Original Article

Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials

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The aim of this study was to evaluate clinical and economic validity of perioperative immunonutrition and effect on postoperative immunity in patients with gastrointestinal cancers. Immunonutrition diet supplemented two or more of nutrients including glutamine, arginine, ω-3 polyunsaturated fatty acids and ribonucleic acids. A meta-analysis of all relevant clinical randomized controlled trials (RCTs) was performed. The trials compared perioperative immunonutrition diet with standard diet. We extracted RCTs from electronic databases: Cochrane Library, MEDLINE, EMBASE, SCI and assessed methodological quality of them according handbook for Cochrane reviewer in June 2006. Statistical analysis was performed by RevMan4.2 software. Thirteen RCTs involving 1269 patients were included. The combined results showed that immunonutrition had no significant effect on postoperative mortality (OR =0.91, p= 0.84). But it had positive effect on postoperative infection rate (OR =0.41, p<0.00001), length of hospital stay (WMD=-3.48, p<0.00001). Furthermore, it improved immune function by increasing total lymphocytes (WMD=0.40, p<0.00001), CD4 levels (WMD=11.39, p<0.00001), IgG levels (WMD=1.07, p=0.0005) and decreasing IL6 levels (WMD=-201.83, p<0.00001). At the same time, we did not found significant difference in CD8, IL2 and CRP levels .There were no serious side effects and two trials found low hospital cost. In conclusion, perioperative diet adding immunonutrition is effective and safe to decrease postoperative infection and reduce length of hospital stay through improving immunity of postoperative patients as compared with the control group. Further prospective study is required in children or critical patients with gastrointestinal surgery.

Key Words: immunonutrition, gastrointestinal surgery, meta-analysis

Introduction

The patient with gastrointestinal cancer always increases risk of malnutrition for several factors: mechanical obstruction, limitation of food intake, tumor-induced cachexia, obstruction of pancreaticobiliary, malabsorption and ongoing blood loss. Malnutrition depresses both cellular immunity and humoral immunity. In addition, complex surgical procedure and injure potentially lead to immunity defection.[1,2] Therefore, infective complications are not infrequent. Although multiple factors have effect on outcome of treatment, such as antibacterial drug, immunoenhancer, aseptic technique and surgical skills, immunonutrition may be a good choice to decrease infection rate in patients underwent gastrointestinal operation, especially for patients with malnutritional immune deficiency.

Immunonutrition contain pharmacologic doses of nutrients including arginine (Arg), ω-3 polyunsaturated fatty acids (ω-3 PUFA), glutamine (Glu) and ribonucleic acid (RNA). All are proved to enhance immune function in vitro and animal experiments. Some clinical trials has been reported to affect the risk of postoperative infection and length of hospital stay in patients underwent operation.[3-15] But the outcome of these studies is inconsistent and new sufficient clinical evidences is absent for gastrointestinal surgery.[16,17]

Meta-analysis has been applied in medicine research to improve statistical efficiency, evaluate the disadvantages of established studies and reach reliable conclusions from the mixed assortment of potentially relevant studies. It is the most promising directions for future research and guideline for clinical treatment.[18]

The study evaluated clinical and economic validity of perioperative immunonutrition and effect on postoperative immunity in patients with gastrointestinal cancers. They were fed with perioperative diet supplemented immunonutrition, including two or more of Arg, Glu, ω-3 PUFA and RNA, comparing standard diet.

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Materials and methods

Including criteria

This meta-analysis included Clinical randomized controlled trials (RCTs) of patients with abdominal cancer undergoing gastrointestinal operation, including gastrectomy, pancreatico-duodenectomy and colectomy. The trials compared perioperative immunonutrition diet with standard diet. Immunonutrition diet supplemented two or more of nutrients including Arg, Glu, ω-3 PUFA and RNA.

Search strategy

A computerized literature search was applied to the following electronic databases: the Cochrane Library (2006.6), MEDLINE (PubMed) (1966-2006.6), EMBASE (1980-2006.6) and ISI web of knowledge (SCI) (2006.6). The search was undertaken in June 2006. Literature reference proceedings were searched by hand at the same time. The researching words were immunonutrition. Other useful researching words included glutamine, arginine, ω-3 fatty acids, ribonucleic acids, gastrointestinal operation, surgery, postoperative, perioperative, RCT or clinical trials. Only English literatures was included and full text was found following.

Data collection

RCTs were identified and extracted by two reviewers independently according the handbook for Cochrane reviewer (V4.2.2). Research team decided the included data finally. Methodological quality of each study was assessed using the Jadad scale [19] and included trials should be high quality. Published studies were extracted by following selection criteria: Study design - RCT, Population - hospitalized adult patients undergoing gastrointestinal operation, Intervention - perioperative diet supplemented immunonutrition or standard diet. Outcome variables included the following: mortality, length of hospital stay, postoperative infection, immune markers, the adverse effects and hospital cost.

