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POSTOPERATIVE COURSE OF PERITONITIS: THE ROLE OF CYTOKINE IMBALANCE

Research article

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Abstract

Peritonitis is an inflammation of the peritoneum as a result of intraabdominal infection. Gram-negative bacteria produce endotoxins, which leads to the release of cytokines (TNF-α) and interleukins 1 and 6 (IL-1, IL-6). They contribute to the formation of toxic mediators, which leads to a complex, multifactorial syndrome, which can be of varying severity and leads to functional disorders of one or more vital organs and systems. It was found that patients with peritonitis had an imbalance of inflammatory and anti-inflammatory cytokines. This leads to the suppression of the cellular link of immunity. The relationship between the level of cytokine production and the severity of the course of the postoperative period was also established. Thus, it is advisable for patients with peritonitis to use immunomodulators to eliminate an imbalance in the cytokine system and the likelihood of postoperative complications.

Keywords: peritonitis, cytokines, clinical study, pathogenesis, inflammation.

ПОСЛЕОПЕРАЦИОННОЕ ТЕЧЕНИЕ ПЕРИТОНИТА: РОЛЬ ЦИТОКИНОВОГО ДИСБАЛАНСА

Научная статья

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Аннотация

Перитонит — это воспаление брюшины в результате внутрибрюшной инфекции. Грамотрицательные бактерии продуцируют эндотоксины, что приводит к высвобождению цитокинов (TNF-α) и интерлейкинов 1 и 6 (IL-1, IL-6). Они способствуют образованию токсических медиаторов, что приводит к сложному, многофакторному синдрому, который может быть различной степени тяжести и приводит к функциональным нарушениям одного или нескольких жизненно важных органов и систем. Было обнаружено, что у пациентов с перитонитом наблюдался дисбаланс воспалительных и противовоспалительных цитокинов. Это приводит к подавлению клеточного звена иммунитета. Также была установлена взаимосвязь между уровнем продукции цитокинов и тяжестью течения послеоперационного периода. Таким образом, пациентам с перитонитом целесообразно применять иммуномодуляторы для устранения дисбаланса в системе цитокинов и вероятности послеоперационных осложнений.

Ключевые слова: перитонит, цитокины, клиническое исследование, патогенез, воспаление.

Introduction

Peritonitis is an inflammation of the peritoneum, it is a complex of severe pathophysiological reactions with impaired functions of all organs and systems of the body. As a rule, inflammation develops locally, but almost all body systems participate in its implementation to one degree or another [1]. According to modern concepts, the leading role in the pathogenesis of peritonitis belongs to disorders of immune homeostasis, which are aggravated by surgical trauma and anesthesia. The involvement of many types of cells, subcellular elements and organ systems in the process of inflammation determines the formation of complex mechanisms of regulation of inflammatory and immune reactivity, both at the local and at the organizational level [2]. The cytokine system plays a leading role in the development of an inflammatory reaction. Normally functioning mechanisms of the immune system prevent the uncontrolled release of cytokines and other inflammatory mediators. According to many authors, under the influence of surgery, an imbalance in the immune system develops in the body of patients, characterized by a predominance of the activity of T-2 helpers and their production of cytokines that have an antagonistic effect on the functional activity of T-1 helpers [1], [2], [3]. In the blood, at the very beginning of inflammation, pro– and anti-inflammatory cytokines appear simultaneously: IL-8, IL-12 and IL-10 [3].

The aim of our study was to study the production of pro- and anti-inflammatory cytokines in the dynamics of the disease, depending on the severity of the course of the postoperative period in patients with advanced peritonitis.

Materials and methods

The clinical study included 30 patients who were treated in the intensive care unit of the Regional Clinical Hospital of Vladivostok, aged 18 to 70 years, who were operated on for various forms of common peritonitis (perforation of the stomach

