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Effect of early enteral immunonutrition intervention on gastrointestinal hormones, stress hormones and immune response after pancreatic cancer surgery

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ABSTRACT

Objective: To study the effect of early enteral immunonutrition intervention on gastrointestinal hormones, stress hormones and immune response after pancreatic cancer surgery. **Methods:** A total of 68 patients who received radical operation for pancreatic cancer in Chengdu Third People's Hospital between May 2015 and February 2017 were selected as the research subjects and randomly divided into TPF-T group and TP group who received early postoperative enteral immunonutrition intervention and conventional enteral nutrition intervention respectively. The levels of gastrointestinal hormones MTL, GAS, CGRP, Ghrelin and stress hormones ACTH, Cor,R, AT-II, ALD in serum as well as the levels of immune cells CD4+T, CD8+T, NKT, Treg, Breg, MDSC in peripheral blood were detected before surgery as well as 3 d and 7 d after surgery. **Results:** 3 d and 7 d after surgery, MTL, GAS, CGRP and Ghrelin levels in serum as well as CD4+T cell, CD8+T cell and NKT cell levels in peripheral blood of both groups of patients were significantly lower than those before surgery while ACTH, Cor, R, AT-II and ALD levels in serum as well as Treg, Breg and MDSC levels in peripheral blood were significantly higher than those before surgery, and MTL, GAS, CGRP and Ghrelin levels in serum as well as CD4+T cell, CD8+T cell and NKT cell levels in peripheral blood of TPF-T group were significantly higher than those of TP group while ACTH, Cor, R, AT-II and ALD levels in serum as well as Treg, Breg and MDSC levels in peripheral blood were significantly lower than those of TP group. **Conclusion:** Early postoperative enteral immunonutrition intervention can regulate the gastrointestinal hormone secretion, inhibit stress response and improve immune response.

1. Introduction

Pancreatic cancer is a type of malignant tumor in the digestive tract with extremely high malignant degree, and patients with pancreatic cancer who are eligible for surgical indications need to undergo radical resection in time. The radical operation for pancreatic cancer is with wide range of resection and causes great surgical trauma, which will not only affect the postoperative gastrointestinal peristalsis and the body's nutritional status, but will also cause stress reaction activation and immune response inhibition. Perioperative related research in recent years has shown that early enteral nutrition intervention after gastrointestinal surgery can not only improve the nutritional status of the body, but can also promote gastrointestinal peristalsis function recovery and protect the intestinal mucosal barrier function[1]. Enteral immunonutrition preparation is a newly developed enteral nutrition preparation, which contains the arginine and ω-3 polyunsaturated fatty acids with immunoregulation activity and anti-oxidative stress activity[2]. In the following studies, we specifically analyzed the effect of early enteral immunonutrition intervention on gastrointestinal hormones, stress hormones and immune response after pancreatic cancer surgery.

2. Case information and research methods

2.1 General case information

A total of 68 patients who received radical operation for pancreatic cancer in Chengdu Third People's Hospital between May 2015 and February 2017 were selected as the research subjects, and all the patients were in line with the surgical indications and diagnosed with pancreatic cancer by postoperative pathological examination. Radom number table was used to divide the 68 patients into two

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groups, 34 cases in each group, and they received different enteral nutrition interventions respectively. TPF-T group received enteral immunonutrition intervention, including 19 men and 15 women that were 420-58 years old; TP group received routine enteral nutrition intervention, including 20 men and 14 women that were 41-56 years old. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Enteral nutrition intervention

TPF-T group received early postoperative enteral immunonutrition intervention, which was as follows: duodenal nutrition tube was embedded via the nose, Supportan was selected as enteral immunonutrition preparation, a small amount of saline, about 300 mL was provided via the nasal feeding tube from the 2nd day after operation, Supportan was provided if there was no discomfort, the first-day dose was 1/3-1/2 of the total dose, the second-day dose was 2/3 of the total dose, the dose from the third day was the total dose, and the starting infusion speed was 30 mL/h and then gradually increased to 80-100 mL/h, which was lasting for 1 week. TP group of patients received early postoperative regular enteral nutrition intervention, which was as follows: the nasal feeding tube was embedded in the same way as that of TPF-T group, Nutrison Fibre was selected as enteral nutrition preparation, and the infusion dose and speed were the same as those of TPF-T group.

