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Effect of anti-adhesion agents on cytokine profile in an experimental model of postoperative intra-abdominal adhesions

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Many attempts have been made to prevent peritoneal adhesions using anti-adhesion agents, barriers and other therapeutic approaches, but their efficacy has not been widely accepted.

Purpose – to determine the effects of mezogel, a mixture of metronidazole, dextran, and contrykal enriched with oxygen based on the pro- and anti-inflammatory cytokine concentration in rats with simulated postoperative peritoneal adhesions.

Materials and methods. A total of 90 outbred white rats, divided into three groups of 30 animals each, underwent laparotomy and mechanical injury of the small bowel wall until a drop of blood appeared. After mechanical injury of the small bowel wall, the abdominal wound in group 1 animals (control) was closed with a layered suture technique; group 2 animals (comparison) were administered one mL of mezogel into the abdominal cavity before layer-by-layer suturing; group 3 animals (experimental) were introduced one mL of a specially prepared mixture of metronidazole, dextran, and contrykal (in a ratio of 1:1:0.1, respectively) enriched with oxygen into the abdominal cavity before the laparotomy wound was closed. Each surgical intervention lasted 15–20 minutes. On days 5, 10 and 21 of the experiment interleukin (IL) 4, IL-6, IL-10 and tumour necrosis factor alpha (TNF-α) were determined in the blood by enzyme immunoassay using corresponding test kits manufactured by Bender Medsystems (Austria).

Results. The levels of the anti-inflammatory cytokines IL-4 and IL-10 increased dynamically in groups 2 and 3, while group 1 showed their decrease. The proinflammatory cytokine IL-6 and TNF-α concentration decreased in the experimental and comparison groups during the study period. On day 5 in groups 2 and 3, compared to group 1, the IL-6 concentration was reduced by 28.4% (p=0.029) and 41.0% (p=0.006), respectively. Group 3 animals had a 17.6% (p=0.043) lower IL-6 level compared to group 2 animals. On days 10 and 21 a dynamic decrease in IL-6 was observed in the animals of groups 2 and 3. Group 3 animals had the lowest TNF-α, 41.9 % (p=0.001) lower than in group 1, and 31.7 % (p=0.118) lower than in group 2. There were significant strong relationships detected between IL-10 and IL-6 in all groups on day 5 of the study.

Conclusions. The administration of anti-adhesion agents, mezogel and an oxygen-enriched mixture of metronidazole, dextran, and contrykal, inhibits inflammation, which is expressed as a decrease in the concentrations of IL-6 and TNF-α. These agents lead to a negative interaction of anti-inflammatory cytokines with pro-inflammatory cytokines, in particular IL-4 with IL-6 and IL-10 with IL-6, indicating a greater prophylactic effect.

The experiments with laboratory animals were provided in accordance with all bioethical norms and guidelines.

No conflict of interests was declared by the authors.

Keywords: postoperative intra-abdominal adhesions, mezogel, metronidazole, dextran, contrykal, cytokines, correlation.

Вплив протиспайкових засобів на цитокіновий профіль в експериментальній моделі з післяопераційними внутрішньочеревними спайками

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Зроблено багато спроб запобігти утворенню перитонеальних спайок за допомогою антиспайкових препаратів, бар'єрів та інших терапевтичних методів, але їхня ефективність не отримала широкого визнання.

Мета – визначити ефекти мезогелю, суміші метронідазолу, декстрану і контрикалу, збагаченої киснем, за концентрацією про- і протизапальних цитокінів у щурів із модельованими післяопераційними перитонеальними спайками.

Матеріали та методи. Усього досліджували 90 безпородних білих щурів, поділених на три групи по 30 голів, яким виконували лапаротомію та механічне пошкодження стінок тонкої кишки до появи краплі крові. Тваринам 1-ї групи (контрольної) після механічного ушкодження стінки тонкої кишки шкіру живота пошарово зшивали; тваринам 2-ї групи (порівняння) до пошарового зшивання в черевну порожнину вводили мезогель у кількості 1 мл; тваринам 3-ї групи (дослідної) до закриття лапаротомної рани в черевну порожнину вводили по 1 мл спеціально приготованої суміші метронідазолу, декстрану та контрикалу, збагаченої киснем (у співвідношенні 1:1:0,1). Кожне операційне втручання тривало 15–20 хв. На 5, 10 і 21-шу добу експерименту в крові визначали ІЛ-4, ІЛ-6, ІЛ-10 і фактор некрозу пухлини-альфа (ФНП-α) методом імуноферментного аналізу з використанням відповідних тест-систем фірми «Bender Medsystems» (Австрія).