Data analysis

The statistical analysis was performed by RevMan4.2 software, which was provided by the Cochrane Collaboration. A p value of <0.05 was considered statistically significant. Heterogeneity was checked by chi-square test. Meta-analysis was done with fixed effects model when results of the trials had no heterogeneity. If the results had heterogeneity, random effects model was used. The result was expressed with odds ratio (OR) for the categorical variable and weighted mean difference (WMD) for the continuous variable, and with 95% confidence intervals (CI). Meta-analysis guideline was the handbook for Cochrane reviewer (v 4.2.2) from Cochrane Collaboration.

Result

There were 226 papers relevant to the searching words. Then reviewers screened the titles, scaned the abstracts, read the entire articles and evaluated the methodological quality of studies. Thirteen RCTs involving 1269 patients were included. Characteristics of studies included in meta-analysis presented in Table 1. It was not excluded that some patients repeated in some trials from previous studies.

There were 6 trials[3,5,7-9,15] reported the mortality difference and other trials reported naught mortality in both immunonutrition groups and control groups. The combined results showed that immunonutrition, comparing standard diet, had no significant effect on mortality (OR =0.91, 95%CI [0.37, 2.26], p= 0.84). But immunonutrition had positive effect on postoperative infection rate (11 trials, OR =0.41, 95%CI [0.30, 0.54], p<0.00001), length of hospital stay (8 trials, WMD=-3.48, 95%CI [-4.70, -3.26], p<0.00001). Furthermore, It also improved immunity by increasing total lymphocytes (3 trials, WMD=0.40, 95%CI [0.21, 0.59], p<0.00001), CD4 levels (3 trials, WMD=11.39, 95%CI [6.20, 16.58], p<0.00001), IgG levels (2 trials, WMD=1.07, 95%CI [0.46,1.67], p=0.0005) and decreasing IL6 levels(5 trials, WMD=-201.83, 95%CI[-328.53, -75.14], p<0.00001). At the same time, we did not found significant difference in CD8 levels (3 trials, WMD =-1.57, 95%CI [-3.39, 0.26], p=0.09), IL2 levels (4 trials, WMD =17.47, 95%CI [-80.10, 115.04], p= 0.73), and CRP levels (3 trials, WMD =-12.70, 95%CI [-32.17, 2.77, p= 0.20). The results were presented in Table 2. There was no serious side effects reported, which patients can not tolerated. Two trials [8,10] found lower hospital cost in patients with immunonutrition than control group.

Discussion

Since 1990, standard nutrition has been modified by adding immunonutrients in clinical nutrition trials. Investigated and interested immunonutrients included Arg, ω-3 PUFA, Glu and RNA. [20] (1) Arginine stimulates T-cell proliferation, IL-2 production, natural killer cell's cytotoxic effects and generation of lymphokine activated killer cells.[21] It also produce nitric oxide to improve macrophage effects and bactericidal activity. (2) ω-3 PUFA up-regulates immune response through the modulation of eicosanoid synthesis and regulation of cell membranes.[22] (3) Glutamine is the most abundant free amino acid in the body and plays a vital role in amino acid transport and nitrogen balance. It is a fuel for rapidly dividing cells such as enterocytes, lymphocytes so as to protect mucosa barricade and enhance immune function. [23] (4) RNA, especially uracil, appears essential to the normal maturation of lymphocytes. It can also improve immunosuppression through effect of T lymphocyte in animals after bacterial challenge. [24]

Although there is no significant reduction in postoperative infective complication rate in each of 6 trials, [3,5-8,13] the finally combined analysis proves a significant decrease of postoperative infection risk and short length of hospital stay. In addition, they have financial impact on hospitalization cost. Although the cost for the immunonutrition diet are higher than for standard diet, there is a substantial reduction of total cost because of saving cost of infection treatment and supernumerary hospital stay. Therefore, immunonutrition should be recommended. Reduction of infection rate comes from the improvement of immune mechanisms for killing bacteria. Moreover, it is more important to down-regulate the exuberant inflammatory and discordant inflammatory response that

Table 1. Characteristics of studies included in meta-analysis of perioperative immunonutrition for gastrointestinal surgery

