European Review for Medical and Pharmacological Sciences 2015; 19: 1345-1350

The effect of low-nitrogen and low-calorie parenteral nutrition combined with enteral nutrition on inflammatory cytokines and immune functions in patients with gastric cancer: a double blind placebo trial

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Abstract. – OBJECTIVE: The aim of this study is to investigate the effect of low-nitrogen and low-calorie parenteral nutrition (PN) combined with enteral nutrition (EN) on the inflammatory cytokines and immune function in patients with gastric cancer.

PATIENTS AND METHODS: Between May 2012 and May 2014, 90 patients undergoing surgery for gastric cancer in our institution were involved in this double blind placebo study and randomly divided into experimental group and control group, 45 patients of each group. Patients in the control group would receive total parenteral nutrition (TPN) whereas patients in the experimental group would be supported with low-nitrogen and low-calorie PN combined with EN.

RESULTS: On the 7th postoperative day 7, levels of IgA, IgM and IgG in experimental group were significantly higher than those in the control group and preoperative values ($p < 0.05$). CRP level was significantly lower than that of controls and preoperatively ($p < 0.05$). Levels of IL-2 and TNF-α were significantly higher than those of controls and preoperatively ($p < 0.05$).

CONCLUSIONS: As low-nitrogen and low-calorie PN combined with EN can effectively improve the immune function, reduce the inflammatory reactions and improve the postoperative quality of life (QoL) and prognosis in patients with gastric cancer, it is suitable for clinical application.

Key Words:
Parenteral nutrition, Enteral nutrition, Gastric cancer, Inflammatory cytokines, Immune function.

Introduction

Currently, surgery is the most effective therapeutic strategy against gastric cancer; however, the surgery-induced stress response manifested primarily by systemic inflammatory and immune response can aggravate malnutrition in patients, resulting in reduced postoperative immune function or fatigue[1]; therefore, the implementation of effective nutritional support is crucial for improving the postoperative nutrient consumption and promoting the prognosis as well as the quality of rehabilitation in patients with gastric cancer. Many lines of evidences have shown that irrational nutritional support can aggravate the stress response and is extremely detrimental to the postoperative recovery[2-4]. Between May 2012 and May 2014, 45 patients with gastric cancer would receive nutritional support using low-nitrogen and low-calorie parenteral nutrition combined with enteral nutrition in our institution. Significant favorable outcomes were achieved, resulting in significant improvement in the patients' inflammatory cytokine levels and immunity as well as postoperative quality of life and nursing satisfaction.

Patients and Methods

Clinical Data

Patients

Between May 2012 and May 2014, 90 patients undergoing surgical therapy for gastric cancer were involved in this double-blind study and equally divided into a control group and an experimental group, 45 patients for each group.

Inclusion Criteria

Patients with the following conditions were included in the study: (1) diagnoses confirmed by preoperative pathological study; (2) no metastasis; (3) no immunosuppressants and corticosteroid therapy within one month prior to surgery; (4) transfusion therapy had not been used and the blood loss less than 400 ml during surgery; (5) informed consent was signed.

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Exclusion Criteria

Patients presented suffering from following conditions were excluded from the study: (1) a history of hyperthyroidism, diabetes mellitus and other metabolic diseases; (2) accompanied by dysfunction of the heart, the kidney and the liver; (3) preoperative history of chemotherapy and radiotherapy; (4) a history of asthma and drug allergies; (5) immune dysfunction or systemic infection; (6) severe acid-base imbalance and water-electrolyte imbalance.

Groups

The experimental group composed of 25 males and 20 females, with age range of 40-75 years (mean age 62.5±5.3 years), weight of 45-73 kg (mean weight 60.5±7.8 kg). The control group composed of 25 males and 20 females, with age range of 40-75 years (mean age 62.5±5.3 years), weight range of 45-73 kg (mean weight 60.3±7.5 kg). No significant differences were observed in the gender, age, or weight between two groups (p>0.05).

Methods

Nutritional Support

Nutritional Support Strategies and Formula

Patients of the control group received total parenteral nutrition (TPN), whereas patients of experimental group were supported by low-nitrogen and low-calorie parenteral nutrition (PN) combined with enteral nutrition and supplemented by targeted nursing interventions. Details were as follows. Intravenous nutritional support was commenced on 2nd postoperative day in patients of both groups, using the formula designed by a nutritionist. The nutrition solution was prepared by the nutrition service center, with 3L solution for each bag. PN solutions were administered by peripherally inserted central catheter (PICC). The major ingredients of PN solution contain lipid emulsion, compound amino acid, water-soluble and fat soluble vitamins, glucose, electrolytes and trace elements.