Результати. Рівні протизапальних цитокінів ІЛ-4 і ІЛ-10 динамічно підвищувалися у 2 і 3-й групах, тоді як у 1-й групі відзначалося їхнє зниження. Концентрація прозапальних цитокінів ІЛ-6 і ФНП-α у порівняльній і дослідній групах у період дослідження знижувалася. На 5-ту добу у 2 і 3-й групах порівняно з 1-ю групою концентрація ІЛ-6 була зниженою на 28,4% (p=0,029) і на 41,0% (p=0,006) відповідно. У тварин 3-ї групи рівень ІЛ-6 порівняно з рівнем у тварин 2-ї групи був на 17,6% (p=0,043) нижчим. На 10 і 21-шу добу спостерігалося динамічне зниження ІЛ-6 у тварин 2 і 3-ї груп. У тварин 3-ї групи були найнижчі значення ФНП-α – на 41,9% (p=0,001) нижчі, ніж у 1-й групі, і на 31,7% (p=0,118) нижчі, ніж у 2-й групі. Значущі сильні зв'язки визначалися між ІЛ-10 і ІЛ-6 у всіх групах на 5-ту добу дослідження.

Висновки. Введення антиспайкових засобів: мезогелю і суміші метронідазолу, декстрану і контрикалу, збагаченої киснем, інгібує запалення, що виражається зниженням концентрації ІЛ-6 і ФНП-α. Зазначені засоби призводять до негативної взаємодії протизапальних цитокінів із прозапальними цитокінами, зокрема, ІЛ-4 з ІЛ-6 та ІЛ-10 з ІЛ-6, що свідчить про більший профілактичний ефект.

Під час проведення експериментів із лабораторними тваринами всі біоетичні норми та рекомендації дотримано.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: післяопераційні внутрішньочеревні спайки, мезогель, метронідазол, декстран, контрикал, цитокіни, кореляція.

Peritoneal adhesions frequently occur after abdominal surgeries with a prevalence of 93% [18]. Postoperative adhesions are pathological fusions formed between the surfaces of body cavities, starting from the connective tissue layer and ending with a fibrous bridge with nerves and vessels growing through [9]. In order to prevent postoperative adhesions, patients have to undergo additional surgeries, which increases the medical expenses and physical burden. A number of film or liquid products are widely used to prevent postoperative adhesions, which typically serves as barriers to separate the contact surfaces of injured tissues. Products commonly used in the clinic include polylactic acid film, seprafilm, medical sodium hyaluronate, medical chitosan, etc. They have been found to reduce adhesion formation in many animal models and in some clinical practices [1,10,11]. Simultaneous comparisons of the anti-adhesion efficacy of a wide list of commercial products with the same animal model or clinical practice have been reported [7]. Many attempts have been made to prevent peritoneal adhesions using anti-adhesion agents, barriers and other therapeutic approaches, but their efficacy has not been widely accepted. So far, the only reliable treatment for adhesions is surgery, which, in turn, is accompanied by an increased risk of recurrent adhesions. Despite considerable progress in modern perioperative medicine, only limited preventive approaches are available; and atraumatic surgery remains the most important factor. Basically, researches are focused on two main strategies for preventing adhesions: firstly, intraoperative application of mechanical barriers and, secondly, new concepts of immunomodulation.

The postoperative adhesions develop mainly due to fibrinolytic inhibition and extracellular matrix degradation, inflammatory reactions and tissue hypoxia. Adhesions develop as a result of various phenomena, including coagulation, inflammation and fibrinolysis, while traumatized sites heal. The results of evaluation of several substances, which are constituents of agents and barriers inhibiting peritoneal adhesions, are presented [14]. Inflammatory cells such as lymphocytes, macrophages, and neutrophils infiltrate the wound after peritoneal injury under the conditions of inflam-

Table 1
Cytokine levels in experimental models of postoperative intraperitoneal adhesions