Reference No	Author	Publishing Date (year)	Study Design	Surgeries/Disease	NO of patients (IN/Con)	Type of immunonutrtion	Last time of immunonutrition
3	Daly	1992	RCT	Upper GI operation / malignancies	41/44	Arg RNA ω-3PUFA	Postoperative 1 - hospital discharge
4	Daly	1995	Double-blind RCT	Upper GI operation / malignancies	30/30	Arg RNA ω-3PUFA	Postoperative 1 - hospital discharge
5	Schilling	1996	RCT	Major GI operation / cancer	14/14	Arg RNA ω-3PUFA	Postoperative 1- normal diet
6	Braga	1996	Double-blind RCT	Gastrectomy, pancreatico-duodenectomy / cancer	20/20	Arg RNA ω-3PUFA	Postoperative 1- 7 days
7	Gianotti	1997	RCT	Gastrectomy, pancreatico-duodenectomy / cancer	87/87	Arg RNA ω-3PUFA	Postoperative 1- 7 days
8	Senkal	1997	Double-blind RCT	Upper GI operation for malignancies	77/77	Arg RNA ω-3PUFA	Postoperative 1- 5 days
9	Braga	1999	Double-blind RCT	Gastrectomy, colorectomy,pancreatico-duodenectomy / cancer	85/86	Arg RNA ω-3PUFA	Preoperative 7 days - Postoperative 7 days
10	Senkal	1999	Double-blind RCT	Upper GI tract operation	78/76	Arg RNA ω-3PUFA	Preoperative 5 days - Postoperative 10 days
11	Wu GH	2001	Double-blind RCT	GI operation / cancer	25/23	Glu Arg ω-3PUFA	Postoperative 1- 8 days
12	Braga	2002	RCT	colorectomy / cancer	50/50	Arg ω-3PUFA	Preoperative 5 days
13	Jiang XH	2004	RCT	Gastrectomy, colorectomy / cancer	60/60	Glu Arg ω-3PUFA	Postoperative 1- 9 days
14	Chen da W	2005	RCT	Gastrectomy / cancer	20/20	Glu Arg ω-3PUFA	Postoperative 2- 9 days
15	Farreras	2005	RCT	Gastrectomy / cancer	30/30	Arg RNA ω-3PUFA	Postoperative 1- 8 days

RCT=randomized controlled trial, Arg=arginine, RNA=ribonucleic acid, ω-3PUFA=ω-3 polyunsaturated fatty acids, Glu=glutamine, GI= gastrointestinal, IN=immunonutrtion group, Con=control group

Table 2. Results from meta-analysis of perioperative immunonutrition for gastrointestinal system surgery

Outcome	Studies (reference number)	Participants	Statistical method	Effect size (95% CI)	*p*
mortality	6 [3,5,7-9,15]	739	OR (fixed)	0.91 [0.37, 2.26]	0.84
postoperative infection rate	11 [3-10,12, 13,115]	1181	OR (fixed)	0.41 [0.30, 0.54]	<0.00001
Length of hospital stay	8 [3-10]	901	WMD (random)	-3.48 [-4.70, -3.26]	<0.00001
total lymphocytes	3 [5,11,14]	156	WMD (fixed)	0.40 [0.21, 0.59]	<0.0001
CD4 levels	3 [11,13,14]	208	WMD (random)	11.39 [6.20, 16.58]	<0.0001
CD8 levels	3 [11,13,14]	208	WMD (fixed)	-1.57 [-3.39, 0.26]	0.09
IgG levels	2 [13,14]	160	WMD (fixed)	1.07 [0.46, 1.67]	0.0005
IL6 levels	5 [7,9,11,13,14]	553	WMD (random)	-201.83 [-328.53, -75.14]	0.002
IL2 levels	4 [7,11,13,14]	382	WMD (random)	17.47 [-80.10, 115.04]	0.73
CRP levels	3 [5,9,11]	247	WMD (random)	-12.70 [-32.17, 2.77]	0.20

IL=interleukin, CRP=C-reactive protein, CI=confidence intervals, OR=odds ratio, WMD=weighted mean difference.

occurs after surgery. We find improvement of humoral immune and cellular immune after operation comparing standard diet. There is higher concentration of IgG levels and total number of T lymphocytes; CD4 levels and ratio of CD4/CD8 increases and IL6 levels decreases.

In this study, immunonutrition does not change post-operative mortality. In a meta-analysis for the critically illness, Heyland *et al* [16] stated that immune-enhancing diets offered no advantages to mortality or infections. He suggested that there may be an increased rate of death among those who get the "immune-enhancing" diet. In another meta-analysis for both critical illness and cancer surgery, Heys *et al* [17] did not found effect on mortality. We think that mortality is affected not only by infective complication, but also by surgical technique, perioperative care, preoperative patients characteristics and choice of operation type. With surgery advanced, there is nough mortality reported in patients receiving both immunonutrition group and standard nutrition group in some trials recently. [5,6,10-14]

All included trials found some adverse effects, such as vomiting, diarrhea, cramps, bloating. But these discomforts seemed to be minor and did not need particular treatment. There was no serious adverse effects, which patients can not tolerated. Then perioperative diet adding immunonutrition may be effective and safe just as a standard nutrition during perioperative treatment.

The patients included in this meta-analysis were adults. Therefore, further trials are required in children for special gastrointestinal surgery. The patients with both critically illness and gastrointestinal operation should be paid attention. Other factors, such as preoperative malnutrition status, prevented application of antibiotics and standardization of operation, should be considered in further study.

In conclusion，immunonutrition is effective and safe to decrease postoperative infection and reduce length of hospital stay through increasing humoral immunity and cellular immunity of postoperative patients as compared with the control group. Further prospective study is required in children or critical patients with gastrointestinal surgery.

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