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Концентрація інтерлейкіну–10 у сироватці крові хворих з внутрішньочеревними інфекціями в періопераційному періоді

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Intra–abdominal infections: the blood serum interleukin–10 in perioperative period

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Реферат

Мета. Оцінити концентрацію інтерлейкіну–10 (ІЛ–10) у сироватці крові пацієнтів з внутрішньочеревними інфекціями (ВЧІ).

Матеріали і методи. Клінічні зразки отримані у 56 пацієнтів з ВЧІ різного походження (у 24 – з післяопераційними абсцесами, у 12 – з первинними абсцесами в черевній порожнині, у 20 – з перитонітом) за день до оперативного втручання та на 2 – 3–й і 5 – 7–й дні після оперативного втручання.

Результати. Не виявлено достовірної різниці між показниками концентрації ІЛ–10 у сироватці крові пацієнтів з ВЧІ різного походження в періопераційному періоді. Достовірно відрізнялися показники концентрації IL–10 у сироватці крові пацієнтів з ВЧІ до оперативного втручання та на 2 – 3–й і 5 – 7–й день після оперативного втручання і здорових осіб.

Висновки. Концентрація IL–10 у сироватці крові пацієнтів з ВЧІ різного походження на рівні 6,78 пг/мл і вище має прогностичне значення: чутливість тесту – 92,86%, специфічність – 80,65%. Потрібні подальші дослідження, спрямовані на виявлення специфічного збудника ВЧІ та вивчення цитокінової реакції.

Ключові слова: внутрішньочеревні інфекції; інтерлейкін–10; сироватка крові; періопераційний період.

Abstract

Objective. To assess the blood serum IL–10 concentration in patients with intra–abdominal infections.

Materials and methods. Clinical specimens were obtained from 56 patients, suffering intra–abdominal infections of various origin: 24 patients – with postoperative abscesses, 12 – with primary intra–abdominal abscesses, and 20 – with diffuse or local peritoneal collection at the day before surgical intervention, on 2nd–3rd day and on 5th–7th day after it.

Results. There was no trustworthy difference established between the blood serum IL–10 concentrations in patients with different origin of intra–abdominal infections in perioperative period. The significant difference was established, while comparing concentrations of IL–10 in the blood serum in patients with intra–abdominal infections before and on the days 2–3 and 5–7 postoperatively, and in healthy persons.

Conclusion. Concentration of the blood serum IL–10 ≥ 6.78 pg/mL in patients with different origin of intra–abdominal infections has significant prognostic significance: sensitivity (92.86%) and specificity (80.65%). Further studies, targeting a specific causative agent of nosocomial infection and the cytokine response, are needed.

Keywords: intra–abdominal infections; interleukin–10; the blood serum; perioperative period.

Introduction

Intra–abdominal infections (IAI) are the second most common cause of infectious mortality in intensive care units [1, 2]. Complicated intra–abdominal infection, which extends into the peritoneal space, is associated with abscess formation and peritonitis [3]. Complicated intra–abdominal infection are an important cause of morbidity and mortality, especially poorly managed. One multi–centred observational study in 132 medical institutions worldwide during 4–month period with 4553 patients with complicated IAI has shown mortality 9.2% (416/4533) [4]. Nowadays the mechanisms of the postoperative immune dysfunction are still subject of numerous studies [5]. The inflammatory reaction based on the postoperative immune suppression predisposes for septic complications. Postoperatively acquired immune dysfunction is associated with a higher mortality rate in case of septic complications [6]. Interleukin–10 (IL–10), first recognized for its ability to inhibit activation and effector function of T–cells, monocytes, and macrophages, is a multifunctional cytokine. The principal routine function of IL–10 appears to be to limit and ultimately terminate inflammatory responses [7]. IL–10–deficient mice spontaneously develop colitis suggesting that IL–10 exerts in vivo immune regulatory effects largely in the intestinal tract. In human, IL–10 has also been confirmed as a susceptibility gene for inflammatory bowel disease [8]. Moreover, anti–inflammatory IL–10 enhance B cell function (proliferation, immunoglobulin secretion) and encourage the development of cytotoxic T cells [8]. However, the role of IL–10 in clinical approaches to the diagnosis of complicated and non–complicated IAI is not fully comprehend.

Objective: investigation of pro–inflammatory IL–10 serum concentration in patients with different origin of IAI in perioperative period.