and duodenum, acute destructive cholecystitis, purulent-inflammatory complications of pancreatic necrosis). All patients were operated on urgently under combined general anesthesia. Surgical intervention was performed in all cases after appropriate preoperative preparation. After surgery, the patients were in the intensive care unit during the entire clinical period, where they underwent complex therapy and the necessary examinations. Patients, depending on the severity of the disease, that patients with peritonitis had a course of the postoperative period, were divided into three groups: group 1 – with moderate severity (10 persons); group 2 – with severe course of the postoperative period (13 persons); group 3 – with repeated relaparotomy (7 persons). The severity of the course of the postoperative period was assessed according to the examination of patients and the analysis of the compliance of the clinical picture with the criteria of systemic inflammatory response syndrome (SIRS, or SIRS – Systemic Inflammatory Response Syndrome) and sepsis, formulated at the Conciliatory Conference of the American College of Pulmonologists and the Society of Critical Condition Medicine in Chicago in 1991 with additions by R.C. Bone and Rangel-Frausio and R.P. Wensel 8]. At the same time, two subgroups were identified in group 2 of patients: 1 subgroup with an uncomplicated postoperative period (8 patients); 2 subgroups – with complications of the postoperative period (nosocomial pneumonia with a fatal outcome – 5 persons). Studies were carried out in the dynamics of the postoperative period in 1–3 and 5–7 days. The sampling of the material (blood) was carried out on an empty stomach in the morning.

The concentration of pro-inflammatory (IL-8, IL-12 (070) and IL-12 (p40)) and anti-inflammatory (IL-10) cytokines was determined. Determination of IL-8, IL-10 and IL-12 (070) and IL-12 (p40) was carried out by enzyme immunoassay using reagents "R & D diagnostic Inc" (USA) [4]. As a control in the study of cytokine levels in blood sera, 30 samples of blood serum from gratuitous practically healthy donors permanently residing in Vladivostok were used.

Results and their discussion

In the course of the conducted studies, it was found that patients with peritonitis have an imbalance in the system of pro- and anti-inflammatory cytokines. In all comparison groups, a significant increase in IL-8 production was recorded, which is a strong chemoattractant. It activates and attracts neutrophils to the focus of inflammation, enhances their adhesion and degranulation, activates the release of superoxide radicals and phagocytosis [5]. It was revealed that the production of this cytokine was higher than that of the control group throughout the entire study period both in the group with an average severity of the course of the postoperative period, and in the groups with severe course and relaparotomy. At the same time, the content of IL-8 in blood serum in groups 3 and 2 was 659.39 ±172.29 pg/ml and 466.73±98.62 pg/ml, respectively, exceeding the level of IL-8 in group 1 by 204.98182.42 pg/ml, and correlated with the severity of the course of the postoperative period of peritonitis, reflecting the process of hyperactivation of the immune system (table 1).

At the same time, in the dynamics of the disease in group 2 of patients with a severe course of the postoperative period, an increase in the level of IL-8 production was observed both in subgroup I (patients with uncomplicated course) and in subgroup II (patients with complicated course of the postoperative period), compared with the control group by 5–7 days (table 2). This regularity was also revealed in group 3 of patients with relaparotomy. A high level of IL-8 (more than 80 pg/ml) at the onset of the disease can serve as a criterion for the development of postoperative complications.

Table 1 - Dynamics of cytokines in patients with peritonitis depending on the severity of the course of the postoperative period

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Investigated cytokines		The level of cytokines in the groups (M±m, pg/ml)			
		I group*	II group**	III group***	Healthy donors****
IL-8	I	62.20±21.35	157.6±38.76	171.00±67.62	13.4 ±1.3
	II	204.98±82.43	466.73±98.62	659.39±172.3	
IL -10	I	29.52±2.05	27.44±6.13	14.62±5.80	14.14 ±0.8
	II	27.90±9.44	41.88±6.11	23.27±1.73	
IL -12p70	I	8.90±3.64	4.34±2.75	2.96±2.47	7.46 ±0.6
	II	58.37±12.12.95	10.13±2.94	4.05±0.66	
IL -12 p40	I	200.54± 40.17	76.68±23.97	129.69±31.40	17.58 ±10.95
	II	34.95±8.57	2068±19.62	14.46±3.25	

*Note: * - n= 10; ** - n= 13; *** - n= 7; **** - n= 30; I - study for 1-3 days; II - study for 5-7 days*

Table 2 - The level of cytokines in the blood serum of patients with severe postoperative peritonitis

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Investigated cytokines	Investigated cytokines in the groups (M±m, pg/ml)		
	I group*, n= 10	II group**, n= 13	Healthy donors***, n= 30

IL -8	I	642.53±207.34	82.70±29.11	13.4 ±1.3
	II	137.31±65.64	254.58±183	
IL -10	I	142.69±61.36	7.4±2.37	14.14 ±0.8
	II	38.99±7.21	38.73±5.56	
IL -12p70	I	5.21±2.63	3.18±0.71	7.46 ±0.6
	II	6.97±2.45	11.37±3.89	
IL -12 p40	I	91.30±35.83	56.40±10.40	17.58 ±10.95
	II	181.78±19.13	116.31±51.26	