2.3 Serum hormone content detection

Before operation as well as 3 d and 7 d after operation, 5 mL peripheral venous blood was collected from two groups of patients and centrifuged to separate serum, and enzyme-linked immunosorbent assay kit was used to detect the contents of MTL, GAS, CGRP, Ghrelin, ACTH, Cor, R, AT-II and ALD.

2.4 Peripheral blood immune cell content detection

Before operation as well as 3 d and 7 d after operation, 3 mL peripheral venous blood was collected from two groups of patients and anti-coagulated with EDTA to incubate the monoclonal antibody of CD3, CD4, CD8, CD11b, CD14, CD19, CD24, CD25, CD38 and LA-DR, and then flow cytometer was used to determine the contents of CD4+T cells, CD8+T cells, NKT cells, Treg, Breg and MDSC cells.

2.5 Statistical methods

SPSS 22.0 software was used to input test indicators, data between two groups were by t test and $P<0.05$ was the standard of statistical significance in differences in test results.

3. Results

3.1 Perioperative serum gastrointestinal hormone levels

Before operation as well as 3 d and 7 d after operation, analysis of serum gastrointestinal hormones MTL, GAS, CGRP and Ghrelin between two groups of patients was as follows: serum MTL, GAS, CGRP and Ghrelin levels were not significantly different between two groups of patients before operation (P>0.05); 3 d and 7 d after surgery, serum MTL, GAS, CGRP and Ghrelin levels of both groups of patients were significantly lower than those before surgery, and serum MTL, GAS, CGRP and Ghrelin levels of TPF-T group were significantly higher than those of TP group (P<0.05).

3.2 Perioperative serum stress hormone levels

Before operation as well as 3 d and 7 d after operation, analysis of serum stress hormones ACTH (pmol/L), Cor (nmol/L), R (ng/mL), AngII (pg/mL) and ALD (pg/mL) between two groups of patients was as follows: serum ACTH, Cor, R, AT-II and ALD levels were not significantly different between two groups of patients before operation (P>0.05); 3 d and 7 d after surgery, serum ACTH, Cor, R, AT-II and ALD levels of both groups of patients were significantly higher than those before surgery, and serum ACTH, Cor, R, AT-II and ALD levels of TPF-T group were significantly lower than those of TP group (P<0.05).

3.3 Perioperative peripheral blood immune cell levels

Before operation as well as 3 d and 7 d after operation, analysis of peripheral blood CD4+T cell, CD8+T cell and NKT cell as well as Treg, Breg and MDSC cell between two groups of patients was as follows: peripheral blood CD4+T cell, CD8+T cell and NKT cell as well as Treg, Breg and MDSC cell levels were not significantly different between two groups of patients before operation (P>0.05);

Table 1.
Changes in perioperative serum gastrointestinal hormone levels (pg/mL).

Groups	n	Time	MTL	GAS	CGRP	Ghrelin
TPF-T group	34	Before operation	236.51±33.25	183.46±22.14	107.44±14.51	75.21±9.35
		3 d after operation	172.34±20.34$^{*\#}$	131.35±17.82$^{*\#}$	75.41±9.34$^{*\#}$	46.53±7.24$^{*\#}$
		7 d after operation	204.41±28.45$^{*\#}$	148.53±16.67$^{*\#}$	82.31±11.04$^{*\#}$	57.42±7.84$^{*\#}$
TP group	34	Before operation	238.12±36.15	184.11±21.35	108.25±13.26	74.67±9.71
		3 d after operation	139.54±15.62$^{\#}$	93.53±11.52$^{\#}$	60.31±8.49$^{\#}$	33.74±5.24$^{\#}$
		7 d after operation	162.35±19.26$^{\#}$	112.48±14.27$^{\#}$	68.48±9.35$^{\#}$	45.12±6.75$^{\#}$

*: comparison between TPF-T group and TP group, $P<0.05$; $^{\#}$: comparison between before and after operation, $P<0.05$.

Table 2.
Changes in perioperative serum stress hormone levels.