Group	IL-4, pg/mL	IL-10, pg/mL	IL-6, pg/mL	TNF-α, pg/mL
Day 5				
1	16.3±1.0	37.84±3.53	220.64±21.67	38.54±1.97
2	17.04±3.33	40.98±4.90	158.02±7.46*	32.78±5.58
3	17.88±3.18	45.38±4.26	130.22±8.50*,**	22.38±1.74*
Day 10				
1	14.22±1.42	30.74±2.53	252.06±23.55	43.96±5.51
2	17.88±1.46	45.54±5.89*	150.72±12.82*	30.98±4.74
3	19.14±1.41*	46.42±5.10*	128.48±4.70*	22.52±2.30*
Day 21				
1	16.3±1.0	37.84±3.53	220.64±21.67	38.54±1.97
2	18.64±1.15	47.38±3.30	137.56±6.87*	28.40±3.76*
3	20.0±1.76	48.92±2.34*	125.7±4.28*	20.32±1.58*

Note: * – statistical significance of differences in the parameter of the control group; ** – statistical significance of differences in the parameters between groups 2 and 3.

matory and coagulation pathway activation [3]. The number of polymorphonuclear neutrophils increases in the first two days after injury, and the number of macrophages increases in five to six days [18]. Interleukin-1, TNF-α, IL-6 and other adhesion-associated cytokines are secreted by macrophages [15,19]. Lesional tissue releases cytokines that act individually and synergistically to induce a humoral inflammatory tissue reaction in response to injury. There is currently insufficient information on the role of IL-6, IL-8, and IL-10 in the adhesion development, although theoretically they are mediators of the cellular response to injury [8].

Thus, although great efforts have been made for prevention, postoperative adhesions remain a challenging surgical problem.

The purpose of the study is to determine the effects of mezogel, an oxygen-enriched mixture of metronidazole, dextran, and contrykal on the concentrations of pro- and anti-inflammatory cytokines in rats with simulated postoperative peritoneal adhesions.

Methods of the research

The study was conducted on white outbred rats kept under the normal test conditions in the vivarium of the Research and Development Centre of the Azerbaijan Medical University. Before the experiment, the animals were placed in a special room in turns for one month. Management of rats and experimental studies were performed according to the Guide for the Care and Use of Laboratory Animals (2011) [12].

There was a health check of the animals before the operative procedure began. A total of 90 rats divided into three groups were used. Each group included 30 rats kept in three cages with 10 animals in each. After calypsol anaesthesia under sterile conditions, all rats were fixed dorsally on a special wooden board; hair on the abdominal surface was shaved with a sharp razor; and then the abdominal skin was incised using a midline access 3–4 cm long. The surface of the small bowel segment found carefully in the abdominal cavity on the left was mechanically injured with a clean toothbrush until bleeding appeared. After mechanical injury the abdominal wound in group 1 animals (control) was closed using a layered suture technique; in group 2 animals (comparison) one mL of mezogel was introduced into the abdominal cavity and then the abdominal skin was sutured with a layered technique. In group 3 animals (experimental), one mL of specially prepared mixture of metronidazole, dextran, and contrykal (in a ratio of 1:1:0.1, respectively) + O_2 was introduced into the abdominal cavity and the abdominal wound was closed with a layered suture technique. Each surgical intervention lasted 15–20 minutes. On days 5, 10, and 21 of the experiment, the serum IL-4, IL-6, IL-10, and TNF-α levels were measured by enzyme immunoassay using corresponding test kits manufactured by Bender Medsystems (Austria).

The results were statistically processed by nonparametric analysis using SPSS for Windows software (version 16.0, SPSS Inc., Chicago, IL, USA). The parameters were expressed as mean ± standard deviation (SD), numbers, and percentages. The Student's t-test was calculated to compare the mean values between the groups. The strength of correlation relationships between the selected indicators was calculated using the Spearman's rank correlation coefficient. Statistical estimates were considered significant at $p<0.05$.

Discussion of the research

In the course of the study, the levels of pro- and anti-inflammatory cytokines were measured in the blood of animal models (Table 1).