*Note: * - n= 10; ** - n= 13; *** - n= 30; group 2; I - study for 1-3 days; II - study for 5-7 days*

The analysis made it possible to establish a change in the level of IL-12 production. Being a pro-inflammatory cytokine, it is produced by macrophages, neutrophils, dendritic cells, activated lymphocytes. One of the most important effects of IL-12 is the ability to turn the differentiation of ThO towards ThI, in addition, it is a link between the mechanisms of nonspecific protection and a specific immune response. At the same time, IL-12 is a key cytokine for enhancing the cell-mediated immune response and initiating effective anti-infective protection against viruses, bacteria, fungi and protozoa [7]. IL-12 has in its structure heavy – 40kD (p40) and light –35kL (p35) chains. Functional activity is shown by the IL-12p70 heterodimer. The p40 multimodimer of the pogo period. Thus, as a result, it is a natural antagonist of IL-12, which is produced by macrophages in response to inflammatory stimuli simultaneously with IL-12, but in significant excess. Under natural conditions, IL-12p40 homodimers bind to the IL-12 receptor without showing biological activity [6]. In our study, an increase in the level of IL-12p70 production was recorded in patients in group 1 for 5–7 days, which indicates an increase in the cell-mediated immune response and the initiation of anti-infectious disease. In patients in group 2 with severe postoperative peritonitis and patients with laparotomy, on the contrary, IL-12p70 production indicators were low in the dynamics of the study, with a slight increase in its level k5-7 days, while remaining lower than the control group. This may indicate a decrease in the ability of monocytes/macrophages to produce IL-12p70 in this category of patients. At the same time, changes in the level of production of IL-12p40, which is a natural antagonist of IL-12, were detected [6], [7]. In group 2 of patients with a severe course of the postoperative period, a high level of production of this cytokine was detected already at the onset of the disease in both 1 (91.30+35.83) and II (56.40+10.40) subgroups with maximum values for 5–7 days, which may indicate on immune dysregulation in relation to inhibition of cellular mechanisms of immunity. Analyzing the indicators of IL-12p40 production in the group of moderate severity and in the group with relaparotomy, we revealed the same regularity [8]. Monitoring of IL-10 products revealed certain differences. If in the group of patients with moderate severity of the postoperative period, the production indicators of this cytokine were higher than those of the control group, at the same time in 1-3 and 5–7 days were determined at the same level, then the content of IL-10 for 5–7 days. In groups with severe course ($p<0.05$) and relaparotomy ($p<0.001$) increased.

The pro-inflammatory cytokine IL-10 is produced by Th2 cells, suppresses the synthesis of cytokines produced by Thl cells, and also reduces the activity of macrophages and the production of pro-inflammatory cytokines [3], [7].

The level of production of anti-inflammatory IL-10 in the 2nd group of patients was higher ($p<0.05$) in patients with uncomplicated course of the postoperative period, compared with the control. At the same time, in 1–3 days, the indicators of the production of this cytokine in patients with relaparotomy and patients with nosocomial pneumonia were lower than those of the control group, which can serve as a criterion for the development of postoperative complications. However, in this subgroup, IL-10 production significantly increased by 5–7 days. ($p<0.001$), which may be a prognostically favorable criterion for the further course of postoperative studies, a correlation was revealed between the level of IL-10 production and the severity of the course of the postoperative period of peritonitis.

Our study revealed a correlation between the level of IL-8 and IL-10 production in both subgroups in patients with severe postoperative period. A similar pattern is determined in the group of patients with relaparotomy [9], [10].

Conclusion

1. With peritonitis, an imbalance develops in the system of pro- and anti-inflammatory cytokines, which leads to the formation of secondary insufficiency of the cellular link of immunity associated with the disease itself, surgical trauma, the use of anesthesia.

2. Multidirectional indicators of IL-12p70 and iL-12p40, a decrease in IL-10 production indicate the inhibition of Thl cell activity.

3. Increasing the level of IL-8 and IL-12 p40 for 5 days. It may indicate the development of postoperative complications.

4. It is advisable to use immunomodulators in patients with peritonitis to eliminate an imbalance in the cytokine system and the likelihood of postoperative complications.

During the research, the authors found that patients with peritonitis had an imbalance of inflammatory and anti-inflammatory cytokines. Correlations between the level of cytokine production and the severity of the course of the postoperative period were revealed.

Конфликт интересов

Не указан.

Рецензия

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Conflict of Interest

None declared.

Review

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