Materials and Methods

Clinical specimens were obtained from 56 patients with different IAI attended at the Zaytsev Institute of General and Emergency Surgery in 2016–2018. Inclusion criteria. Patients with primary and secondary IAI. All patients were divided into three group: Group 1 – 24 patients with POA, Group 2 – 12 patients with primary intra–abdominal abscesses (PIAA), and Group 3 – 20 patients with diffuse or local peritoneal collection (PC) due to IAI only. Exclusion criteria. Patients who do not presented IAI and those who do not agreed to participate of this study. For immunological analysis, it was obtained of 5 ml blood from 31 healthy volunteers (Control Group) and each patient by vacuum sterile disposable tubes (Vacutainer) at the day before surgical intervention, on 2nd–3rd day and on 5th–7th day after surgical intervention. Serum was centrifuged at 800 g for 10 min at 4°C and has stored at –20 °C. Extracellular IL10 in the serum was assessed with VectorBESTUkraine test system cytokines kit, according to manufacturer's instructions in immune enzyme analyser "LabLine–90" (Austria). Ethical Considerations. This study was approved by the Ethics Committee of the Kharkiv National Medical University (Report No 6 from 05.10.2016). Informed consent was obtained for every patient. Statistical descriptive analyses was performed with the MedCalc Software (Acacialaan 22 B–8400 Ostend, Belgium), Kruskal–Wallis ANOVA test (KW), and ROC–curve analysis were used. For all statistical methods, $p < 0.05$ was considered statistically significance.

Results

Among 56 patients with IAI were recruited from hospital with average age 56 years old (ranging from 19 to 83 years), 26 were men. The common comorbidities were systemic hypertension and diabetes mellitus type 2. About half (26/56) reported previous recent surgery due to IAI. The similar amount (26/56) of the patients underwent

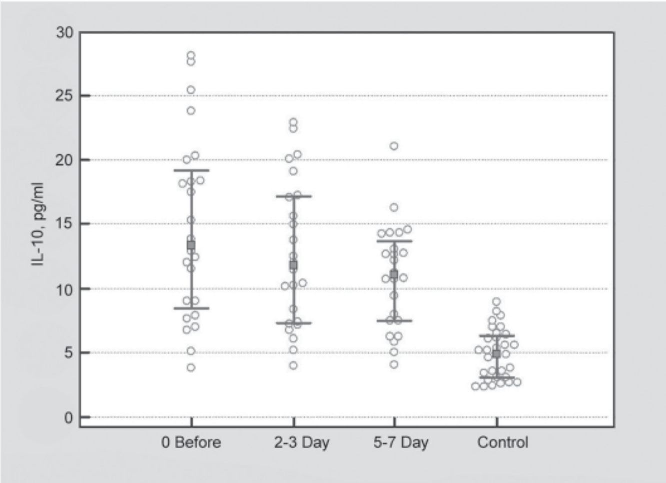

Fig 1.
Distribution serum IL–10 level in patients with POA before and after 2–3 days and 5–7 days of surgical intervention.

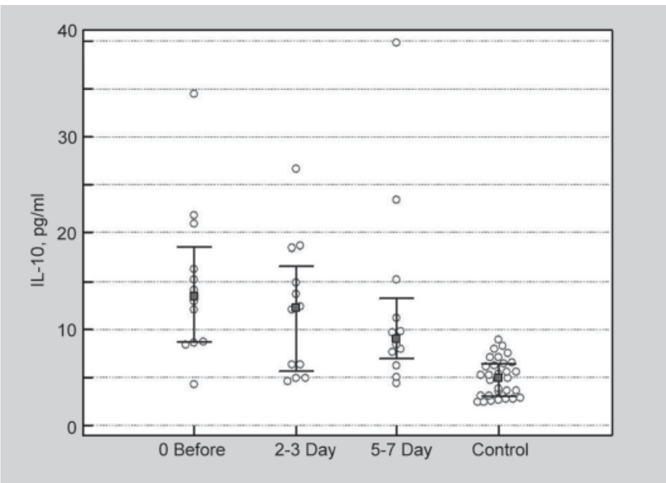

Fig. 2.
Distribution serum IL–10 level in patients with PIAA before and after 2–3 days and 5–7 days of surgical intervention.