Therapeutic Regimens

As to the experimental group, intravenous nutrition was administered at 20 kcal/(kg.d), with nitrogen of 0.09-0.11 g/(kg.d) and non-protein calorie of 16-20 kcal/(kg.d). Enteral nutrition (EN) support was started on the 2nd postoperative day and the administration speed, concentration and the volume of nutrition solutions were gradually increased according to patients' conditions and tolerance. As to the control group, patients were supplied with intravenous nutrition at 30-35 kcal/(kg.d), with nitrogen of 0.19-0.21 g/(kg.d) and non-protein calorie of 28-32 kcal/(kg.d).

Management of Nutritional Support

For EN support, conditions of patients during EN administration were closely monitored, including the temperature, volume, administration speed of nutrition solutions as well as the appetite, urine and bowel movement and weight of patients. The administration speed was immediately reduced or the administration stopped once patients presented intolerance to the treatment, including nausea and vomiting, abdominal distension and abdominal pain. Patients were remained in infusion posture for 30min upon completion of infusion so as to prevent them from choking and aspiration caused by regurgitation. In addition, care of EN feeding tube is of paramount importance for EN therapy. Accordingly, fall out and dislocation of feeding tube should be rigorously avoided to maintain smooth flow of solution through the tube. In the present study, PN was administered intravenously through PICC. Intravenous access should be closely monitored during PN support. Local conditions, including the occurrence of bleeding, exudates, pain, swelling, and induration, should be recorded; moreover, the patients should avoid being wet and overloaded. The film was replaced once it was detached. Intensive nursing care was performed to prevent bending of PICC or passive pressure on the intubated limb.

Outcome Measures

Collection of Laboratory Data

Immunoglobulins (Ig) including IgA, IgM, and IgG as well as inflammatory cytokines including interleukin-2 (IL-2), C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) were measured in the patients of two groups preoperatively as well as on the 7th and 14th postoperative day.

Follow-up

All patients were followed for 6 months. Quality of life (QoL) was evaluated and compared be-

tween two groups by using a QoL measure, validated short form 36 (SF-36) items questionnaire, which yields an 8-scale health profile of physical and emotional health, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health**.** Higher score represents better QoL.

Statistical Analysis

Statistical analyses were performed by using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as ± S and normality tests performed. Differences between two groups were analyzed by *t* test. Data at different multiple time points were compared by repeated measures analysis of variance (repeated measures ANOVA). Qualitative data were expressed in number of cases or ratios as general data, and their differences between groups were analyzed using chi-square test. $p < 0.05$ was considered statistically significant.

Results

Comparison of Igs Levels Between Groups Postoperatively and on Postoperative Day 7 and Day 14

Igs levels preoperatively as well as on the 7th and 14th postoperative day of such two groups are presented in Table I. These data were replicates obtained at three time points. Accordingly, repeated measures ANOVA was performed. The results of general analysis showed that except IgG, significant differences were observed in levels of IgA and IgM between two groups, between three time points as well as under the interaction of groups and time points ($p < 0.05$). These findings indicated that levels of IgA and IgM were significantly different between groups and between time-points; besides, these levels varied significantly with time; therefore, the following meticulous analysis was performed and the results demonstrated that no significant differences were found in preoperative Ig levels between groups. However, on postoperative day 7, the levels of

Table I. Comparison of immunoglobulin levels between groups preoperatively and on postoperative day 7 and day 14 (g/L, $\bar{x} \pm s$).