Groups	n	Time	ACTH	Cor	R	AT-II	ALD
TPF-T group	34	Before operation	2.92±0.41	122.25±14.85	1.89±0.25	2.85±0.54	256.51±33.52
		3 d after operation	4.61±0.74$^{*\#}$	172.71±19.23$^{*\#}$	3.27±0.46$^{*\#}$	4.29±0.56$^{*\#}$	379.76±41.25$^{*\#}$
		7 d after operation	4.14±0.56$^{*\#}$	158.34±18.35$^{*\#}$	2.74±0.35$^{*\#}$	3.74±0.42$^{*\#}$	313.52±36.86$^{*\#}$
TP group	34	Before operation	3.03±0.42	121.98±13.48	1.93±0.22	2.91±0.48	255.31±31.29
		3 d after operation	6.25±0.83$^{\#}$	226.73±28.92$^{\#}$	4.31±0.57$^{\#}$	5.57±0.71$^{\#}$	486.61±62.35$^{\#}$
		7 d after operation	5.42±0.77$^{\#}$	192.15±21.45$^{\#}$	3.88±0.47$^{\#}$	4.86±0.59$^{\#}$	423.42±55.62$^{\#}$

*: comparison between TPF-T group and TP group, $P<0.05$; $^{\#}$: comparison between before and after operation, $P<0.05$.

Table 3.
Changes in perioperative peripheral blood T cell levels.

Groups	*n*	Time	CD4+T cell	CD8+T cell	NKT cell
TPF-T group	34	Before operation	43.15±5.95	37.59±5.28	1.18±0.19
		3 d after operation	35.61±4.47*#	31.03±4.58*#	0.91±0.12*#
		7 d after operation	38.49±5.52*#	33.54±5.07*#	1.04±0.15*#
TP group	34	Before operation	43.77±6.03	38.01±5.61	1.21±0.17
		3 d after operation	30.21±3.58#	27.54±3.25#	0.78±0.09#
		7 d after operation	33.53±4.48#	29.03±3.57#	0.87±0.10#

*: comparison between TPF-T group and TP group, $P<0.05$; #: comparison between before and after operation, $P<0.05$.

Table 4.
Changes in perioperative peripheral blood inhibitory immune cell levels.

Groups	*n*	Time	Treg	Breg	MDSC
TPF-T group	34	Before operation	3.41±0.45	4.28±0.52	2.03±0.35
		3 d after operation	4.98±0.76*#	6.88±0.79*#	3.26±0.52*#
		7 d after operation	4.12±0.49*#	5.41±0.67*#	2.77±0.39*#
TP group	34	Before operation	3.45±0.48	4.33±0.57	2.08±0.32
		3 d after operation	7.04±0.88#	8.49±1.02#	4.47±0.58#
		7 d after operation	6.65±0.79#	7.61±0.88#	3.82±0.44#

*: comparison between TPF-T group and TP group, $P<0.05$; #: comparison between before and after operation, $P<0.05$.

3 d and 7 d after surgery, peripheral blood CD4+T cell, CD8+T cell and NKT cell levels of both groups of patients were significantly lower than those before surgery while Treg, Breg and MDSC levels were significantly higher than those before surgery, and peripheral blood CD4+T cell, CD8+T cell and NKT cell levels of TPF-T group were significantly higher than those of TP group while Treg, Breg and MDSC levels were significantly lower than those of TP group ($P<0.05$).

4. Discussion

The value of enteral nutrition support early after pancreatic cancer surgery has received more and more recognition, which can effectively improve the nutritional status of the body and promote the recovery of gastrointestinal function[3,4]. Enteral immunonutrition preparations are the new types of enteral nutrition preparations developed in recent years, which contain arginine, ω-3 polyunsaturated fatty acids and other nutrients, and have the value for resisting oxidative stress and improving immune function[5,6]. The changes of gastrointestinal function after gastrointestinal surgery are closely related to abnormal secretion of gastrointestinal hormones such as MTL, GAS, CGRP and Ghrelin. MTL and GAS are the gastrointestinal hormones secreted by small intestine Mo cells and gastric antrum G cells, the former can promote the intestinal cyclical migrating motor complex, and the latter can promote the secretion of gastric acid and protease, and also promote gastrointestinal peristalsis[7]; CGRP is a kind of polypeptide with dilation activity, which can regulate the vasomotor in the gastric mucosa and affect the contraction of smooth muscle and the secretion of gastric acid; Ghrelin is a polypeptide hormone secreted by X/A-like cells in gastric mucosa, which has the function of promoting gastric emptying and enhancing gastric motility[8]. In order to define the effect of enteral immunonutrition intervention on the recovery of gastrointestinal function after pancreatic cancer surgery, perioperative serum levels of above gastrointestinal hormones were analyzed in the study, and the results showed that serum MTL, GAS, CGRP and Ghrelin levels of both groups of patients significantly decreased after operation, and serum MTL, GAS, CGRP and Ghrelin levels of TPF-T group were significantly higher than those of TP group. This indicates that the trauma of pancreatic cancer surgery can suppress the secretion of gastrointestinal hormones after surgery, and enteral immunonutrition intervention can regulate the secretion of gastrointestinal hormones and promote the recovery of gastrointestinal function.