According to figures from Table 1, the levels of anti-inflammatory cytokines IL-4 and IL-10 dynamically increased in groups 2 and 3, while in group 1, their decrease was observed. In the control group (group 1), the level of IL-4 decreased by 12.8% (t=1.20, p=0.270) on day 10 of the experiment compared to its level on day 5. On day 21, the IL-4 level increased to its baseline level, i.e. the one seen on day 5. In group 2, IL-4 on days 10 and 21 exceeded values on day 5 by 4.7% (t=0.24, p=0.824) and 8.6% (t=0.45, p=0.663), respectively. The increase in the serum IL-4 concentration in group 3 animals compared to group 2 was 4.1% (t=0.41, p=0.695). In group 3, the IL-4 concentration on days 10 and 21 increased by 8.0% (t=0.36, p=0.728) and 10.6% (t=0.58, p=0.578), respectively, compared to that on day 5. Comparison of the IL-4 concentration in the blood of animals of groups 3 and 2 showed its increase in group 3 by 4.3% (t=0.38, p=0.714). A comparative analysis between the experimental groups on day 5 showed that the IL-4 level in groups 2 and 3 was higher than in group 1 by 4.3% (t=0.21, p=0.837) and 8.8% (t=0.47, p=0.650), respectively. No differences in IL-4 levels were found between groups 2 and 3. On day 10, in groups 2 and 3, the IL-4 level was 20.5% (t=1.05, p=0.328) and 25.7% (t=2.46, p=0.043) higher, respectively, than in group 1. During this period, the difference in the IL-4 level between groups 2 and 3 animals was 6.6% (t=0.62, p=0.554). On day 21 of the study, in groups 2 and 3, the IL-4 concentration was 12.5% (t=1.67, p=0.139) and 18.5% (t=1.93, p=0.095) higher, respectively, than in group 1.

In the control group (group 1) similar trends of the IL-10 and IL-4 levels were observed. On day 10, compared to day 5, the IL-10 level in this group decreased by 18.8% (t=1.63, p=0.146). On day 21, the IL-10 concentration increased and reached the baseline level. In group 2, the cytokine level on days 10 and 21 increased by 10.0% (t=0.60, p=0.570) and 13.5% (t=1.08, p=0.314), respectively, compared to that on day 5. Comparison of the IL-10 concentration in the blood of animals in this group on day 21 with the value obtained on day 10 showed its increase by 3.9% (t=0.27, p=0.793). In group 3, the level of IL-10 on day 10, compared to its level on day 5, was almost the same, while on day 21 it was slightly higher by 7.2% (t=0.73, p=0.490). On day 21, the IL-10 concentration was 5.1% higher than on day 10 (t=0.45, p=0.669). Comparison of IL-10 level between the experimental models on day 5 revealed that a relatively high level of this cytokine was detected in group 3 animals, which, when compared to groups 1 and 2, revealed the difference of 16.6% (t=1.36, p=0.215) and 9.7% (t=0.68, p=0.520), respectively. The difference in the IL-10 level between groups 1 and 2 was insignificant, 7.6% (t=0.52, p=0.619). On day 10 of the study, the IL-10 level in animals of groups 2 and 3 was 32.5% (t=2.31, p=0.054) and 33.8% (t=2.75, p=0.028) higher, respectively, than in group 1. There was almost no difference between groups 2 and 3. On day 21, the mean IL-10 level was 20.1% higher in group 2 (t=1.97, p=0.089), and 22.6% higher in group 3 (t=2.62, p=0.035) than in group 1. There was little difference between the IL-10 levels in groups 2 and 3 (3.1%, t=0.38, p=0.715).

The proinflammatory cytokine IL-6 and TNF-α concentration decreased in the experimental and comparison groups during the study period. In the control group, the IL-6 level on day 10 increased by 12.5% (t=0.98, p=0.359) compared to that on day 5 of the experiment. On day 21, the mean IL-6 level decreased by 12.5% (t=0.98, p=0.359) compared to its level on day 10 and reached the level recorded on day 5. In group 2, the IL-6 level on day 10 was slightly decreased by 4.6% (t=0.49, p=0.638) and on day 21 by 12.9% (t=2.02, p=0.083) compared to that on day 5. The decrease in the IL-6 level on day 21 compared to the level of this cytokine on day 10 was 8.7% (t=0.90, p=0.396). In group 3, the IL-6 concentration on day 10 slightly decreased by 4.6% (t=0.49, p=0.638) and on day 21 by 12.9% (t=2.02, p=0.083), compared to that on day 5. The IL-6 level on day 21 as compared to the level on day 10 was almost the same. A comparative analysis of the serum IL-6 concentration in the experimental animal models showed that on day 5 the cytokine concentration in groups 2 and 3 compared to group 1 decreased by 28.4% (t=2.73, p=0.029) and 41.0% (t=3.88, p=0.006), respectively. The IL-6 level was 17.6% (t=2.46, p=0.043) lower in group 3 compared to its level in the animals of group 2. On day 10, the IL-6 level in groups 2 and 3 animals decreased by 40.2% (t=3.78, p=0.007) and 49.0% (t=5.15, p=0.001), respectively, compared to the cytokine level in group 1. In group 3 animals compared to group 2, the IL-6 level was 14.8% lower (t=1.63, p=0.147). On day 21, the mean serum IL-6 concentration was 37.6% (t=3.65, p=0.008) and 43.0% (t=4.30, p=0.003) lower in groups 2 and 3 animals than in group 1. In group 3 animals compared to group 2 the IL-6 level was 8.6% lower (t=1.47, p=0.186).