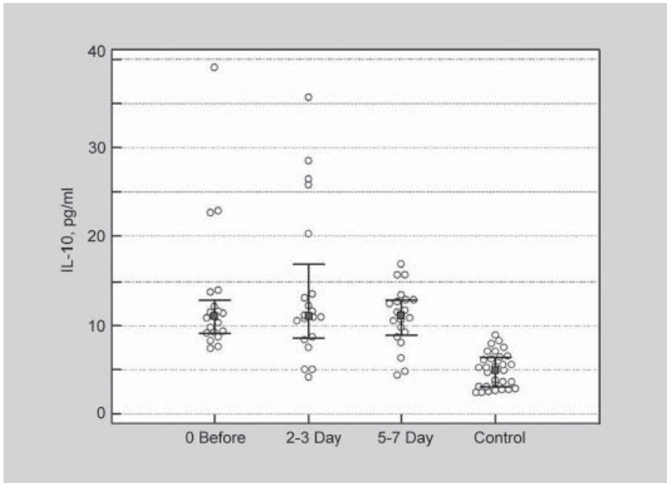

Fig. 3.
Distribution serum IL–10 level in patients with PC before and after 2–3 days and 5–7 days of surgical intervention.

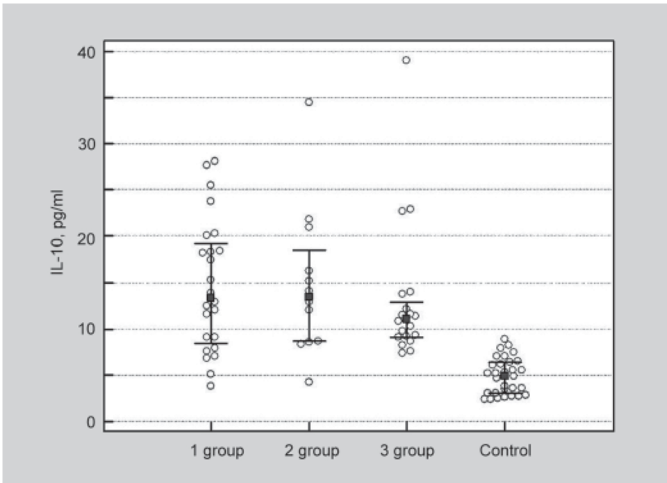

Fig. 4.
Distribution serum IL–10 level in patients with different origin of IAI before surgical intervention.

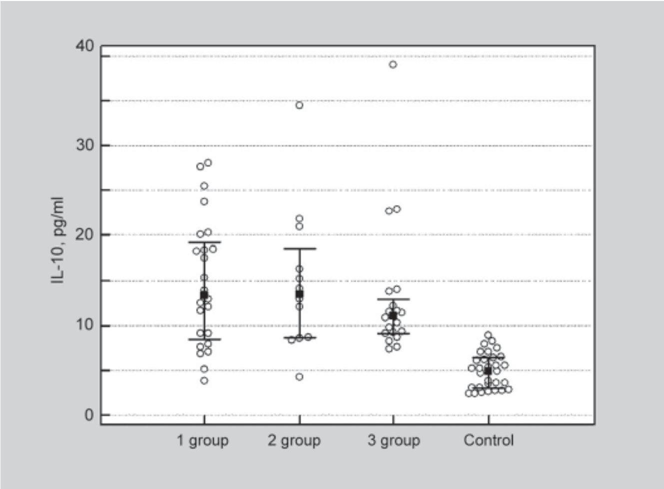

Fig. 5.
Distribution serum IL–10 level in patients with different origin of IAI at 2–3 days postsurgical intervention.

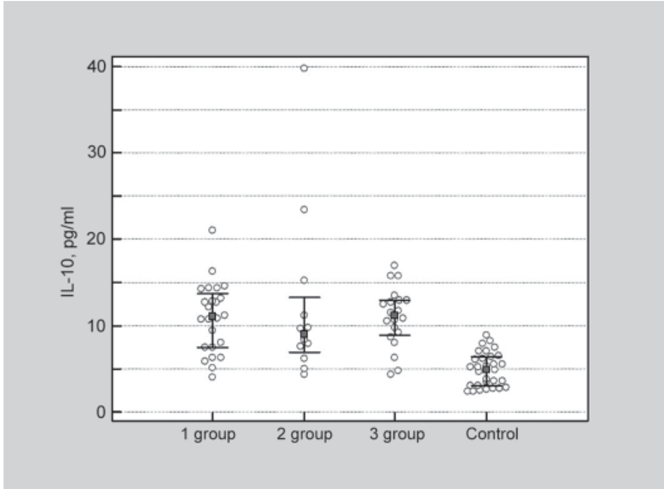

Fig. 6.
Distribution serum IL–10 level in patients with different origin of IAI at 5–7 days postsurgical intervention.

surgery using minimally invasive technologies (*Table 1*). All patients took antibacterial therapy according hospital local protocol.