The pancreatic cancer surgery is with extensive range of resection and large tissue trauma, and the body will be in a stress state after the surgical trauma, which will cause the synthesis and secretion disorders of a variety of endocrine hormones[9,10]. The arginine and ω-3 polyunsaturated fatty acids in immune-type gastrointestinal nutrition preparations can increase the expression of antioxidant enzymes and participate in the process of anti-oxidative stress. Adrenal gland is the endocrine gland that plays an important role in stress reaction process, and external stimuli can increase the secretion of pituitary ACTH and act on the adrenal cortex, and thus promote the massive synthesis and secretion of cortical hormone Cor. Under stress state, Cor can promote gluconeogenesis, elevate blood sugar level, improve the cardiovascular system sensitivity to catecholamine, guarantee the circulatory function, stabilize the lysosome membrane and avoid tissue damage[11]. In addition to the changes of adrenal cortex function, the circulatory function and water sodium metabolism under stress state will be affected by different degree, and RAAS system adjusts the vasomotor as well as sodium and water excretion to participate in the process of stress reaction. Increased R secretion is initial link in the activation of RAAS system, and it acts on angiotensinogen and makes it split to angiotensin I, and angiotensin I becomes active AT-II under the catalysis of ACE, which can not only promote the vasoconstriction, but also increase the secretion of ALD and affect water sodium metabolism[12,13]. In order to define the effect of enteral immunonutrition intervention on stress reaction degree after pancreatic cancer surgery, the chagnes in serum levels of above stress hormones were analyzed in the study, and the results showed that serum ACTH, Cor, R, AT-II and ALD levels of both groups of patients after surgery were significantly higher than those before surgery, and serum ACTH, Cor, R, AT-II and ALD levels of TPF-T group after surgery were significantly lower than those of TP group. This indicates that the trauma from pancreatic cancer surgery can cause the activation of the postoperative stress reaction and the increase of stress hormone secretion, and enteral immunonutrition intervention can adjust the stress hormone secretion and inhibit the extent of stress reaction.

Surgical trauma will not only affect the secretion of stress

hormones, but will also inhibit the immune response of the body. Immune-type gastrointestinal nutrition preparations have significant immune regulation effect and can enhance the body's immunity. T lymphocytes are important immune cells in the body and participate in the cellular immune response process. T lymphocyte differentiation and maturation experience positive selection and negative selection, and the mature T cells involved in cellular immune response include CD4+T cells and CD8+T cells[14,15]. NKT cell is the newly discovered T cell type in recent years, which expresses the TCR of T cells and the NKR of NK cells at the same time, and can mediate cell immune response and exert the cytotoxic effect[16]. In the study, analysis of the contents of these T cells subsets showed that peripheral blood CD4+T cell, CD8+T cell and NKT cell levels of both groups of patients after surgery were significantly lower than those before surgery, and peripheral blood CD4+T cell, CD8+T cell and NKT cell levels of TPF-T group after surgery were significantly higher than those of TP group. This indicates that the trauma from pancreatic cancer surgery can inhibit the immune response after surgery, and enteral immunonutrition intervention can promote the differentiation and maturation of T cells and improve the immune response. The immune response in vivo is also affected by a variety of inhibitory immune cell subsets. Treg and Breg are the T cell subset and B cell subset respectively that can secrete IL-10 and exert immunosuppressive effect[17,18], MDSC is the inhibitory cell that takes CD14 and CD11b as surface markers, which synthesizes arginase to degrade arginine and lead to immunosuppression[19,20]. Further analysis of the contents of these inhibitory immune cell subsets showed that peripheral blood Treg, Breg and MDSC levels of both groups of patients after surgery were significantly higher than those before surgery, and peripheral blood Treg, Breg and MDSC levels of TPF-T group after surgery were significantly lower than those of TP group. This shows that enteral immunonutrition intervention can reduce the number of inhibiting immune cells, which is conducive to improving the immune response.

Early enteral immunonutrition intervention after pancreatic cancer surgery can regulate the secretion of gastrointestinal hormones, promote the recovery of gastrointestinal function, reduce the stress response and improve the immune response.

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