The TNF-α concentration in group 1 on day 10 compared to the level on day 5 was higher by 12.33% (t=0.93, p=0.385). On day 21, TNF-α level decreased to the value observed on day 5. In group 2, the concentration of this cytokine on days 10 and 21 decreased by 5.5% (t=0.25, p=0.813) and 13.4% (t=0.65, p=0.536), respectively,

Table 2
Correlation coefficient (r) between pro- and anti-inflammatory cytokines in the blood of experimental models over time

Cytokines	Group 1 (n=5)	Group 2 (n=5)	Group 3 (n=5)
Day 5			
IL-4 – IL-10	0.459, p>0.05	-0.221, p>0.05	-0.255, p>0.05
IL-4 – IL-6	0.740, p<0.01	0.116, p>0.05	0.442, p>0.05
IL-4 – TNF-α	-0.133, p>0.05	-0.029, p>0.05	0.091, p>0.05
IL-10 – IL-6	0.866, p<0.001	0.937, p<0.001	-0.835, p<0.001
IL-10 – TNF-α	0.435, p>0.05	0.658, p<0.05	-0.182, p>0.05
IL-6 – TNF-α	0.381, p>0.05	0.477, p>0.05	-0.322, p>0.05
Day 10			
IL-4 – IL-10	-0.390, p>0.05	-0.321, p>0.05	0.181, p>0.05
IL-4 – IL-6	-0.142, p>0.05	0.019, p>0.05	-0.325, p>0.05
IL-4 – TNF-α	0.118, p>0.05	-0.327, p>0.05	-0.477, p>0.05
IL-10 – IL-6	-0.777, p<0.01	0.197, p>0.05	-0.921, p<0.001
IL-10 – TNF-α	0.094, p>0.05	0.937, p<0.001	0.579, p<0.05
IL-6 – TNF-α	-0.548, p>0.05	0.430, p>0.05	-0.391, p>0.05
Day 21			
IL-4 – IL-10	0.459, p>0.05	0.802, p<0.001	0.805, p<0.001
IL-4 – IL-6	0.740, p<0.01	0.289, p>0.05	-0.219, p>0.05
IL-4 – TNF-α	-0.133, p>0.05	0.209, p>0.05	0.794, p<0.01
IL-10 – IL-6	0.866, p<0.01	-0.289, p>0.05	-0.185, p>0.05
IL-10 – TNF-α	0.435, p>0.05	0.494, p>0.05	0.524, p<0.05
IL-6 – TNF-α	0.381, p>0.05	-0.167, p>0.05	-0.677, p<0.05

compared to that on day 5. The TNF-α level on day 21 decreased by 8.3% (t=0.43, p=0.683) compared to its level on day 10. In group 3, the TNF-α concentration on day 10 tended to increase compared to its level on day 5, but on day 21 it reached the value existing on day 5 of the experiment. Comparative between-group analysis of the serum TNF-α concentration in animals on day 5 showed that group 3 animals had the lowest values, which was 41.9% (t=6.15, p=0.001) lower than in group 1 and 31.7% (t=1.78, p=0.118) lower than in group 2. On day 10 of the experimental study, the TNF-α level in group 3 animals was lower by 48.8% (t=3.59, p=0.009) than in group 1 and by 27.3% (t=1.61, p=0.152) than in group 2. TheTNF-α level in group 2 was 29.5% lower (t=1.79, p=0.117) than in group 1. On day 21, the mean serum TNF-α concentration in groups 2 and 3 animals decreased by 28.3% (t=2.39, p=0.048) and 47.3% (t=7.21, p=0.001), respectively, compared to group 1. Group 3 animals had a 28.4% lower TNF-α level (t=1.98, p=0.088) compared to group 2.

