;60:389-397.
2. Akbarshahi H, Andersson B, Nordén M, Andersson R. Perioperative nutrition in elective gastrointestinal surgery--potential for improvement? Dig Surg 2008;25:165-174.
3. Suchner U, Kuhn KS, Fürst P. The scientific basis of immunonutrition. Proc Nutr Soc 2000;59:553-563.
4. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg 2009;13:569-575.
5. Bounous G. Whey protein concentrate (WPC) and glutathione modulation in cancer treatment.

Anticancer Res 2000;20:4785-4792.
6. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A, Colombo S, et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. JPEN J Parenter Enteral Nutr 1999;23:314-320.
7. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg 2002;137:174-180.
8. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006;25:224-244.
9. Klek S, Kulig J, Sierzega M, Szybinski P, Szczepanek K, Kubisz A, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. Ann Surg 2008;248:212-220.
10. Marshall K. Therapeutic applications of whey protein. Altern Med Rev 2004;9:136-156.
11. Helminen H, Raitanen M, Kellosalo J. Immunonutrition in elective gastrointestinal surgery patients. Scand J Surg 2007;96:46-50.
12. Kirk HJ, Heys SD. Immunonutrition. Br J Surg 2003;90:1459-1460.
13. Goonetilleke KS, Siriwardena AK. Systematic review of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy. JOP 2006;7:5-13.
14. Grimble RF. Immunonutrition. Curr Opin Gastroenterol 2005;21:216-222.
15. Senesse P, Assenat E, Schneider S, Chargari C, Magné N, Azria D, et al. Nutritional support during oncologic treatment of patients with gastrointestinal cancer: who could benefit? Cancer Treat Rev 2008;34:568-575.
16. Calder PC. Immunonutrition in surgical and critically ill patients. Br J Nutr 2007;98 Suppl 1:S133-139.
17. Moskovitz DN, Kim YI. Does perioperative immunonutrition reduce postoperative complications in patients with gastrointestinal cancer undergoing operations? Nutr Rev 2004;62:443-447.
18. Wyncoll D, Beale R. Immunologically enhanced enteral nutrition: current status. Curr Opin Crit Care 2001;7:128-132.
19. Jones NE, Heyland DK. Pharmaconutrition: a new emerging paradigm. Curr Opin Gastroenterol 2008;24:215-222.
20. Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg 1999;134:428-433.
21. Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg 1997;226:567-577.
22. 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;25:716-726.
23. Calder PC. Immunonutrition. BMJ 2003;327:117-118.
24. Giger U, Büchler M, Farhadi J, Berger D, Hüsler J, Schneider H, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol 2007;14:2798-2806.
25. Xu J, Zhong Y, Jing D, Wu Z. Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. World J Surg 2006;30:1284-1289.
26. Andersson R, Andersson B, Andersson E, Eckerwall G, Nordén M, Tingstedt B. Immunomodulation in surgical practice. HPB (Oxford) 2006;8:116-123.
27. Van Way CW 3rd. Perioperative immunonutrition: good idea or more hype? JPEN J Parenter Enteral Nutr 2006;30:539-540.
28. Mazaki T, Ebisawa K. Enteral versus parenteral nutrition after gastrointestinal surgery: a systematic review and meta-analysis of randomized controlled trials in the English literature. J Gastrointest Surg 2008;12:739-755.

29. Koretz RL, Avenell A, Lipman TO, Braunschweig CL, Milne AC. Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. Am J Gastroenterol 2007;102:412-429.

30. Shrikhande SV, Shetty GS, Singh K, Ingle S. Is early feeding after major gastrointestinal surgery a fashion or an advance? Evidence-based review of literature. J Cancer Res Ther 2009;5:232-239.

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