IL–10 as an anti–inflammatory cytokine was investigated in serum of 56 patients with different origin of IAI before and during 7 days after surgical intervention. The lower detect in 31 patients of Control group was 2.35 pg/mL, upper – 8.94 pg/mL for IL–10. Median serum concentration of IL–10 in Control group was 4.87 pg/mL. There was no found difference between distribution of serum IL–10 in patients of Group 1 in perioperative period (*Fig. 1*) (KW test H=3.0, p=0.2169). We have took significant difference of serum IL–10 between Group 1 and Control group in perioperative period (*Fig. 1*) (KW test H=47.0, p=0.0001).

No any significant difference of serum IL–10 distribution in patients of Group 2 in perioperative period (KW test H=1.7, p=0.4171) and significant difference with Control group (*Fig. 2*) (KW test H=29.7, p=0.0001).

Same data we have took of serum IL–10 distribution in patients of Group 3 in perioperative period – without any significant difference (KW test H=0.2, p=0.9196) except Control group (*Fig. 3*) (KW test H=47.2, p=0.0001).

The comparison of the serum levels of IL–10 did not expect difference in individuals with different origin of IAI (*Fig.4 – Fig. 6*). For example, the median [minimal and maximal] serum concentration of IL–10 was 13.3 [3.7; 28.1] pg/mL in Group 1, 13.4 [4.2; 34.4] pg/mL in Group 2, and 11.0 [7.3; 39.0] in Group 3 at the day before surgical intervention (KW test H=0.6, p=0.7539). The median [minimal and maximal] serum concentration of IL–10 was 11.7 [4.0; 22.9] pg/mL in Group 1, 12.2 [4.5; 26.6] pg/mL in Group 2, and 11.0 [4.1; 35.6] in Group 3 at the 2–3 day after surgical intervention (KW test H=0.5, p=0.7838). The median [minimal and maximal] serum concentration of IL–10 was 11.0 [4.0; 21.0] pg/mL in Group 1, 9.0 [4.3; 39.7] pg/mL in Group 2, and 11.1 [4.3; 16.9] in Group 3 at the 5–7 day after surgical intervention (KW test H=0.7, p=0.6885). The significance was in compare concentration IL–10 in serum in patients with IAI and healthy persons before (KW test H=48.6, p < 0.0001), at the 2–3 day (KW test H=38.0,

Table 1. **Demographic and clinical variables of patient with different origin of IAI**

Data		Groups			Total (n=56)
		1 (n=24)	2 (n=12)	3 (n=20)	
Age, years		58	63	48	56
Median, (min; max)		(30; 78)	(52; 79)	(19; 83)	(19; 83)
Men	No	10	4	12	26
	%	41.6	33.3	60	46.4
Diabetes Mellitus Type 2		2	3	2	7
Systemic arterial hypertension		2	1	2	5
Previous abdominal surgical interventions		24	1	1	26
Duration in hospital, days		14	18	11	13
Median, (min; max)		(7; 98)	(12; 34)	(6; 33)	(6; 98)
Routine surgical intervention (laparotomy)	No	6	4	20	30
	%	25	33.3	100	53.6
Minimally invasive surgical intervention (abscess punction)	No	18	8	-	26
	%	75	66.6	-	46.4

Table 2. **ROC analysis result for serum IL 10 in patients with IAI**

Group	AUC	Concentration	p	Sensitivity	Specificity
1	0.920	≥ 6.54	<0.0001	86.11	80.65
2	0.879	≥ 6.06	<0.0001	83.33	70.97
3	0.941	≥ 7.02	<0.0001	90.00	87.10
Total IAI	0.953	≥ 6.78	<0.0001	92.86	80.65

p < 0.0001), and 5–7 day (KW test H=39.4, p < 0.0001) after surgical intervention.