Parameters groups	IgA		IgM		IgG	
	A: Experimental group n = 45	B: Control group n = 45	A: Experimental group n = 45	B: Control group n = 45	A: Experimental group n = 45	B: Control group n = 45
T1: preoperatively	2.0 ± 0.3	2.0 ± 0.4	1.2 ± 0.4	1.3 ± 0.3	12.8 ± 4.3	12.7 ± 4.2
T2: postoperative day 7	2.6 ± 0.4	2.1 ± 0.5	1.9 ± 0.5	1.5 ± 0.4	13.5 ± 3.3	12.5 ± 5.6
T3: postoperative day 14	2.8 ± 0.6	2.1 ± 0.5	2.1 ± 0.5	1.6 ± 0.7	13.9 ± 4.5	12.9 ± 5.2
General analysis F, *p*	(HF correction: 0.7932)		(HF correction: 0.8447)		(HF correction: 1.0089)	
Comparison between groups	20.039, 0.000		7.858, 0.006		0.614, 0.436	
Comparison between time points	104.603, 0.000		202.561, 0.000		2.862, 0.060	
Interaction between group and time points	60.516, 0.000		53.868, 0.000		1.928, 0.148	
Comparison between groups *t*, *p*	A vs B		A vs B		A vs B	
T1: preoperatively	0.000, 1.000		1.349, 0.181		0.123, 0.903	
T2: postoperative day 7	5.228, 0.000		4.223, 0.000		1.052, 0.296	
T3: postoperative day 14	6.012, 0.000		3.892, 0.000		0.993, 0.323	
Comparison between time points *t, p*	A: Experimental group	B: Control group	A: Experimental group	B: Control group	A: Experimental group	B: Control group
T2 vs T1	10.170, 0.000	1.296, 0.202	7.682, 0.000	2.807, 0.007	1.015, 0.315	0.275, 0.785
T3 vs T1	9.062, 0.000	1.177, 0.245	12.982, 0.000	3.714, 0.001	1.452, 0.154	0.198, 0.844

IgA, IgM and IgG of experimental group were significantly higher than those of controls as well as preoperative levels ($p < 0.01$). Other meticulous analyse data are presented in Table I.

Comparison of Preoperative and Postoperative Inflammatory Cytokines Between Groups

Levels of inflammatory cytokines are presented in Table II. General analysis showed that levels of IL-2, CRP and TNF-α were significantly different between two groups, between three time points and under the interaction of group and time ($p < 0.05$), which implied that levels of these cytokines were significantly different between groups and between various time points; in addition, these levels varied differently with time between two groups.

These analyses combined with major results demonstrated that no significant difference was observed in preoperative cytokine levels between groups; however, on the 7th postoperative day, CRP of experimental group was significantly lower than preoperative level and that of controls ($p < 0.05$), whereas levels of IL-2 and TNF-α were significantly higher than preoperative level and those of controls ($p < 0.05$). Other results are presented in Table II.

Comparison of QoL Six Months Upon Operation Between Groups

The scores of QoL measures in experimental group six months upon operation were significantly higher than those in the control group ($p < 0.05$) (Table III).

Discussion

Gastric cancer is one of the most common malignant tumors in clinical practice, frequently occurring in the elderly. Numerous studies have showed that the majority of patients with advanced stage gastric cancer experienced nutri-

Table II. Comparison of levels of inflammatory cytokines between groups preoperatively and on postoperative day 7 and day 14 ($\bar{x} \pm s$).

Parameters groups	IL-2 (ng/L)		CRP (mg/L)		TNF-α (ng/L)	
	A: Experimental group n = 45	B: Control group n = 45	A: Experimental group n = 45	B: Control group n = 45	A: Experimental group n = 45	B: Control group n = 45
T1: preoperatively	54.3 ± 7.8	54.2 ± 7.7	142.3 ± 15.8	143.5 ± 15.7	135.6 ± 28.5	136.5 ± 27.5
T2: postoperative day 7	65.7 ± 10.2	57.6 ± 5.8	108.5 ± 17.5	135.6 ± 14.5	158.6 ± 14.5	142.6 ± 28.6
T3: postoperative day 14	42.6 ± 8.8	52.7 ± 6.2	92.4 ± 15.3	113.8 ± 15.8	125.8 ± 17.6	132.8 ± 25.6
General analysis F, *p*	(HF correction: 1.0018)		(HF correction: 0.9916)		(HF correction: 1.0007)	
Comparison between groups	8.052, 0.004		20.732, 0.000		12.528, 0.000	
Comparison between time points	110.723, 0.000		218.352, 0.000		108.525, 0.000	
Interaction between group and time points	72.524, 0.000		83.152, 0.000		62.352, 0.000	
Comparison between groups *t*, *p*	A vs B		A vs B		A vs B	
T1: preoperatively	0.000, 1.000		0.120, 0.901		0.003, 0.999	
T2: postoperative day 7	5.325, 0.000		6.252, 0.000		4.728, 0.006	
T3: postoperative day 14	6.562, 0.000		5.882, 0.000		3.893, 0.013	
Comparison between time points *t*, *p*	A: Experimental group	B: Control group	A: Experimental group	B: Control group	A: Experimental group	B: Control group
T2 vs T1	5.682, 0.000	1.086, 0.627	6.523, 0.000	3.382, 0.015	3.859, 0.013	2.815, 0.041
T3 vs T1	7.851, 0.000	1.177, 0.357	8.868, 0.000	4.821, 0.000	4.812, 0.000	0.857, 0.742

Table III. Comparison of QoL at postoperative six month between groups (Score, $\bar{x} \pm s$).