Thus, in the experimental and comparison groups, there was an increase in anti-inflammatory IL-4 and IL-10 and a decrease in pro-inflammatory cytokines, IL-6 and TNF-α.

The correlation relationship between cytokines in the experimental groups at different times of the study was analyzed (Table 2).

According to the Table 2 data, statistically significant strong relationships were detected between IL-10 and IL-6 in all groups on day 5 of the study, and, what's interesting, if in groups 1 and 2 the correlation was direct, then in group 3 it was inverse. Besides, during this time period of the study, a statistically significant moderate correlation was observed in group 2 between IL-10 and TNF-α, which became even stronger on day 10. There was also a strong, inverse, statistically significant correlation relationship between IL-10 and IL-6 in group 3 on day 10. A moderate significant correlation between IL-10 and TNF-α was detected in this group. On day 21 of the experimental study, a strong, significant direct correlation relationship between the anti-inflammatory cytokines IL-4 and IL-10 was detected in groups 2 and 3, whereas in the control group, those cytokines were weakly correlated between themselves. A high correlation between IL-4 and TNF-α was observed in group 3. Moreover, in this group, IL-10 correlated with TNF-α by a moderate direct significant relationship and IL-6 correlated with TNF-α by a moderate inverse significant relationship.

According to the results, pro-inflammatory IL-6 and TNF-α were significantly reduced in the models with introduced anti-adhesion agents. IL-6 is considered a marker of early tissue injury [8] and is induced by TNF-α in mesothelial cells in a time- and dose-depen-

dent manner. The overall identification of the elevated IL-6 levels in intra-abdominal adhesions in both patients and animals [8] indicates a critical role for the lymphocyte balance in the regulation of ongoing inflammatory and regenerative processes involved in adhesion formation. Activated mesothelial cells, which can be induced by inflammation, are known to produce and secrete large amounts of IL-6 in the abdominal cavity [8]. A study showed that IL-6 is a promoter of fibrosis [8]. The therapy with monoclonal antibodies to the IL-6 receptor in a mouse model of abdominal adhesions has been reported to reduce neutrophil recruitment and adhesion formation [17]. Recently, J.M. Tsai et al. [16] sequenced RNA in the isolated superficial mesothelium using a mouse model for adhesions in vivo. They showed that the expression of gene set related to the inflammatory response, encoding cytokines, chemotactic factors, and nuclear factor κB signalling components, is regulated in the early stages after adhesion induction. Overproduction of inflammatory mediators at the early stage plays an important role in the regulation of extracellular matrix formation in postoperative adhesions [17]. It was made an assumption that both TNF-α and IL-6 regulate clotting cascade formation and fibrinogenesis [2]. Antibody therapy to the IL-6 receptor is assumed to reduce surgical adhesion formation [17]. Taken together, the extent of damage determines the degree of inflammatory response, which in turn determines the severity of adhesion formation.

When the peritoneum is injured, inflammatory cells such as neutrophils, monocytes, and lymphocytes migrate to the damaged area [4,5]. TNF-α is mainly secreted by monocytes, which are considered to be one of the main inflammatory cytokines determining the degree of adhesion [14]. J. Rocha et al. [13] investigated the anti-inflammatory effects of rosmarinic acid on thermal injury and found that rosmarinic acid significantly reduced TNF-α level in the blood versus control. According to Ding et al. [6], IL-6 and TNF-α in serum and abdominal exudate played an important role in the development of small bowel obstruction after laparoscopic appendectomy. Peritoneal IL-6 was the most reliable prognostic marker of small bowel obstruction.

We believe that the approaches we presented have the potential to reduce postoperative adhesions.

Conclusions

Based on the results of our study on rats, it was found that the administration of anti-adhesion agents, such as mezogel and an oxygen-enriched mixture of metronidazole, dextran, and contrykal, inhibit inflammation, which is expressed as a decrease in the IL-6 and TNF-α concentrations. These agents lead to a negative interaction of anti-inflammatory cytokines with pro-inflammatory ones, in particular IL-4 with IL-6 and IL-10 with IL-6, indicating a greater prophylactic effect.

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