Having received significant differences in the concentration of serum IL–10 in patients with different origin of the IAI between only healthy individuals, we considered sensitivity and specificity for the test (*Table 2*).

Of note, lowest concentration with significant sensitivity and specificity of serum IL 8 was for primary and secondary intra–abdominal abscesses.

Discussion

Published studies have associated IAI with a prolonged morbidity and significant mortality rate, especially complicated IAI [1, 2, 3, 4]. The 56 cases of IAI with different origin: 24 cases of patients with postoperative intra–abdominal abscesses, 12 cases of patients with primary intra–abdominal abscesses, and 20 cases of patients with peritonitis due to IAI were analyzed in Zaytsev Institute of General and Emergency Surgery. Despite increased knowledge in epidemiology and antibiotic therapy, applying minimally invasive technology, our results were similar to those obtained during last forty years [9].

IAI, especially complicated, are associated with systematically inflammatory processes. It was the aim to measured anti–inflammatory cytokine IL–10 in serum of patients with different origin of IAI in perioperative period. We have also investigated serum level of IL–10 in 31 healthy individuals. There are various data regarding the levels of IL–10 in IAI for human and animals. So, plasma IL–10 level were determined with an enzyme–linked immunosorbent assay in preanaesthesia, 0, 2, and 4 hours during surgery, and at the end of surgery, followed by sampling on the morning of postoperative days 1 and 3 by Kato M. et al. in 10 patients [10]. Before anaesthesia and at 0 hours of surgery, IL–10 was not detected. The plasma levels of IL–10 was significant elevated and achieved their maximal value 4 hours after the skin incision, returned to preanaesthesia levels on 3 day. Although this cohort undergo upper abdominal intervention.

In animal's model IL–10 serum levels were increased in patient after complicated abdominal surgery. An IL–10 deficiency decreases the postoperative expression of neutrophil–recruiting chemokines, consequently reduces the neutrophil extravasation into the postsurgical bowel wall and finally protects mice from postoperative ileus [11].

Despite the release of peritoneal IL–10 has not been studied extensively, some studies have shown significantly higher of IL–10 in peritoneum compared with systemic values [12]. The release of pro–inflammatory cytokines is synchronized with the release of anti– inflammatory cytokines are still unclear interpretation [13]. Resent study have shown IL–10 was more likely to be detectable in serum than in secretion peritoneum. For example, only 7% (2/30) of the patients showed IL–10 levels above detection limit in abdominal secretion, while 52% (16/31) patients had IL–10 detected in the serum. In addition, the geometric means of IL10 levels was 14 times higher in serum (2.59 pg/mL, CI: 0.91–11.59) than in secretion (0.18 pg/mL, CI: 0.06–0.71) [14].

We did not find statistical significance in the concentration of serum IL–10 before, at the 2–3 and 5–7 days after surgery in patients with different sources of IAI (*Fig. 1 – 6*). Our data matches the data by João Fernando Gonçalves Ferreira [15]. Modulation of the anti–inflammatory response in the production of IL–10 for all types of IAI is not specific. Our results contrast with a report in 2013 regarding the use of multiplex 39 cytokine measurements for prognosis in sepsis subgroup population of 363 patients [15]. On the other hand, we have established that concentration of serum IL–10 ≥ 6.78 pg/mL in patients with different origin of IAI has significant sensitivity and specificity. Measurement of cytokines should be further investigated as a more sensitive determinant of intra–abdominal inflammatory response. High–quality clinical trials are needed to better understand the role of inflammatory mediators in IAI with different origin.

Conclusion. The serum anti–inflammatory IL–10 difference was not found between IAI with different origin in perioperative period in patients with postoperative abscesses, primary intra–abdominal abscesses, and peritonitis due to IAI. The concentration of serum IL–10 ≥ 6.78 pg/mL in patients with different origin of IAI has significant sensitivity and specificity. It should be further studies targeting a specific causative agent of nosocomial infection and cytokine response.

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Authors' contributions

All the authors contributed equally to this work. All authors read and approved the final manuscript.

Competing interests

The authors who have taken part in this study declared that they do not have any conflict of interest with respect to this manuscript.

Consent for publication

All the authors have consented for publication of this manuscript.

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