Group	Experimental group n = 45	Control group n = 45	Comparison between groups *t, p*
Physical functioning	78.8 ± 13.2	58.6 ± 12.5	7.454, 0.000
Bodily pain	65.8 ± 10.7	50.5 ± 10.2	6.943, 0.000
Role-physical	68.2 ± 10.2	57.5 ± 10.6	4.879, 0.000
General health	67.8 ± 8.8	55.6 ± 10.5	5.974, 0.000
Social functioning	60.2 ± 8.9	45.6 ± 8.8	7.825, 0.000
Vitality	68.5 ± 9.5	44.6 ± 7.8	13.043, 0.000
Mental health	68.4 ± 11.5	59.5 ± 10.2	3.884, 0.000
Role-emotional	61.5 ± 7.8	50.6 ± 7.5	6.757, 0.000

tional deficiency, which, in combination with surgical trauma, can easily cause postoperative immune dysfunction and malnutrition, imposing a certain influence on recovery[5-7]. Nutrition support is an effective strategy to improve the postoperative recovery in patients with gastric cancer. Rational postoperative nutritional support can improve patients' immunity and reduce expression of inflammatory factors, exhibiting significant implications in improving postoperative QoL. Conversely, irrational nutritional support may aggravate stress response in patients, affecting postoperative recovery and prognosis of the disease.

EN is an effective therapeutic approach to ensure hormone secretion from gastrointestinal tract and peristalsis. In addition, EN can regulate the function of the intestinal mucosal barrier, maintain the integrity of intestinal mucosal function, prevent intestinal bacterial translocation and reduce the occurrence of infection[8]; however, due to poor postoperative tolerance, patients with gastric cancer are prone to experience complications such as abdominal distension, abdominal pain and diarrhea, limiting the implementation of early EN. Conventional TPN can supply patients with adequate nutrition; however, due to poor self-regulation of infused nutrients in some patients, stress response and infection rate are increased[9,10]. In consideration of both, a selection of a scientific and rational nutritional support is of great significance to guarantee the efficacy of postoperative nutritional support in patients with gastric cancer and improve prognosis of the disease.

In recent years, a few studies have shown that compared to conventional standardized TPN, low-nitrogen and low-calorie TPN can effectively reduce the occurrence of negative nitrogen balance, supply energy, reduce the prevalence of metabolic and infectious complications and improve immunity[11,12]. In the present study, on the basis of postoperative conditions of patients with gastric cancer, 45 patients in experimental group were supported with low-nitrogen and low-calorie PN combined with EN. The results showed that levels of IgA, IgM and IgG in experimental group were significantly increased on the 7th postoperative day, and significantly higher than those of controls and preoperatively ($p < 0.01$). These results implied that this strategy can effectively improve immunity, which is consistent with the results as reported previously[12,13].

Under normal physiological conditions, levels of inflammatory cytokines should relatively stable, but change significantly when damage to the body occurs. IL-2, CRP and TNF-α are important inflammatory mediators, which can effectively reflect the extent of inflammatory reaction in the body[13,14]. CRP is an acute phase protein synthesized in liver cells when the body is subjected to microbial invasion or tissue damage. IL-2 is an important factor in the regulation of immune response. TNF-α exhibits a significant anti-tumor effect[15,16]. On the 7th postoperative day, CRP of experimental group was significantly lower than that of controls and preoperative level ($p < 0.05$), whereas levels of IL-2 and TNF-α were significantly higher than those of controls and preoperatively ($p < 0.05$). In consideration of circumstances, low-nitrogen and low-calorie PN combined with EN can regulate the expression of inflammatory cytokines. It may improve systemic and local inflammations and induce anti-tumor effect by up-regulating levels of IL-2 and TNF-α. Furthermore, the significant decrease in CRP level indicated that this strategy can reduce inflammatory reactions induced by surgical trauma and improve prognosis of the disease, resulting in higher scores of QoL in experimental group six months upon operation while compared to the control group ($p < 0.05$).

Conclusions

Low-nitrogen and low-calorie PN combined with EN can effectively improve the immune function, reduce the inflammatory reactions and improve the postoperative QoL and prognosis in patients with gastric cancer, it is suitable for implementation in clinical practice.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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